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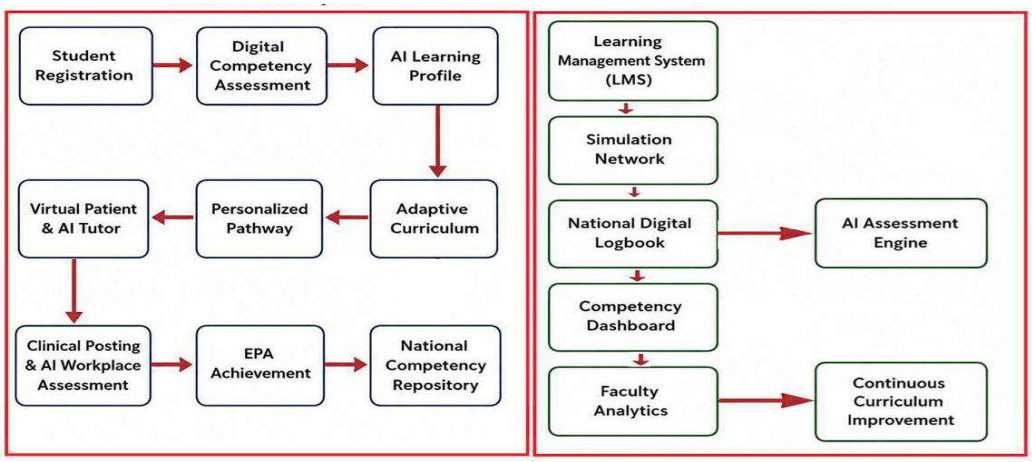
Union Minister for Health and Family Welfare Jagat Prakash Nadda has reviewed the preparedness for the National Eligibility-cum-Entrance Test for Postgraduate (NEET-PG) 2026 to ensure the smooth, secure, transparent and technology-enabled conduct of the examination

NBEMS: Education, Monitoring & Assessment Framework



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EDITORIAL

National Board of Examinations in Medical Sciences in India & The National Healthcare Transformation Framework

Minu Bajpai[1,*] and Abhijat C. Sheth[2]

[1]*Vice-President & Honorary Executive Director, National Board of Examinations in Medical Sciences, New Delhi*
[2]*Chairman of National Medical Commission & President, National Board of Examinations in Medical Sciences, New Delhi*

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Patient Care, Medical Education and Research

Executive Framework and Core Pillars

The **National Healthcare Transformation Framework** positions India at the cutting edge of global medical innovation by establishing an AI-assisted Learning Healthcare System designed to continuously evolve through data-driven insights. Formulated as a crucial milestone toward the national vision of '**Viksit Bharat 2047'**, the framework orchestrates a paradigm shift where patient care, medical education, and biomedical research are seamlessly optimized through interoperable digital architecture. At its core, this framework guarantees that technology remains a strategic enabler under strict ethical governance, prioritizing patient privacy and ensuring all automated insights culminate in clinician-led decision-making.

*Corresponding Author: Minu Bajpai
Email: bajpai2b@gmail.com

This comprehensive transformation rests firmly upon four foundational digital pillars that structurally bridge the gap between abstract technology and real-world clinical practice (Figure 1):

FOUR FOUNDATIONAL PILLARS OF DIGITAL HEALTH	
1. ABDM PUBLIC INFRASTRUCTURE	Unified identifiers (ABHA) and secure, consent-driven data portability routes.
2. ARTIFICIAL INTELLIGENCE	Multi-modal analytical diagnostics, predictive analytics, and automation.
3. UNIFIED EHR/ EMR SYSTEM	Incentivised standardisation of legacy clinic and hospital medical data.
4. CLINICAL DATA LAKE & LABS	Ethical genomic repositories, registries and population biological data networks.

Figure 1. Four Foundational Pillars of Digital Health

Ayushman Bharat Digital Mission (ABDM)

Serving as the overarching digital public infrastructure (DPI), ABDM has scaled exponentially, crossing over 93 crore (930 million) unified Ayushman Bharat Health Accounts (ABHA) and over 104 crore linked electronic health records. By utilizing its secure, time-bound, and revocable consent-management architecture, ABDM functions as a privacy-first data superhighway. This allows AI models to securely access longitudinal patient history to pre-fill clinical workflows, minimize administrative backlogs, and drive targeted, localized health interventions.

Artificial Intelligence

AI acts as the core analytical engine of this framework, with India's domestic healthcare AI market projected to grow at an unprecedented CAGR of over 40% to tap into multi-billion dollar valuations over the coming decade. Supported by government-backed initiatives like the newly introduced **Strategy for AI in Healthcare for India (SAHI)** and the **BODH benchmarking platform** for clinical AI validation, advanced machine learning and generative AI models are transitioning from theoretical concepts to clinical reality. These technologies power decentralized diagnostic tools—such as contactless, smartphone-camera-based vital assessments and rapid automated imaging triage for critical trauma—democratizing advanced care across Tier-2 and Tier-3 cities.

Electronic Medical Records/Electronic Health Records (EMR/EHR)

The fundamental bedrock for training reliable healthcare algorithms

relies heavily on standardizing fragmented data. Through the central implementation of the Digital Health Incentive Scheme (DHIS), the National Health Authority incentivizes private and public clinics, laboratories, and hospitals to rapidly digitize legacy records into structured EMRs. This shift unlocks secure, longitudinal patient tracking, allowing multi-modal clinical data to be read seamlessly by optical character recognition (OCR) and deep learning algorithms to predict biomarker shifts and track chronic disease progressions over years.

National Clinical Data & Biobank Network

To prevent algorithmic bias and fuel indigenous biomedical discoveries, the final pillar establishes a robust, highly curated network of clinical data repositories and physical biobanks. This interconnected ecosystem provides researchers and AI developers with ethically sourced, high-quality, and anonymized genomic and phenotypic data reflective of India's vast genetic diversity. By leveraging these secure biobanks alongside real-time data from the ABDM framework, Indian researchers can accelerate native drug discovery, refine epidemiological surveillance models, and ensure that AI-assisted algorithms are natively calibrated for the unique health profile of the Indian population.

Core Architectural Operations (Algorithms 1, 2 and 3)

The framework translates its vision into practice through three operational algorithms that manage care delivery, skill building, and translational discovery.

The operationalization of Algorithm 1 represents a standardized roadmap for intelligent, data-driven patient care, functioning entirely within the architecture of the Ayushman Bharat Digital Mission (ABDM) (Figure 2).

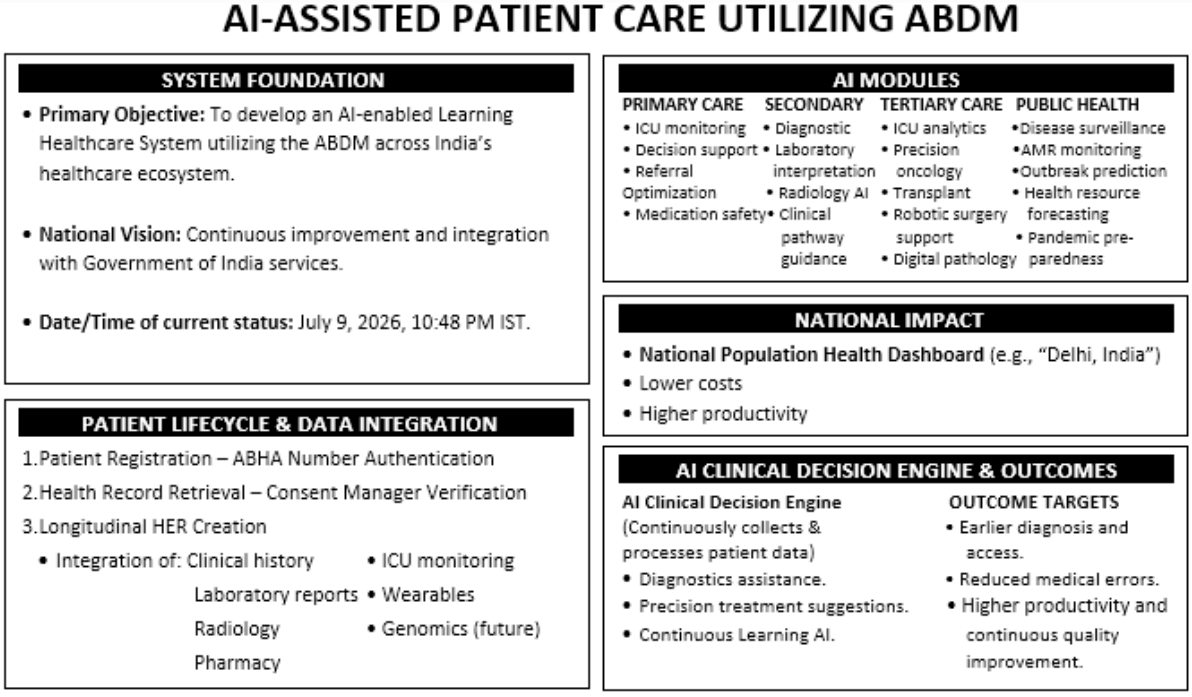

Figure 2. Algorithm 1: Patient Care Delivery Flow

The **National Board of Examinations in Medical Sciences (NBEMS)** currently plays an important enabling role in India's healthcare transformation by strengthening specialist medical education, assessment standards, workforce development, and quality assurance across the health system.

- **Standardising postgraduate medical education:** NBEMS conducts national-level postgraduate and postdoctoral examinations and awards qualifications such as DNB, DrNB, and FNB, helping create a common benchmark for specialist training across institutions.
- **Expanding the specialist workforce:** By accrediting hospitals beyond traditional medical colleges, including large public and private hospitals, NBEMS helps increase training capacity for specialists in clinical disciplines where India faces shortages.
- **The Joint Accreditation Scheme & district-level healthcare capacity:** NBEMS programmes in district hospitals and non-medical-college institutions help bring postgraduate training closer to service-delivery settings, strengthening secondary and tertiary care outside major academic centres.
- **Improving quality of clinical training:** Through accreditation norms, curriculum requirements, faculty standards, logbooks, practical assessments, and exit examinations, NBEMS pushes hospitals to maintain structured clinical learning environments.
- **Contributing to universal healthcare goals:** A better-trained specialist and family medicine workforce supports national programmes such as Ayushman Bharat, emergency care, maternal and child health, non-communicable disease management, and critical care services.
- **Promoting family medicine and broad-based care:** NBEMS has an important role in developing family physicians and generalist specialists who can manage comprehensive care, especially in district, rural, and community-linked health systems.
- **Enabling skill-based and fellowship training:** Through fellowship and super-specialty pathways, NBEMS supports focused training in high-need areas such as emergency medicine, critical care, oncology, cardiology, reproductive medicine, and other advanced specialties.
- **Strengthening examination integrity and digital systems:** NBEMS uses national entrance and exit examinations, digital processes, secure testing systems, online applications, credentialing, and academic records, helping modernise medical education governance.
- **Linking education with healthcare delivery:** Unlike purely classroom-based education systems, NBEMS training is embedded in functioning hospitals, so trainees contribute to patient care while receiving supervised specialist education.
- **Supporting India's global healthcare ambitions:** By maintaining nationally recognised qualifications and specialist training standards, NBEMS contributes to the preparation of Indian doctors for global opportunities and supports the broader vision of "Heal in India" and "Heal by India."

The system actively runs continuous **Drug Interaction Alerts**, matches parameters to generate **Precision Treatment Suggestions**, and optimizes the continuum of care by supplying automated **Referral Recommendations** and **Telemedicine Support** through India's expanding Unified Health Interface (UHI) framework. To ease administrative overhead, the engine employs natural language processing for **Clinical Documentation Automation** and maintains an active feedback loop via **Outcome Monitoring**. By analyzing post-treatment results, the **Continuous Learning AI** optimizes its underlying algorithms, while concurrently reporting anonymized, macro-level health metrics to a centralized **National Population Health Dashboard** for administrative planning.

Decentralised AI Tiers of Care

Preventive Care

Uses predictive risk stratification, tailored lifestyle recommendations, automatic vaccination reminders, and algorithmic monitoring for maternal, child, and geriatric demographics.

Primary Care

Deploys lightweight diagnostic models for instant symptom assessment, immediate clinician decision support, medication safety checks, and optimized referral routing.

Secondary Care

Introduces automated diagnostic assistance to non-metropolitan setups through AI-driven laboratory interpretation and Radiology AI (such as chest X-ray screening and CT lesion tracking).

Tertiary Care

Powers high-throughput compute environments to handle complex medical scenarios, driving real-time predictive ICU analytics, multi-omic precision oncology matchmaking, digital pathology, and autonomous robotic surgery assistance.

Public Health

Aggregates localised data streams to perform cross-border disease surveillance, machine-learning-driven outbreak prediction, and vigilant Antimicrobial Resistance (AMR) trend monitoring.

Real-World Operational Milestones

Recent digital health milestones reinforce the feasibility of this data pipeline. The National Health Authority (NHA) has registered over **93 crore (930 million) unified ABHA accounts** and systematically linked over **104 crore (1.04 billion) digitized health records**. To facilitate immediate data intake at crowded hospital OPDs, India's decentralized **"Scan and Share" QR-token architecture** has issued over **23.21 crore digital queue tokens**, slashing average patient waiting and registration times from 60 minutes down to less than 5 minutes. Citizen-facing applications like the revamped **Aarogya Setu 2.0** have deployed integrated OCR systems to automatically translate legacy physical medical reports into global HL7-FHIR standards, creating clean data feeds for emerging tools like the SAHI framework.

ALGORITHM 2: AI-Assisted Medical Education Pipeline

The modernization of medical training under Algorithm 2 transitions traditional medical education into a hyper-personalized, objective framework aligned with the National Medical Commission's (NMC) updated Competency-Based Medical Education (CBME) parameters (Figure 3).

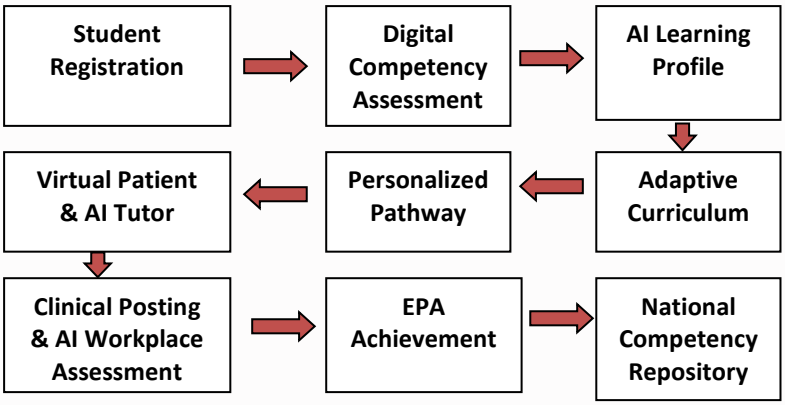

Figure 3. Medical Education Pipeline

Once students' progress to physical Clinical Posting, their performance is tracked via an **AI Workplace Assessment** engine that evaluates clinical reasoning at the point of care. Milestone achievements are authenticated as **Entrustable Professional Activities (EPA) Achievements** and automatically logged into a secure **Digital Logbook**. A live **Competency Analytics Dashboard** provides automated Faculty Feedback and precise AI Learning Recommendations, culminating in the secure upload of verified competencies to a centralized **National Competency Repository** (Figure 4a-c).

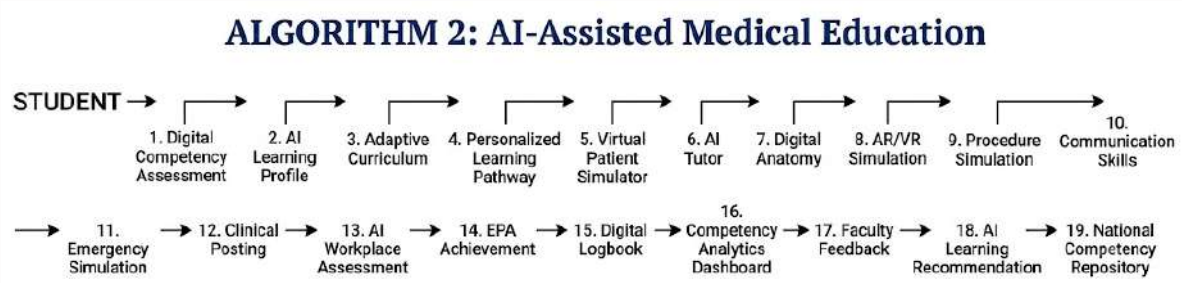

Figure 4a. AI Assisted Medical Education

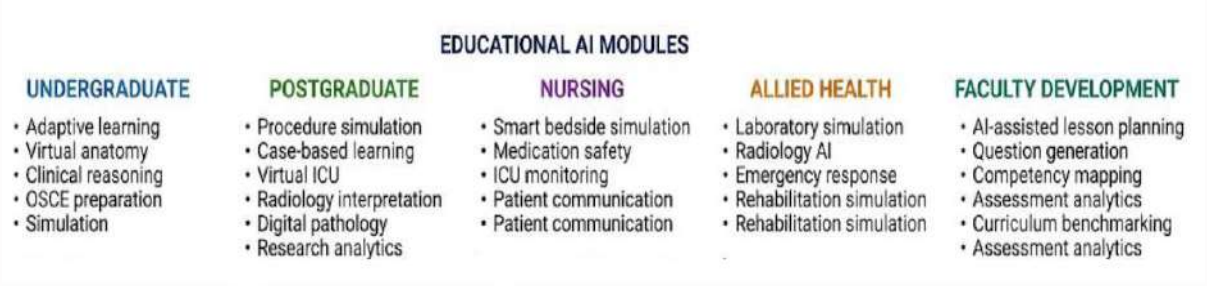

Figure 4b. Educational AI Model

National Educational Platform

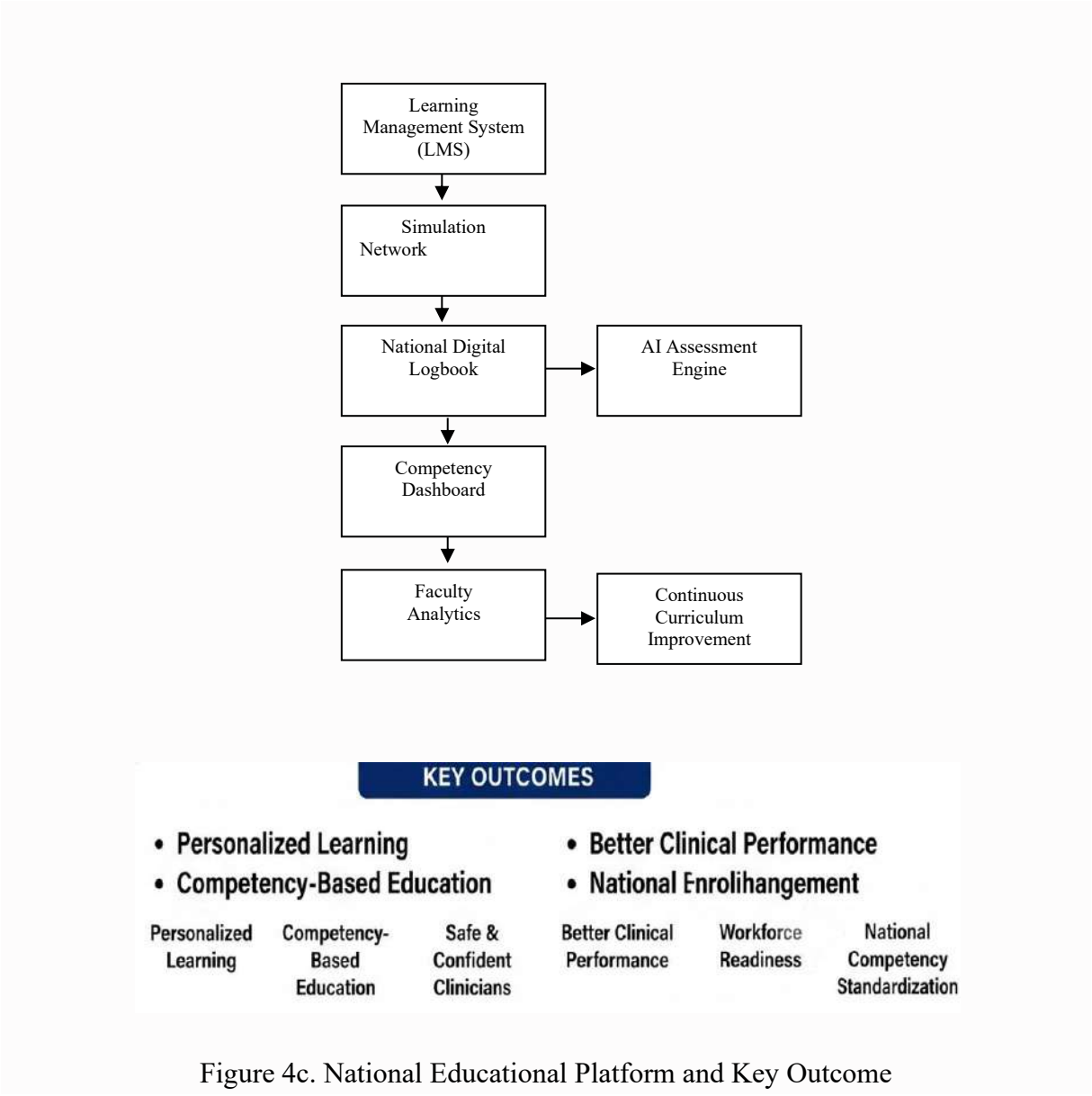

Figure 4c. National Educational Platform and Key Outcome

Specialized Educational Modes

Undergraduate (MBBS)

Focuses on foundational skills through adaptive learning modules, digital virtual anatomy, diagnostic clinical reasoning sandboxes, and objective structured clinical examination (OSCE) preparation.

Postgraduate (MD/MS)

Prioritizes complex care via high-fidelity procedure simulations, interactive case-based learning, virtual ICU environmental training, and AI-driven radiology/pathology interpretation.

Nursing

Targets clinical safety via smart bedside simulations, automated medication safety checkpoints, real-time ICU monitoring familiarization, and communication matrices.

Allied Health

Strengthens paramedical workforces using laboratory workflow simulations, Radiology AI basics, synchronized emergency response protocols, and automated rehabilitation systems.

Faculty Development

Alleviates heavy administrative backlogs by introducing AI-assisted lesson planning, automated question generation, continuous competency mapping, and curriculum benchmarking across regional institutions (Figure 5).

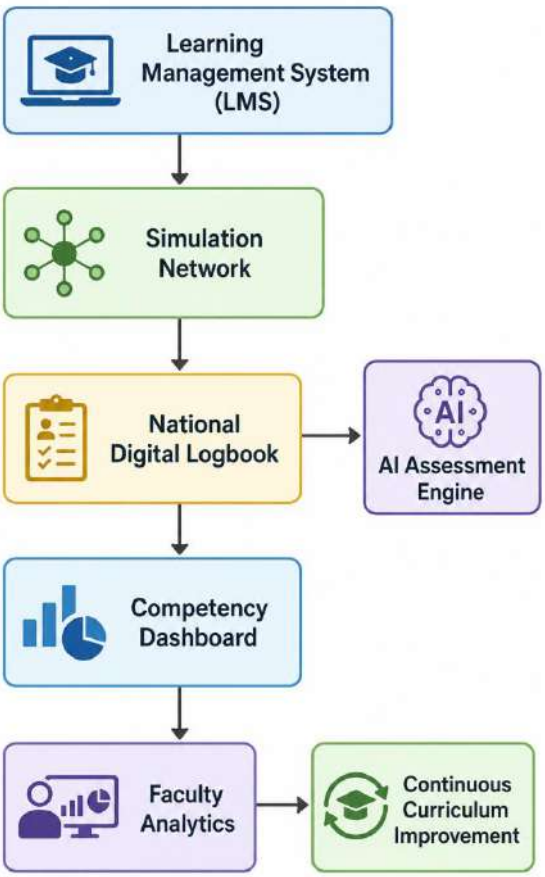

Figure 5. Architecture of the National Educational Platform

At the macro level, this system functions over a unified National Educational Platform that digitizes training delivery from end to end. Core infrastructure data passes sequentially from the base Learning Management System (LMS) to an interconnected, country-wide Simulation Network. These feeds verified operational metrics down to the National Digital Logbook. To eliminate systemic grading bias, the centralized platform routes logbook data directly through an AI Assessment Engine and displays individual progression matrices via a real-time Competency Dashboard. The resulting analytical insights are pushed to a secure Faculty Analytics portal. This gives curriculum architects the aggregated, real-world data required to execute data-backed, Continuous Curriculum Improvement cycles.

ALGORITHM 3: AI-Assisted Research Ecosystem

The operationalization of Algorithm 3 structures an advanced data-to-discovery pipeline that feeds India's evolving medical R&D infrastructure (Figure 6).

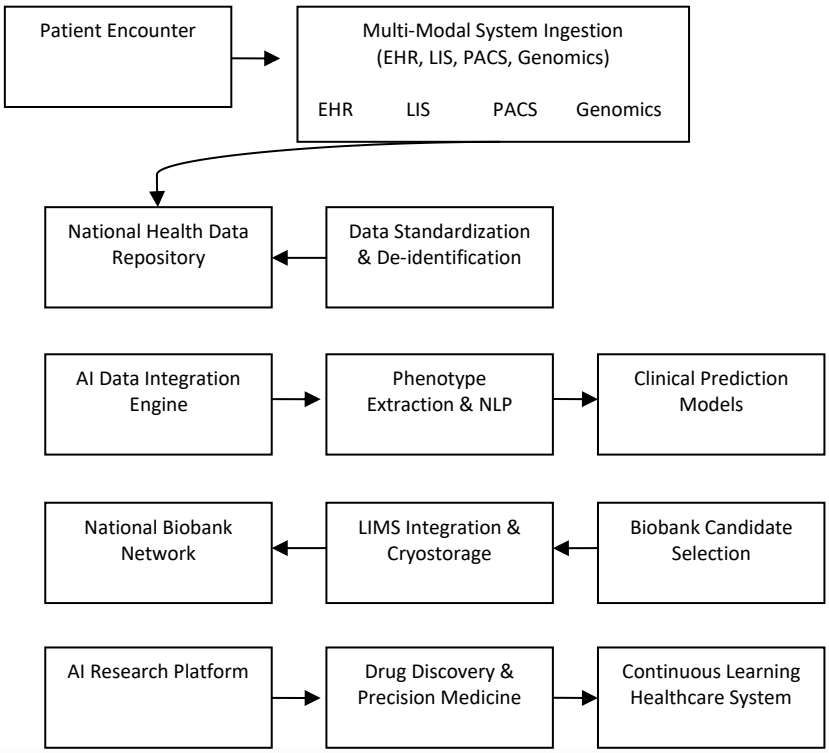

Figure 6. Operationalizing India's Medical R&D Pipeline

At the core of this architecture, an **AI Data Integration Engine** applies Phenotype Extraction, deep Natural Language Processing (NLP), and high-throughput Imaging Analytics to build structured disease models. This pipeline calculates downstream Clinical Prediction Models that automatically perform Candidate Selection for localized clinical studies. Verified candidates are funneled into Biobank Recruitment, triggering automated Biological Sample Collection tracked via end-to-end Barcode Tracking. Following precise Laboratory Processing and seamless LIMS Integration, samples are transferred to automated Cryostorage vaults embedded within the National Biobank Network—anchored by newly deployed infrastructures like the Phenome India National Biobank.

The physical biobank framework interfaces with an analytics-ready AI Research Platform to accelerate indigenous Drug Discovery, optimize multi-centric Clinical Trials, design Precision Medicine models, and formulate targeted Companion Diagnostics calibrated for the Indian phenotype. This secure network produces robust Real-World Evidence to steer Policy Research, sustaining a cyclical, Continuous Learning Healthcare System (Figure 7a-b).

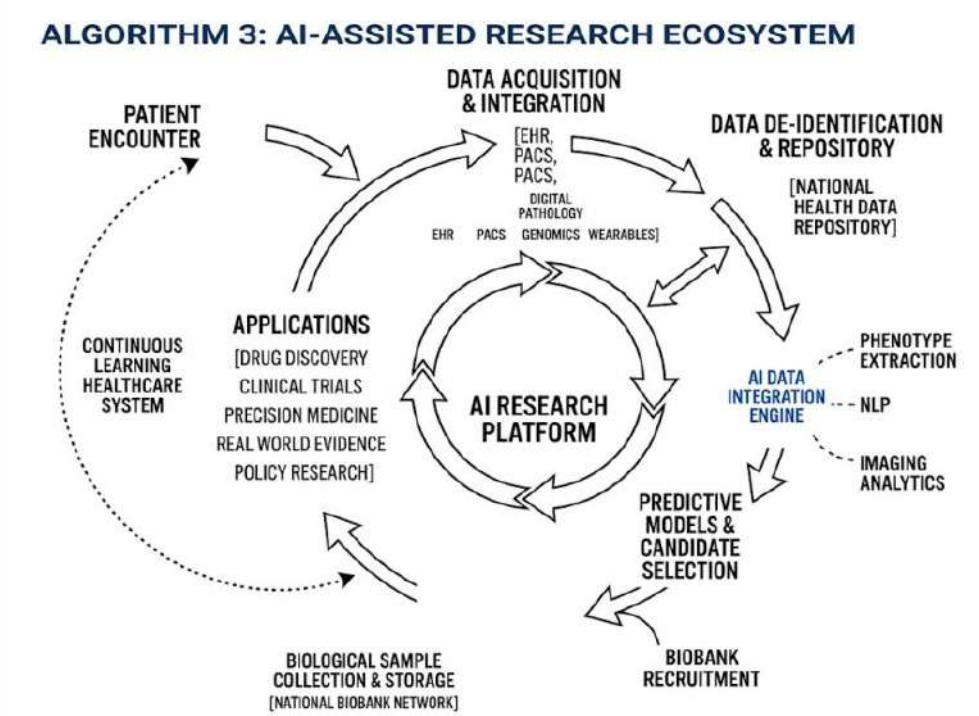

Figure 7a. Algorithm 3 — AI-Assisted Research Ecosystem

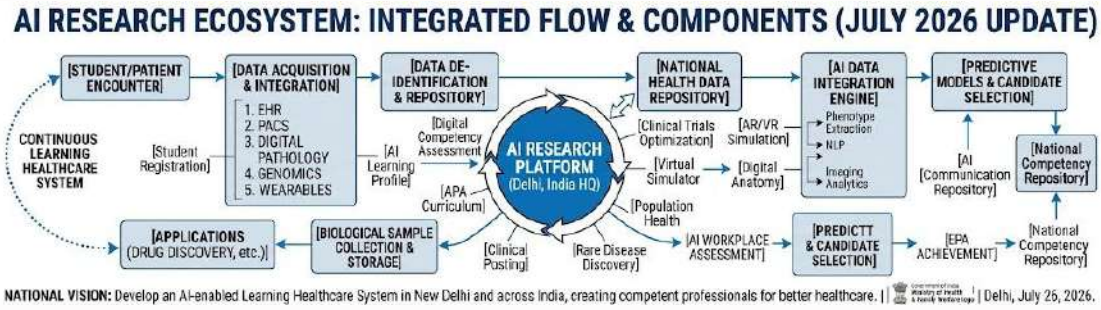

Figure 7b. Research Ecosystem — Integrated Flow and Components

The AI Ecosystem Integration Model

The AI Ecosystem Integration Model builds an interconnected public health network where Artificial Intelligence serves as the primary engine driving the trinity of healthcare missions: Patient Care, Medical Education, and Research. Guided by the vision of a connected landscape, this system runs on a sequential digital pipeline that transforms raw clinical data into nationwide intelligence (Figure 8).

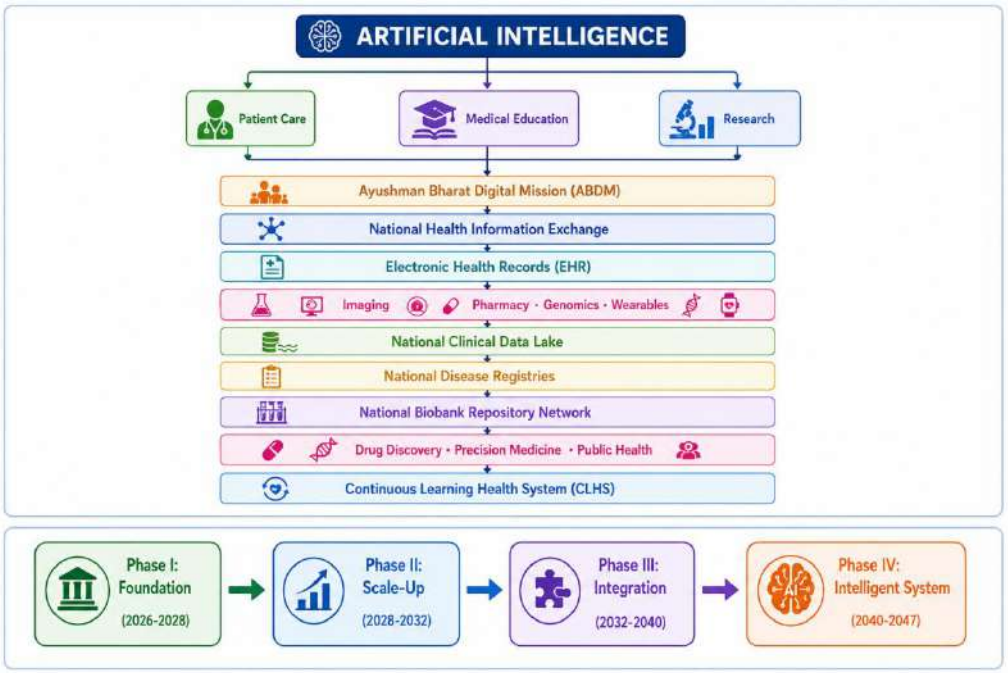

Figure 8. The AI Ecosystem Integration Model

At the foundation, the Ayushman Bharat Digital Mission (ABDM) acts as India's core digital public infrastructure (DPI), providing secure, consent-based identification through unified ABHA numbers. This feeds into the National Health Information Exchange, establishing cross-platform interoperability to map structured Electronic Health Records (EHR/EMR). The pipeline aggregates live multi-modal datasets from laboratories, digital imaging, pharmacies, genomics, and patient wearables, channeling them into a secure National Clinical Data Lake.

To transform these data points into active clinical assets, the ecosystem structures anonymized telemetry into National Disease Registries and coordinates physical biospecimens via the National Biobank Repository Network. AI systems cross-reference this deep network to accelerate Drug Discovery, compute Precision Medicine, and deploy Public Health interventions. This closes the loop on a self-sustaining Continuous Learning Health System, where everyday clinical insights automatically refine future care delivery, targeting comprehensive national transformation by the year 2047 (Figure 9).

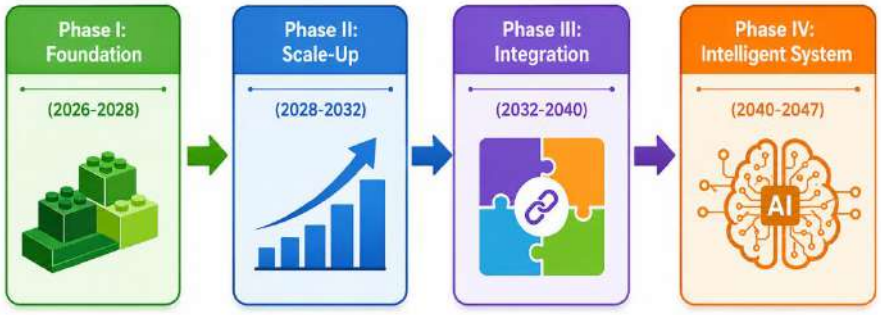

Figure 9. The 20-Year National Development Roadmap (2026–2047)

20-Year National Implementation Roadmap (2026–2047)

The realization of this policy-oriented NITI Aayog/MoHFW roadmap relies on a phased orchestration of workforce, institutional space, and change management tools treated strictly as **augmentation technologies** rather than professional replacements.

Phase I: Foundation (2026–2028)

Focuses on establishing the base architecture. Key actions include enacting the official National AI Policy for Healthcare, setting the National AI Competency Framework, and upgrading digital hospital networks. Initial pilot AI-enabled teaching hospitals will launch alongside faculty development drives to seed basic digital literacy.

Phase II: Scale-Up (2028–2032)

Integrates AI modules formally into all undergraduate and postgraduate health professional curricula. Hospital operations across district and tertiary spaces will adopt active AI-assisted tools, supported by nationwide telemedicine networks and simulation-based clinical training software to expand class capacities.

Phase III: Integration (2032–2040)

Deploys advanced precision medicine, multi-omic genomics tracking, and predictive public health surveillance systems across all states. Institutional workflows adopt automated medical workforce planning and resource forecasting, while AI-enabled quality auditing systems continuously monitor clinical safety standards.

Phase IV: Intelligent Health System (2040–2047)

Realizes a fully mature, interoperable Learning Health System. The network sustains continuous AI-assisted decision support and autonomous administrative workflows under human supervision, positioning India as a global benchmark in data-driven medical education, research, and compassionate patient care (Figure 10a-c).

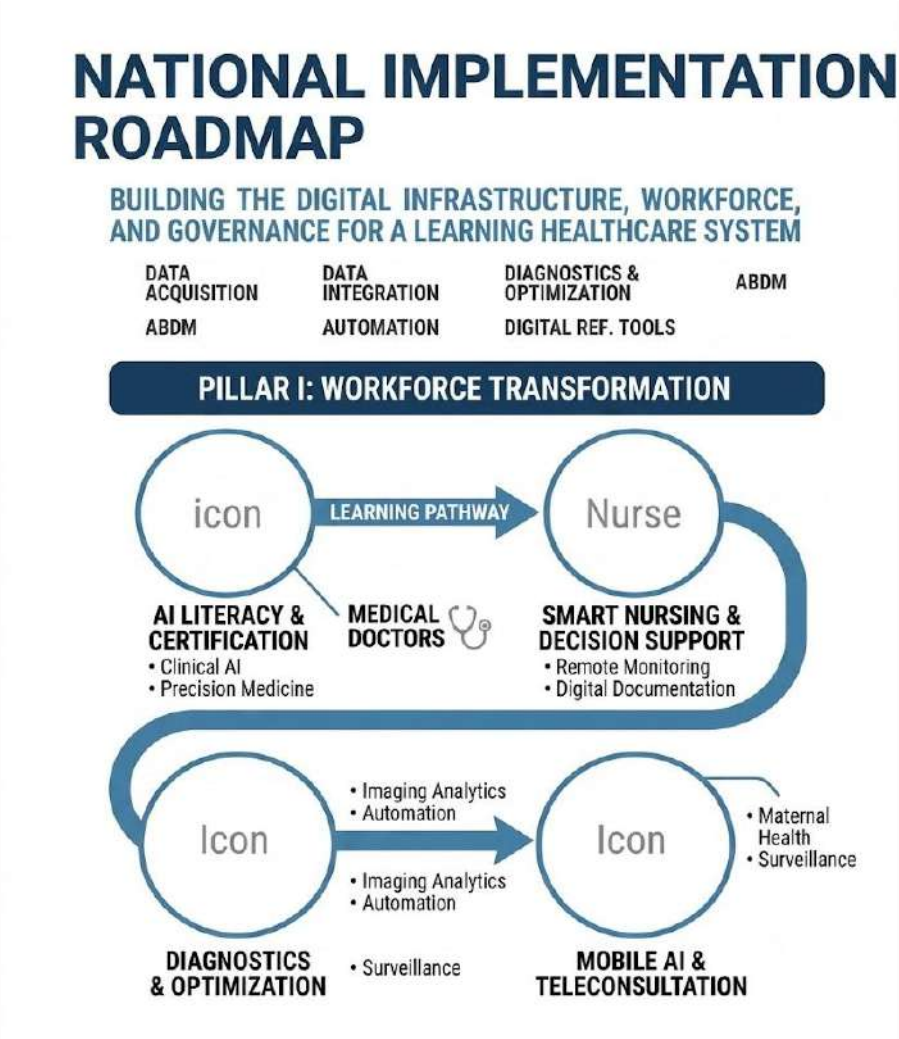

Figure 10a. National Implementation Roadmap

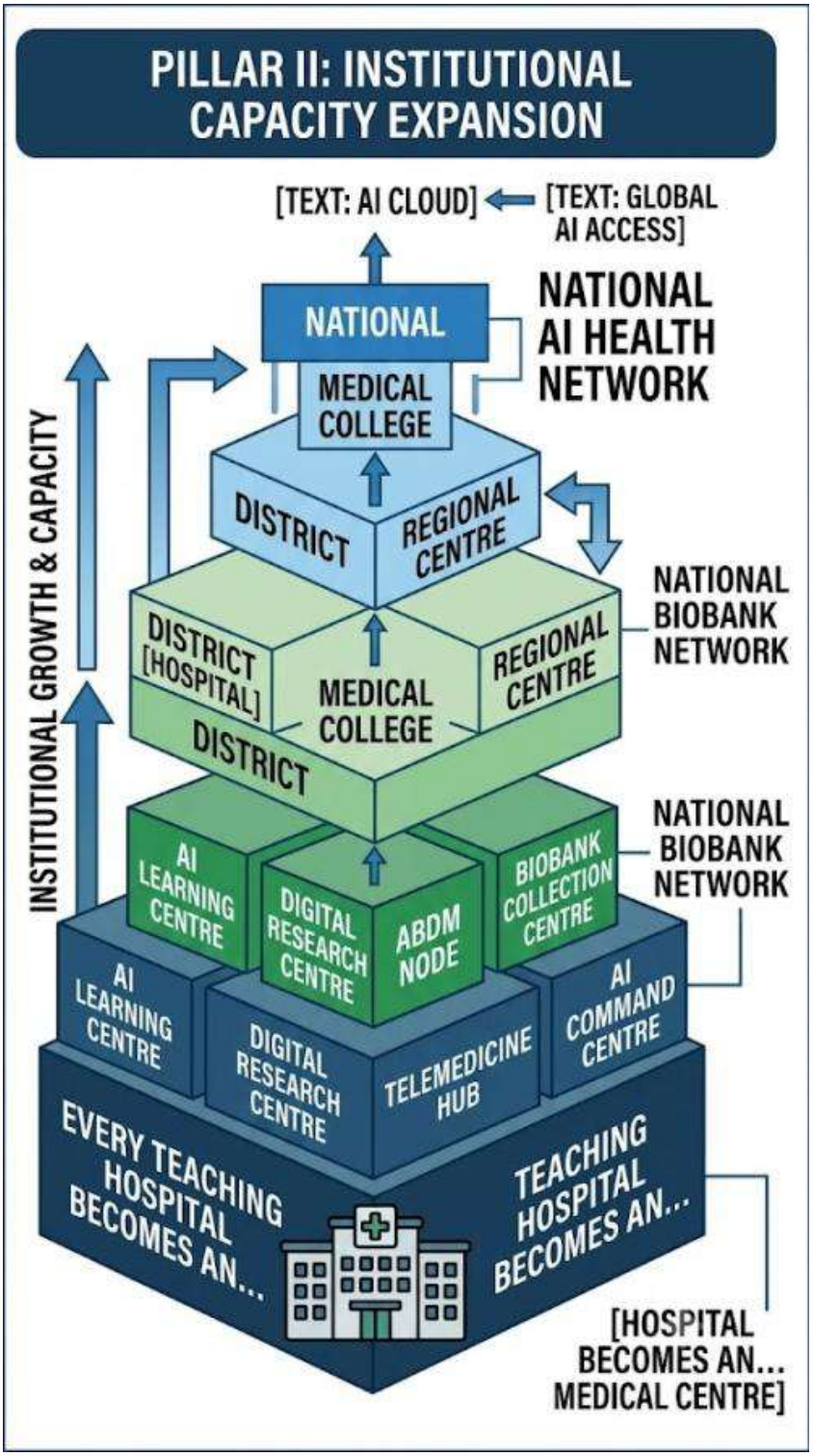

Figure 10b. Pillar II — Institutional Capacity Expansion

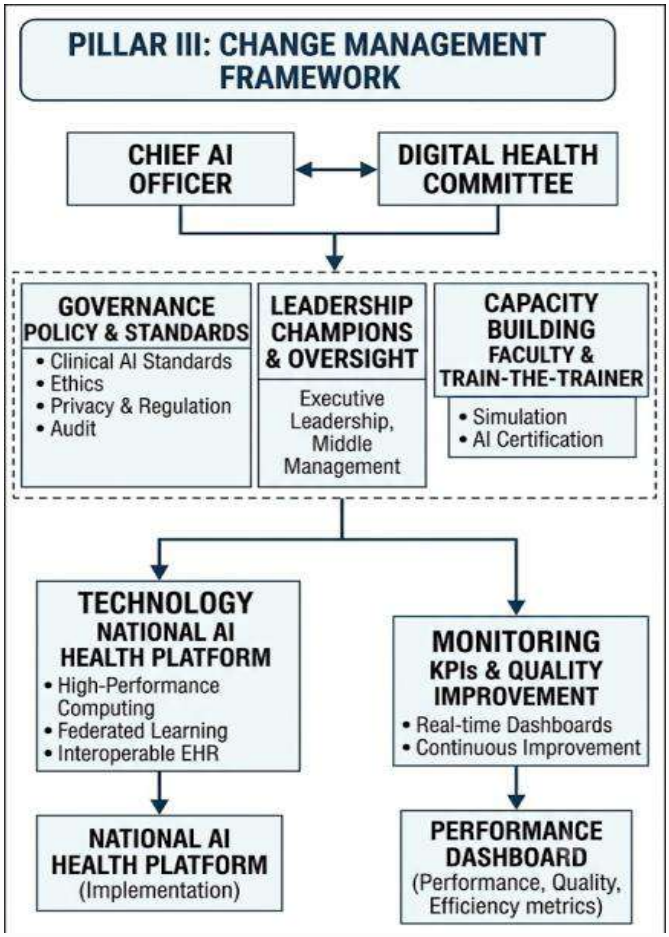

Figure 10c. Pillar III — Change Management Framework

Workforce Augmentation

Training is mapped across five distinct competency tiers (Level 1: Digital Literacy to Level 5: AI Innovation and Leadership) fully tied to workplace-based Entrustable Professional Activities (EPAs):

Medical Doctors

Leverage clinical decision support (CDS), diagnostic imaging AI, precision medicine matching, and automated documentation to maximize face-to-face patient time.

Nursing Workforce

Deploy smart bedside monitors, predictive early-warning alert systems, automated vitals logging, and medication safety checks.

Allied Health Professionals

Optimize workflows using digital pathology software, automated radiology triage, laboratory automation, and rehabilitation robotics.

Community Health (ASHA/ANM/CHOs)

Utilize lightweight, mobile clinical decision tools to perform rural risk prediction, maternal-child wellness monitoring, and localized outbreak surveillance.

Institutional Capacity Expansion

Rather than relying solely on brick-and-mortar development, hospital training throughput scales using virtual patient sandboxes, digital anatomy displays, and AI tutors. Care delivery is optimized across a strict four-tier architecture:

Tier I (District Hospitals)

Focuses on decentralized AI screening, basic decision support, and remote telemedicine links.

Tier II (Medical Colleges)

Operates as advanced regional diagnostic, simulation, and digital education hubs.

Tier III (Regional Referral Centres)

Runs high-performance computing pipelines for precision oncology, robotics, and complex clinical trials.

Tier IV (National AI Healthcare Command Centre)

Aggregates country-wide health intelligence for pandemic preparedness and active workforce resource forecasting.

Change Management Framework

Systemic transition is governed by strict organizational guardrails to ensure smooth technology adoption:

Governance & Leadership

Establishes clear Clinical AI Standards, data protection guidelines, and mandatory clinical safety audits under the oversight of dedicated institutional Chief Clinical AI Officers and change ambassadors.

Process & Technology Transformation

Redesigns clinical pathways with clear human-in-the-loop escalation rules. This relies on an underlying ecosystem of high-performance cloud infrastructure, federated learning nodes to protect regional data privacy, and a national medical imaging repository.

Financing Strategy

Funds are systematically pooled from the Union and State governments, public-private partnerships (PPP), corporate social responsibility (CSR) initiatives, and dedicated health-tech venture capital grants.

The Indispensable Value of the Clinician

While data models excel at identifying statistical patterns across huge, static datasets, medical doctors contribute a critical layer of contextual reasoning, ethical oversight, and biological synthesis that code alone cannot replicate. Doctors serve as the vital Clinical Integrators across the patient service, education, and research triad, ensuring that technologies remain safe, practical, and patient-centered (Figure 11a-d).

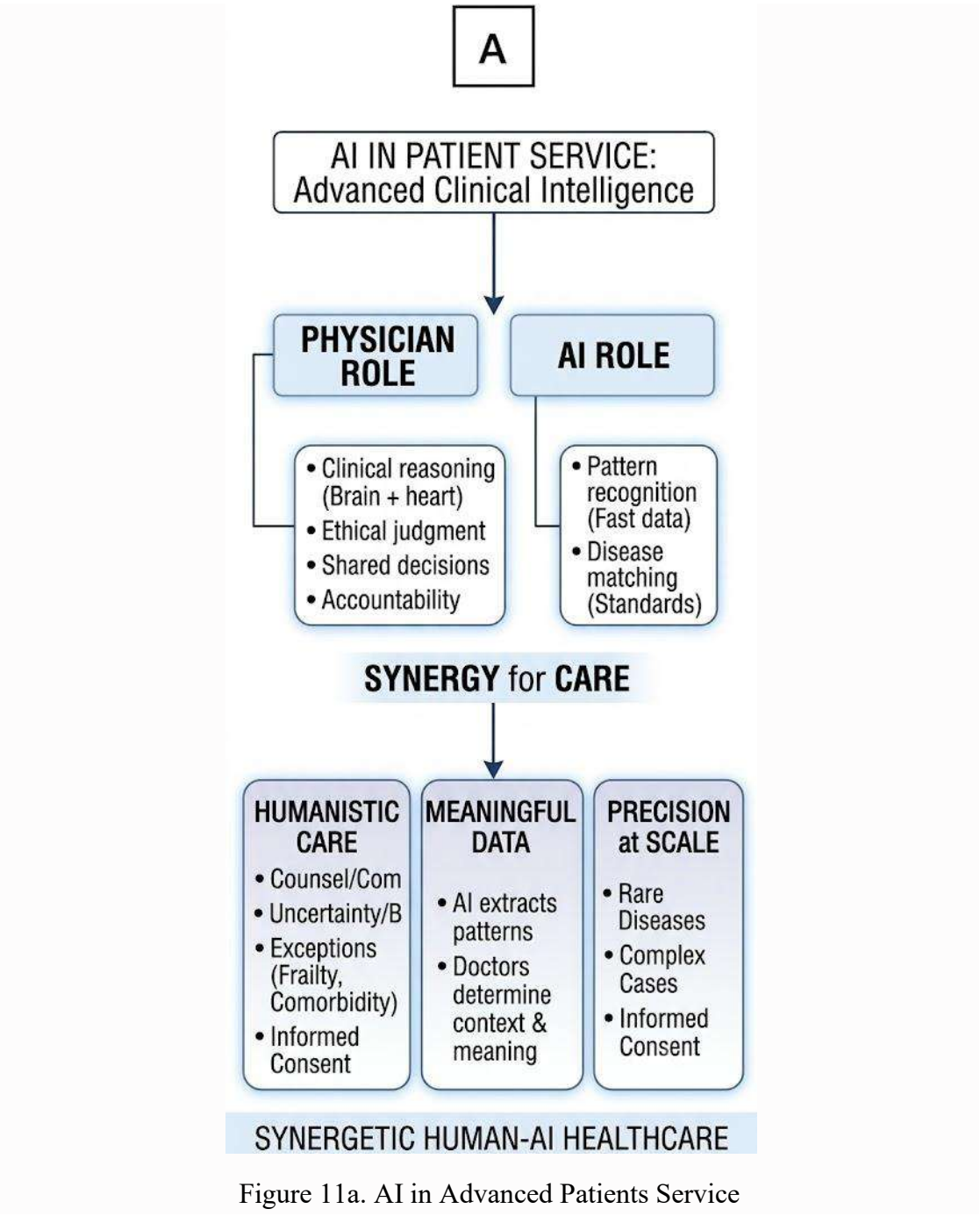

Figure 11a. AI in Advanced Patients Service

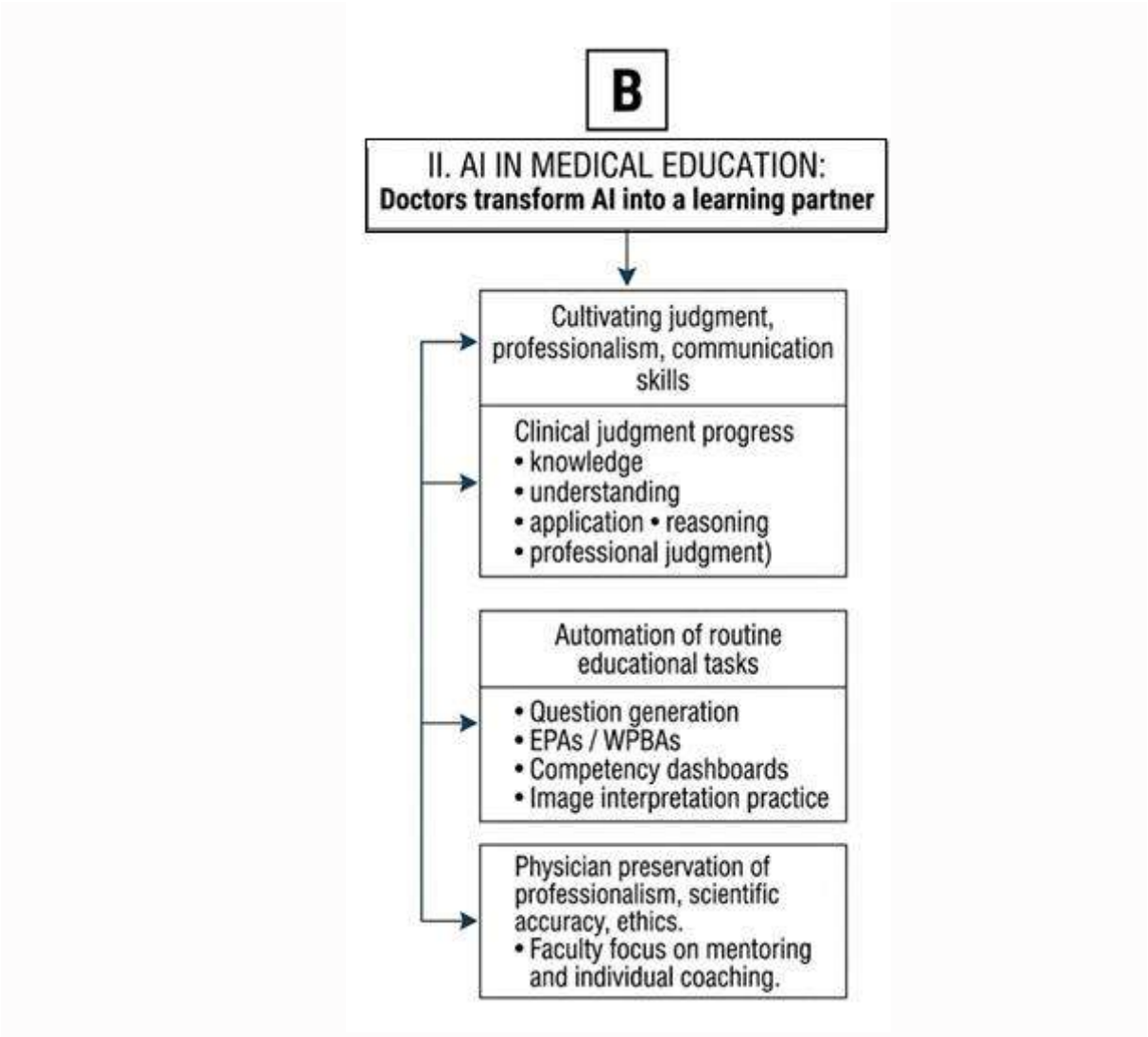

Figure 11b. Doctors Transform AI into Learning Partner

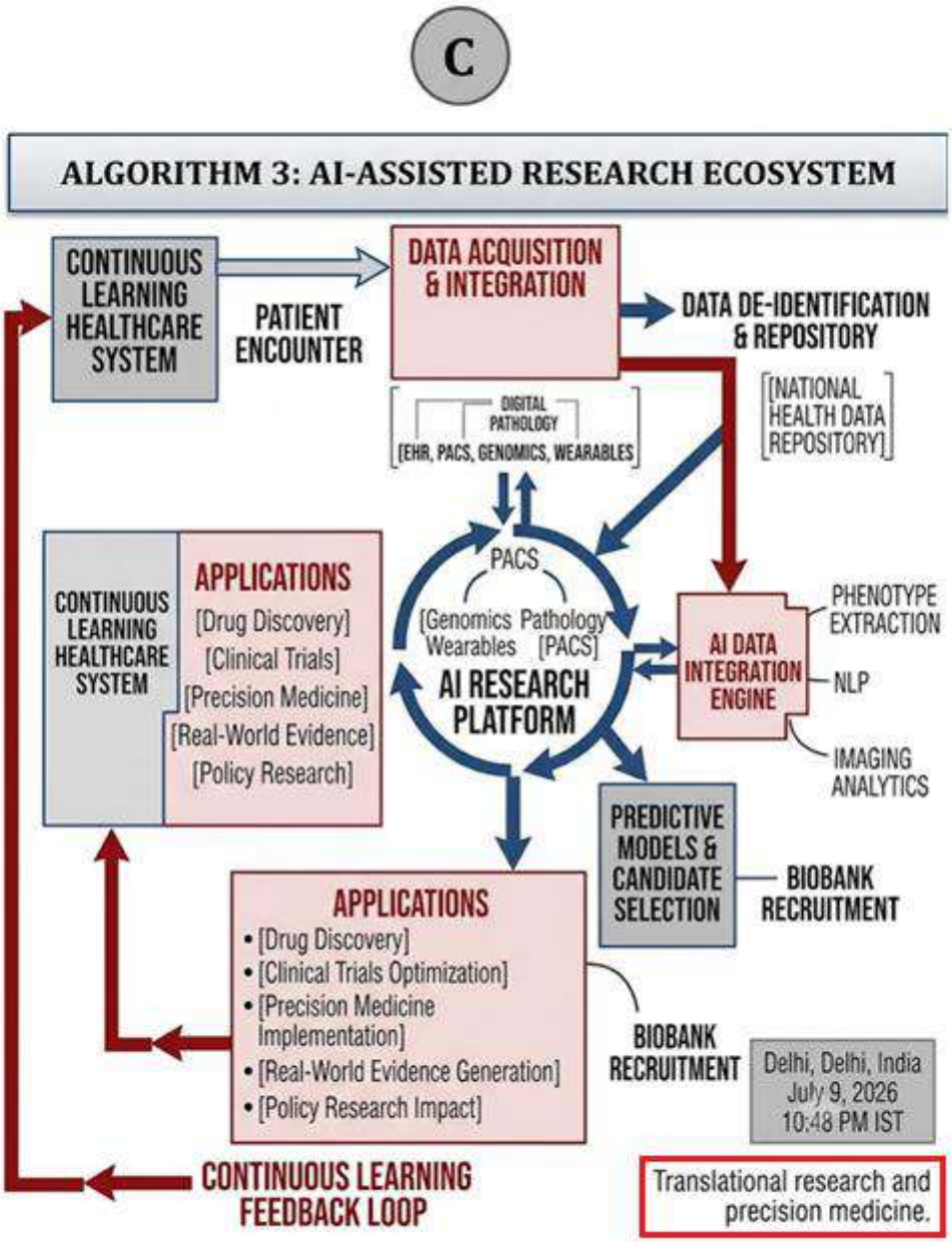

Figure 11c. AI Assisted Research Ecosystem

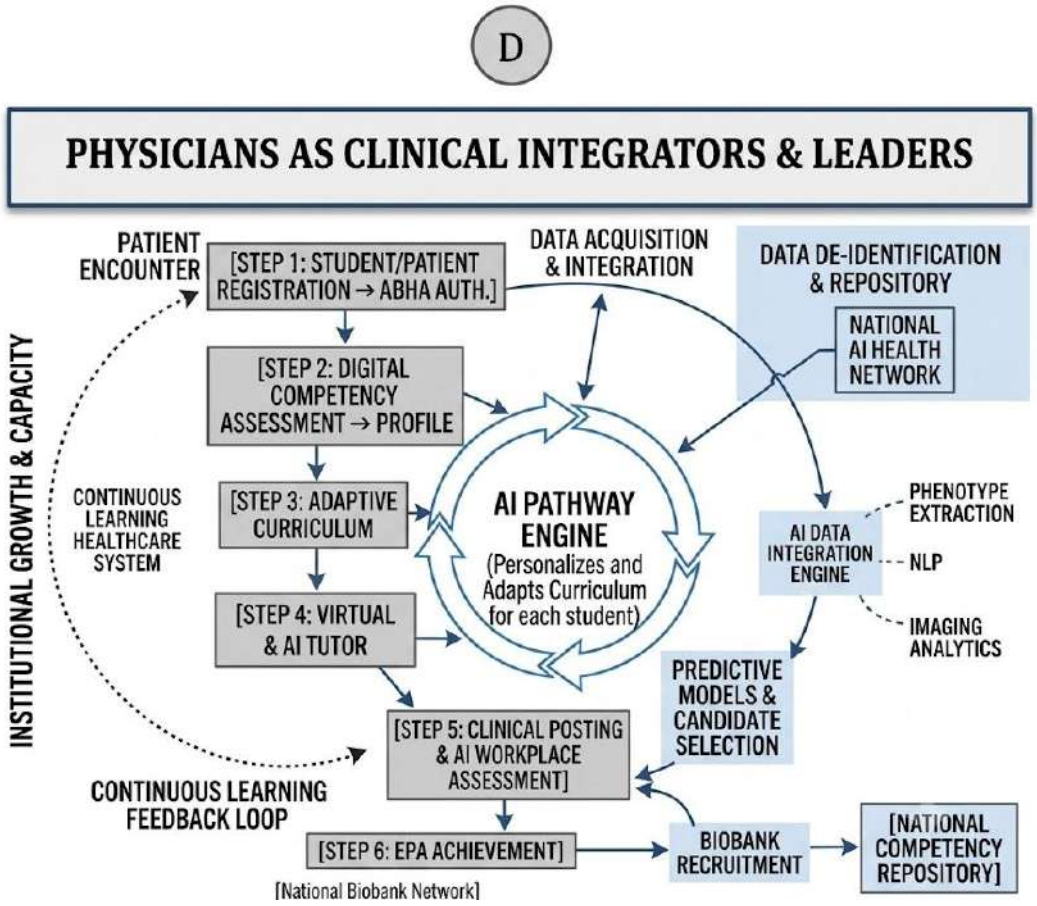

Figure 11d. Physician as Clinical Integrators and Leaders

Table 1. Clinical Strengths vs. Algorithmic Processing

Domain	AI Computational Processing	Physician Human Integration
Data Evaluation	Identifies statistical patterns in massive datasets.	Synthesizes incomplete, conflicting, and rapidly changing clinical information.
Case Integration	Processes uniform inputs matching trained models.	Evaluates clinical exceptions: rare diseases, multi-comorbidities, frailty, and polypharmacy.
Decision Support	Computes statistical probabilities and mathematical risks.	Exercises ethical judgment, deciding when to safely override algorithmic prompts.
Care Delivery	Streamlines administrative structures and documentation.	Delivers humanistic care: empathy, breaking bad news, counseling, and building trust.
System Evolution	Requires curated data and clean labels to learn.	Identifies unmet research needs to convert clinical anomalies into scientific discoveries.

By acting as the definitive bridge between raw technology and real-world clinical care, physicians prevent algorithmic drift, curate the high-quality annotated data needed to train safe local networks, and direct translation pipelines. In this unified national vision, AI does not act as a substitute for the healthcare provider; it serves as a powerful force multiplier that enables multidisciplinary teams to treat the nation with greater precision, efficiency, and human compassion (Table 1).

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LESSONS

Neonatal Thrombocytopenia and Rectal Bleeding as Initial Manifestations of Wiskott-Aldrich Syndrome

Srijan Singh[1,*] and Minu Bajpai[2]
[1]*Department of Neonatology, Yashoda Medicity, Indirapuram, Ghaziabad, India*
[2]*Department of Pediatric Surgery, Yashoda Medicity, Indirapuram, Ghaziabad, India*

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Keywords: Wiskott-Aldrich Syndrome (WAS), thrombocytopenia, hematopoietic stem cell transplant (HSCT), X-linked, primary immunodeficiency disorders, eczema

A male infant was born via lower segment cesarean section (LSCS), to a G2P1L1 mother with a birth weight of 3.78 kg. On day 3 of life, he developed periumbilical redness with a platelet count of 20,000/µL, prompting platelet transfusions. Workup for thrombocytopenia was done. On day 8, he had blood in stools with platelets at 22,000/µL. He received another transfusion and intravenous immunoglobulin (IVIG) and methylprednisolone (for 5 days) were administered. CMV PCR and genotyping for neonatal alloimmune thrombocytopenia (NAIT) were negative. Whole exome sequencing (WES) suggested Wiskott-Aldrich Syndrome (WAS).

*Corresponding Author: Srijan Singh
Email: srijanstar89@gmail.com

The baby was readmitted at 3 months of age in view of bleeding and received IVIG and platelet transfusions, and was discharged. After 2 weeks, he presented to the emergency department with bleeding per rectum approximately 12 hours prior to the current admission, with a platelet count of 9,000/µL. On examination, baby had signs of eczema with mild erythematous maculopapular rash, scaling on the forehead and scalp, along with scattered petechiae (Figure 1). Two units of platelet transfusions were given, after which bleeding stopped. Repeat complete blood count (CBC) showed platelets at 115,000/µL (1.15 lacs/µL). No fresh bleeding was noted post-admission. Baby is now planned for a hematopoietic stem cell transplant (HSCT).

This case highlights early neonatal presentation of WAS with isolated thrombocytopenia and bleeding, confirmed by WES after exclusion of common differentials like infection and NAIT. In

acute episodes, stabilization can be achieved by supportive care including transfusions and IVIG. The infant is receiving under multidisciplinary follow-up for potential immunodeficiency, eczema, autoimmunity, and simultaneously is being planned for definitive therapy (hematopoietic stem cell transplantation-HSCT).

Figure 1. Clinical photographs of the male infant with Wiskott-Aldrich syndrome at approximately 3 months of age. (A) Close-up facial view showing signs of eczema with mild erythematous maculopapular rash, scaling on the forehead and scalp, along with scattered petechiae. (B) Full-body view demonstrating generalized skin involvement with eczematous changes and scaling, crying, and petechial/purpuric lesions consistent with thrombocytopenia. The infant presented with neonatal thrombocytopenia and rectal bleeding; diagnosis was confirmed by whole exome sequencing. Images taken during hospital admission for an acute rectal bleeding episode.

Lessons

Wiskott-Aldrich Syndrome is a rare X-linked primary immunodeficiency caused by mutations in the *WAS* gene. This gene is located on chromosome Xp11.22-23 and encodes the WAS protein (WASp) [1,2]. WASp protein regulates actin cytoskeleton reorganization in hematopoietic cells and is instrumental in immune synapse formation, cell migration, phagocytosis, and platelet function. Mutations in this gene can lead to a spectrum of phenotypes: classic, milder X-linked thrombocytopenia (XLT), and X-linked neutropenia (XLN). Absent WASp expression typically causes classic disease, while residual expression correlates with milder forms [2,3] (Table 1).

Table 1. Phenotypic Spectrum of WAS-Related Disorders

	Pathophysiology	Clinical features
Classic WAS	Absent WASp	Microthrombocytopenia, eczema, infections, autoimmunity, malignancy risk.
XLT	Residual WASp	Milder thrombocytopenia, fewer infections.
XLN	Gain-of-function mutations	Neutropenia, variable other features.

Clinical Presentation and Diagnosis

Thrombocytopenia with small platelets is often the earliest and most consistent feature, present from birth in many cases. Neonatal bleeding (e.g., petechiae, umbilical oozing, bloody stools, or post-circumcision hemorrhage) is common, as seen here. Eczema and infections may appear later or be absent initially. Figure 2 shows the classic clinical features of WAS in an infant. The differential diagnoses of WAS in neonates are NAIT, congenital infections (e.g., CMV), sepsis, and other inherited thrombocytopenias [4,5]. Diagnosis was made in this case by negative NAIT genotyping and CMV PCR, followed by WES. Flow cytometry for WASp expression in lymphocytes can serve as a rapid screen for diagnosis before genetic confirmation. Platelet size (mean platelet volume) is also reduced, although some variants show normal size.

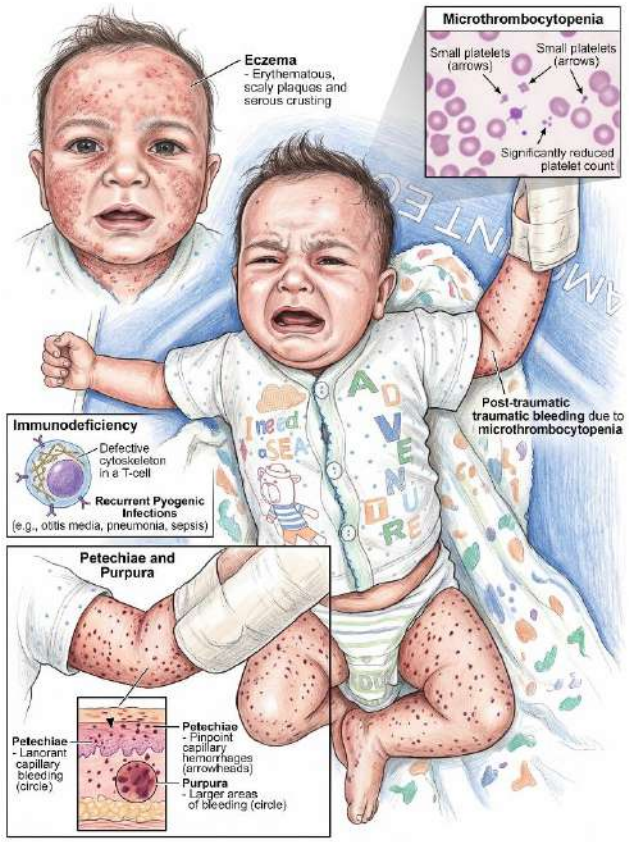

Figure 2. Schematic illustration depicting the classic clinical and laboratory features of Wiskott-Aldrich syndrome (WAS) in a neonate/infant.

Early diagnosis via WES is indispensable in ambiguous neonatal thrombocytopenia, which reduces delays in diagnosis and enables timely intervention. This case underscores the utility of genomic sequencing in refractory or atypical thrombocytopenia, or male predominance.

Management Challenges

Acute bleeding episodes mandate platelet transfusions, though responses can be transient due to intrinsic platelet dysfunction and immune clearance. IVIG does benefit in some cases by modulating autoimmunity and supporting humoral immunity. Corticosteroids were used in our case for presumed immune-mediated components [6]. Prophylactic antibiotics, IVIG transfusion, and eczema management are supportive. Splenectomy may theoretically raise platelet counts but leads to elevated risk of infections and is generally avoided or combined with lifelong prophylaxis.

The definitive treatment is allogeneic HSCT, ideally from a matched sibling or unrelated donor, with excellent outcomes when performed early (before complications like autoimmunity or malignancy) [7]. Gene therapy is an emerging option for patients lacking suitable donors [8]. Patients should be followed up for autoimmunity (e.g., hemolytic anemia, vasculitis, IBD) and malignancy (especially EBV-associated lymphoma) because these conditions can contribute significantly to morbidity.

Prognosis and Broader Implications

Survival is limited in the absence of HSCT due to bleeding, infections, or malignancy [9]. Outcomes are improved by early diagnosis and treatment. This case shows that WAS can present with predominant hematologic features in the neonatal period and can mimick other hematologic ailments. Neonatologists should maintain a high index of suspicion for primary immunodeficiencies in male neonates with persistent thrombocytopenia and bleeding which responds poorly to standard measures. Multidisciplinary care involving hematology, immunology, and genetics is indispensable in managing a case of WAS.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. Ochs HD, Thrasher AJ. The Wiskott-Aldrich syndrome. Journal of Allergy and Clinical Immunology. 2006 Apr 1;117(4):725–38. doi:10.1016/j.jaci.2006.02.005
2. Ochs HD, Filipovich AH, Veys P, Cowan MJ, Kapoor N. Wiskott-Aldrich Syndrome: Diagnosis, Clinical and Laboratory Manifestations, and Treatment. Biology of Blood and Marrow Transplantation. 2009 Jan;15(1 SUPPL.):84–90. doi:10.1016/j.bbmt.2008.10.007
3. Buchbinder D, Nugent DJ, Fillipovich AH. Wiskott-Aldrich syndrome: Diagnosis, current management, and emerging treatments. Application of Clinical Genetics. 2014 Apr 3;7:55–66. doi:10.2147/TACG.S58444

4. Kotwal J. Approach to neonatal thrombocytopenia: Immature platelet fraction has a major role. Med J Armed Forces India. 2011;67(3):212–4. doi:10.1016/S0377-1237(11)60042-7
5. Sillers L, Van Slambrouck C, Lapping-Carr G. Neonatal Thrombocytopenia: Etiology and Diagnosis. Pediatr Ann. 2015 Jul 1;44(7):e175–80. doi:10.3928/00904481-20150710-11
6. Catucci M, Castiello MC, Pala F, Bosticardo M, Villa A. Autoimmunity in Wiskott-Aldrich syndrome: An unsolved enigma. Front Immunol. 2012 Jul 18;3(JUL):27917. doi:10.3389/FIMMU.2012.00209/FULL
7. Burroughs LM, Petrovic A, Brazauskas R, Liu X, Griffith LM, Ochs HD, et al. Excellent outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome: a PIDTC report. Blood. 2020 Jun 4;135(23):2094–105. doi:10.1182/BLOOD.2019002939
8. Ferrua F, Marangoni F, Aiuti A, Roncarolo MG. Gene therapy for Wiskott-Aldrich syndrome: History, new vectors, future directions. Journal of Allergy and Clinical Immunology. 2020 Aug 1;146(2):262–5. doi:10.1016/j.jaci.2020.06.018
9. Haskoloğlu Ş, Öztürk A, Öztürk G, Bal SK, İslamoğlu C, Baskın K, et al. Clinical Features and Outcomes of 23 Patients with Wiskott-Aldrich Syndrome: A Single-Center Experience. Turk J Haematol. 2020;37(4):271–81. doi:10.4274/TJH.GALENOS.2020.2020.0334

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ORIGINAL ARTICLE

A Prospective Observational Study on the Prevalence of Dry Eye in Post-Cataract Surgery Patients in a Tertiary Care Hospital in Perambalur, Tamil Nadu

Arul Rani R,[1,*] Srinithi Srinivasan[1] and J. Priyanga[1]
[1]*Postgraduate, Department of Opthalmology, Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamilnadu*

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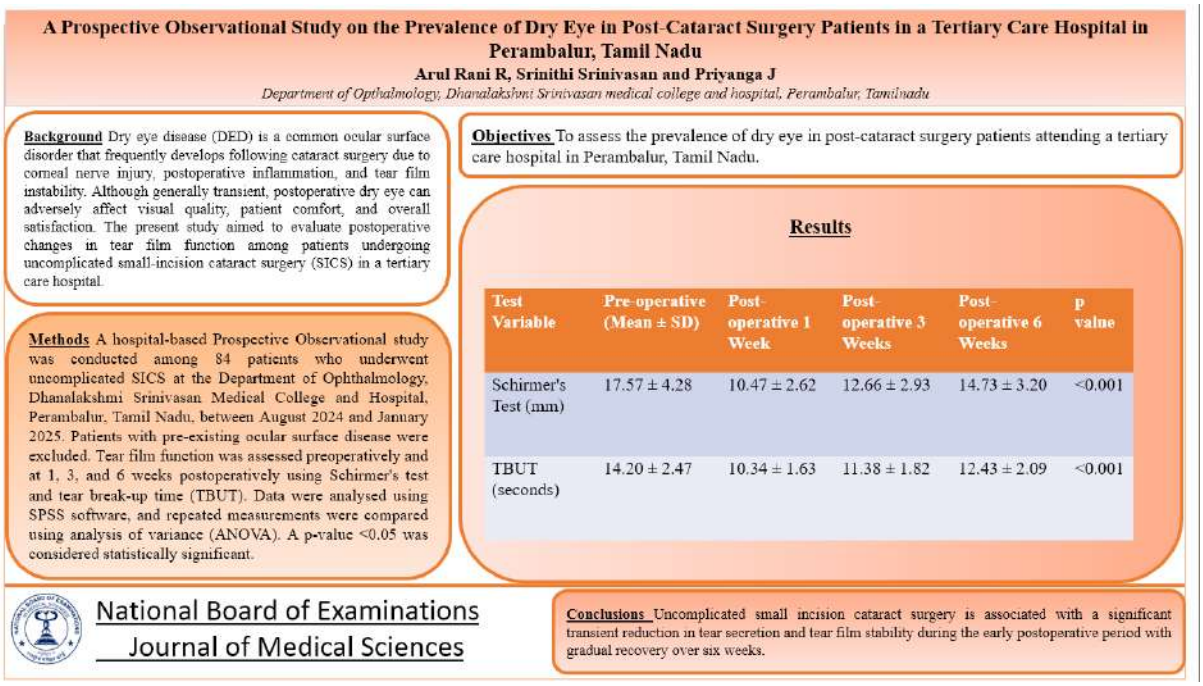
Abstract

Background: Dry eye disease (DED) is a common ocular surface disorder that frequently develops following cataract surgery due to corneal nerve injury, postoperative inflammation, and tear film instability. Although generally transient, postoperative dry eye can adversely affect visual quality, patient comfort, and overall satisfaction. The present study aimed to evaluate postoperative changes in tear film function among patients undergoing uncomplicated small-incision cataract surgery (SICS) in a tertiary care hospital. **Materials and Methods:** A hospital-based Prospective Observational study was conducted among 84 patients who underwent uncomplicated SICS at the Department of Ophthalmology, Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamil Nadu, between August 2024 and January 2025. Patients with pre-existing ocular surface disease were excluded. Tear film function was assessed preoperatively and at 1, 3, and 6 weeks postoperatively using Schirmer's test and tear break-up time (TBUT). **Results:** The majority of participants belonged to the 56–60-year age group (42.9%), with females constituting 53.6% of the study population. Preoperatively 71.4% of patients had Schirmer's test values >15 mm which declined to 9.5% at one week after surgery before improving to 46.4% at six weeks. Mean Schirmer's test values decreased significantly from 17.57 ± 4.28 mm preoperatively to 10.47 ± 2.62 mm at one week and subsequently improved to 14.73 ± 3.20 mm at six weeks ($p < 0.001$). Similarly, all patients had normal TBUT (>10 seconds) before surgery, whereas only 63.1% maintained normal TBUT at one week. Mean TBUT decreased significantly from 14.20 ± 2.47 seconds preoperatively to 10.34 ± 1.63 seconds at one week and improved to 12.43 ± 2.09 seconds by six weeks ($p < 0.001$). **Conclusion:** Uncomplicated small incision cataract surgery is associated with a significant transient reduction in tear secretion and tear film stability during the early postoperative period with gradual recovery over six weeks. Routine postoperative assessment of tear film function and timely initiation of lubricating therapy may improve patient comfort, ocular surface health, and visual rehabilitation following cataract surgery.

Keywords: Dry eye disease, Cataract surgery, Small-incision cataract surgery, Schirmer's test, Tear break-up time, Tear film stability

*Corresponding Author: Arul Rani R
Email: arulrani96@gmail.com

Graphical Abstract



Introduction

Dry eye syndrome (DES) is a common complication after cataract surgery, affecting a significant number of patients [1]. Although cataract surgery is highly successful in restoring vision. It can lead to changes in tear film stability and ocular surface integrity thereby contributing to the development of DES. The reported prevalence of dry eye symptoms post cataract surgery varies considerably among studies based on the diagnostic criteria employed and the population examined [2]. Postoperative dry eye can be caused by intraoperative damage to corneal nerves, alterations in tear film dynamics, and inflammatory responses initiated by the surgical intervention. Pre existing factors such as age related reduction in tear production and meibomian gland dysfunction may also aggravate the condition [3]. Knowledge of the prevalence and associated risk factors of dry eye following cataract surgery is vital in enhancing patient outcomes and directing perioperative management protocols.(4) Against this background, the present study was undertaken to assess the prevalence of dry eye among patients undergoing cataract surgery at a tertiary care hospital in Perambalur, Tamil Nadu.

Objective

To assess the prevalence of dry eye in post-cataract surgery patients attending a tertiary care hospital in Perambalur, Tamil Nadu.

Materials and Methods

A hospital based Prospective Observational study was conducted among patients attending the Ophthalmology Outpatient Department of Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamil Nadu over a period of six months from August 2024 to January 2025. The sample size was calculated using the formula $N = Z^2_{1-\alpha/2} \times p \times (1 - p) / d^2$ considering a reported prevalence of postoperative dry eye of 67.7% from a

comparable tertiary care hospital study conducted in Pondicherry [5] with a 95% confidence level (Z = 1.96) and an allowable error of 10% yielding a minimum required sample size of 84 participants. Patients were selected using a convenient sampling technique. Individuals undergoing uncomplicated small incision cataract surgery (SICS) at the study centre were included while patients with pre existing ocular diseases were excluded. All participants underwent comprehensive ophthalmic evaluation including best-corrected visual acuity assessment, slit lamp examination of the anterior segment, posterior segment evaluation using indirect ophthalmoscopy and slit lamp biomicroscopy with a 90D lens, colour vision testing, applanation tonometry, Schirmer's test using Whatman filter paper strips and tear break-up time (TBUT) measurement. The collected data were entered into Microsoft Excel for data cleaning and subsequently analysed using SPSS statistical software.

Results

The study included 84 patients who underwent uncomplicated small-incision cataract surgery (SICS). The mean age of the patients was 56 to 60 years (42.9%) and females made up 53.6% of the study population. Demographic characteristics of the study population is given in Table 1.

The most common type of cataract is mature cataract (29.8%). Distribution of type of Cataract is given in Table 2. Descriptive findings of Schrimer's test and Tear Break-UP Time (TBUT) before and after cataract surgery is displayed in Table 3 and Table 4 respectively.

Evaluation of tear film function showed a significant postoperative decrease in both Schirmer's test values and tear break up time (TBUT) with maximum deterioration seen during the first postoperative week. The mean Schirmer's test value decreased significantly from 17.57 ± 4.28 mm preoperatively to 10.47 ± 2.62 mm at one week while the mean TBUT declined from 14.20 ± 2.47 seconds to 10.34 ± 1.63 seconds ($p < 0.001$ for both). Progressive improvement in both parameters was observed at 3 and 6 weeks postoperatively, as shown in Table 5.

Using TBUT <10 seconds as the diagnostic criterion, the prevalence of postoperative dry eye was 36.9% at one week, which declined to 21.4% at three weeks and 2.4% at six weeks indicating gradual recovery of tear film stability, as shown in Table 6.

Overall the findings demonstrate that postoperative dry eye following uncomplicated SICS is a common but predominantly transient condition that improves substantially within six weeks after surgery.

Table 1. Demographic Characteristics of the Study Participants (N = 84)

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	45–50	5	6.0
	51–55	8	9.5
	56–60	36	42.9
	61–65	24	28.6
	66–70	10	11.9
	70–75	1	1.2
Sex	Male	39	46.4
	Female	45	53.6

Table 2. Distribution of Cataract Types Among the Study Participants (N = 84)

Type of Cataract	Frequency (n)	Percentage (%)
Mature	25	29.8
NS I	18	21.4
NS II with NS I	19	22.6
NS II	5	6.0
NS II–III	9	10.7
NS III	5	6.0
NS III–IV	1	1.2
NS IV	2	2.4
Total	**84**	**100.0**

Table 3. Schirmer's Test Findings Before and After Cataract Surgery (N = 84)

Schirmer's Test	Pre-operative n (%)	Post-operative 1 Week n (%)	Post-operative 3 Weeks n (%)	Post-operative 6 Weeks n (%)
>15 mm	60 (71.4)	8 (9.5)	18 (21.4)	39 (46.4)
9–14 mm	24 (28.6)	57 (67.9)	61 (72.6)	45 (53.6)
4–8 mm	0 (0.0)	19 (22.6)	5 (6.0)	0 (0.0)
Total	**84 (100.0)**	**84 (100.0)**	**84 (100.0)**	**84 (100.0)**

Table 4. Tear Break-Up Time (TBUT) Before and After Cataract Surgery (N = 84)

TBUT	Pre-operative n (%)	Post-operative 1 Week n (%)	Post-operative 3 Weeks n (%)	Post-operative 6 Weeks n (%)
>10 seconds	84 (100.0)	53 (63.1)	66 (78.6)	82 (97.6)
<10 seconds	0 (0.0)	31 (36.9)	18 (21.4)	2 (2.4)
Total	**84 (100.0)**	**84 (100.0)**	**84 (100.0)**	**84 (100.0)**

Table 5. Comparison of Mean Schirmer's Test and TBUT Values Before and After Cataract Surgery (N = 84)

Test Variable	Pre-operative (Mean ± SD)	Post-operative 1 Week	Post-operative 3 Weeks	Post-operative 6 Weeks	*p* value
Schirmer's Test (mm)	17.57 ± 4.28	10.47 ± 2.62	12.66 ± 2.93	14.73 ± 3.20	**<0.001***
TBUT (seconds)	14.20 ± 2.47	10.34 ± 1.63	11.38 ± 1.82	12.43 ± 2.09	**<0.001***

*p value<0.05-Statistically significant

Table 6. Prevalence of Postoperative Dry Eye Based on TBUT (<10 Seconds) (N = 84)

Follow-up Period	Dry Eye Present n (%)	Dry Eye Absent n (%)
Pre-operative	0 (0.0)	84 (100.0)
1 Week	31 (36.9)	53 (63.1)
3 Weeks	18 (21.4)	66 (78.6)
6 Weeks	2 (2.4)	82 (97.6)

Discussion

Dry eye disease is a well-recognised complication following cataract surgery, primarily resulting from transient disruption of the ocular surface caused by surgical trauma, corneal nerve transection, postoperative inflammation, and instability of the tear film [2, 6, 7]. The present study evaluated postoperative tear film changes in 84 patients undergoing uncomplicated small-incision cataract surgery (SICS) using Schirmer's test and tear break-up time (TBUT) over a six-week follow-up period.

In the present study, the most common age group of patients was 56–60 years (42.9%), followed by 61–65 years (28.6%), with a slight female preponderance (53.6%). The results are similar to those of Krishna Chaithanya et al, who also observed that cataract surgery was more often performed in the older age group, which is in accordance with the

increasing age-related prevalence of cataracts [5]. Schirmer's test showed a significant decrease in tear secretion after surgery. The value of Schirmer's test above 15 mm was found in 71.4% of patients before surgery, while the value was only 9.5% at 1 week after surgery. However, the value of Schirmer's test between 4 and 8 mm was found in 22.6% of patients, indicating transient postoperative aqueous tear deficiency. Follow up showed gradual improvement with 46.4% of patients having Schirmer's values above 15 mm at six weeks and no patient in severe dry eye category. Mean Schirmer's values showed statistically significant fall from 17.57 ± 4.28 mm preoperatively to 10.47 ± 2.62 mm at one week and gradually improving to 14.73 ± 3.20 mm at six weeks ($p<0.001$). Our findings are in concordance with studies done by Li et al., Khanal et al., Dasgupta and Gupta, Ishrat et al. and Zamora et al., who have also reported significant postoperative reduction in tear secretion with gradual recovery in subsequent weeks after cataract surgery [2,3,8,9,10]. Similarly, TBUT showed significant postoperative deterioration in the present study. Before surgery, all the patients had normal TBUT (>10 seconds) whereas only 63.1% maintained normal values during the first postoperative week. Decreased TBUT (5–10 seconds) was seen in 36.9% of patients at one week, which gradually decreased to 21.4% at three weeks and only 2.4% at six weeks. Mean TBUT decreased significantly from 14.20 ± 2.47 seconds preoperatively to 10.34 ± 1.63 seconds during the first postoperative week and then improved to 12.43 ± 2.09 seconds by six weeks ($p<0.001$). These findings are closely similar to those reported by Khanal et al., Dasgupta and Gupta, Ishrat et al., Lu et al., and Miura et al. who have shown that the instability of the tear film in the postoperative period is maximum in the early period and gradually improves with healing of the cornea [3,8,9,11,12]. The transient deterioration in Schirmer's test and TBUT in this study can be explained by various pathophysiological mechanisms. Surgical incision causes disruption of corneal sub-basal nerve plexus, leading to reduction in corneal sensitivity and impaired reflex tear secretion [3,6]. Further, exposure to microscope light, postoperative topical medications and surgically induced inflammation lead to instability of the tear film and damage to the ocular surface [2,6,7]. Meibomian gland dysfunction following cataract surgery has also been reported to aggravate evaporative dry eye and prolong postoperative symptoms [13,14].

An encouraging finding of the present study was the gradual recovery of both Schirmer's test and TBUT during follow-up. The tear film parameters showed significant deterioration during the first postoperative week with progressive improvement at three and six weeks which indicates that the postoperative dry eye after uncomplicated SICS is largely transient. Similar observations have been reported in systematic reviews and meta-analyses conducted by Lu et al., Miura et al. and Ta et al. which concluded that the dry eye symptoms usually peak during the early postoperative period and progressively improve with corneal nerve regeneration and ocular surface healing [11,12,15]. Overall, the present study confirms that uncomplicated SICS is associated with significant but reversible postoperative changes in tear secretion and tear film stability. These findings emphasize the importance of routine postoperative evaluation of tear film function and early

initiation of ocular lubricants to minimise patient discomfort, improve visual quality, and enhance postoperative satisfaction [7,16,17].

Although the present study assessed postoperative dry eye using objective clinical measures, namely Schirmer's test and tear break-up time (TBUT), it did not include a validated symptom-based questionnaire such as the Ocular Surface Disease Index (OSDI). It is well recognized that objective signs of dry eye do not always correlate with patients' subjective symptoms, as the severity of ocular discomfort may be influenced by several individual and psychosocial factors. Therefore, incorporating both objective clinical tests and validated symptom assessment tools would provide a more comprehensive evaluation of postoperative dry eye and should be considered in future studies.

Limitations

The present study has certain limitations. First, it was conducted at a single tertiary care centre with a relatively small sample size of 84 participants, which may limit the generalisability of the findings. Second, participants were recruited using a convenience sampling technique which may have introduced selection bias and limited the representativeness of the study population. Therefore, the findings should be interpreted with caution when extrapolating to broader populations or different healthcare settings. Third patients were followed only up to six weeks after surgery; therefore, long-term recovery of tear film function could not be evaluated. Fourth, only patients undergoing uncomplicated SICS were included, and comparison with phacoemulsification or femtosecond laser-assisted cataract surgery was not performed. Finally, potential systemic and ocular risk factors such as diabetes mellitus, meibomian gland dysfunction, and pre-existing ocular surface abnormalities were not analysed in detail, which may have influenced postoperative tear film changes.

Conclusion

The present study demonstrates that dry eye is a common early postoperative ocular surface change after uncomplicated small incision cataract surgery. Significant reductions in Schirmer’s test values and TBUT were observed during the first postoperative week suggesting decreased tear secretion and tear film instability. Both parameters improved progressively during further follow-up, with substantial recovery by six weeks, although complete normalization was not seen in all patients. These findings suggest that postoperative dry eye is mostly transient and resolves with ocular surface healing. Routine preoperative assessment of tear film function, meticulous postoperative monitoring and early implementation of lubricating therapy can help minimize postoperative discomfort, enhance tear film stability and improve visual rehabilitation and patient satisfaction after cataract surgery.

Clinical Implications

These findings support incorporating tear film evaluation into routine postoperative cataract follow-up, particularly during the early postoperative period. Patients at higher risk or those reporting persistent ocular discomfort may benefit from individualized ocular surface assessment and appropriate management to optimize postoperative visual rehabilitation and patient satisfaction.

Authors' Contributions

ARR has contributed to the conceptualization and definition of the intellectual content of the manuscript, design of the study and Manuscript preparation. SS contributed to the literature search, manuscript editing, and manuscript review. JP contributed towards data acquisition Statistical analysis, Manuscript review and editing. ARR1 will act as the corresponding author of the manuscript

Data availability statement

The datasets generated and analysed in this study are available from the corresponding author on reasonable request. They are not publicly shared because they contain sensitive information that could indirectly identify participants.

Ethical approval

This study has been approved by the Institution Ethics Committee Ref.No: IECHS/IRCHS/No:579

Informed Consent

Written informed consent was obtained from all participants after explaining the study procedures, potential risks and benefits. Consent covered both participation and publication of anonymised findings, with assurance of confidentiality and data privacy.

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

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References

1. Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. Eye (Lond). 2009;23(3):688–693.
2. Li XM, Hu L, Hu J, Wang W. Investigation of dry eye disease and analysis of the pathogenic factors in patients after cataract surgery. Cornea. 2007;26(9 Suppl 1):S16–20.
3. Khanal S, Tomlinson A, Esakowitz L, et al. Changes in corneal sensitivity and tear physiology after phacoemulsification. Ophthalmic Physiol Opt. 2008;28(2):127–134.
4. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136(2):318–326.
5. Krishna Chaithanya GP, Nallamuthu P, Sripal A. Prevalence of dry eye in post cataract surgery patients, in a tertiary care hospital, Pondicherry. Int J Acad Med Pharm. 2023;5(3):839–842.
6. Sutu C, Fukuoka H, Afshari NA. Mechanisms and management of dry eye in cataract surgery patients. Curr Opin Ophthalmol. 2016;27(1):24–30.
7. Naderi K, Gormley J, O'Brart D. Cataract surgery and dry eye disease: a review. Eur J Ophthalmol. 2020;30(5):840–855.
8. Dasgupta S, Gupta R. The course of dry eye following phacoemulsification and manual-SICS: a prospective study based on Indian scenario. Int Eye Sci. 2016;16(10):1789–1794.
9. Ishrat S, et al. Incidence and pattern of dry eye after cataract surgery. Saudi J Ophthalmol. 2019;33(1):34–40.

10. Zamora MG, Caballero EF, Maldonado MJ. Short-term changes in ocular surface signs and symptoms after phacoemulsification. Eur J Ophthalmol. 2020;30(6):1301–1307.
11. Lu Q, Lu Y, Zhu X. Dry eye and phacoemulsification cataract surgery: a systematic review and meta-analysis. Front Med (Lausanne). 2021;8:649030.
12. Miura M, Inomata T, Nakamura M, Sung J, Nagino K, Midorikawa-Inomata A, et al. Prevalence and characteristics of dry eye disease after cataract surgery: a systematic review and meta-analysis. Ophthalmol Ther. 2022;11(4):1309–1332.
13. Jung JW, Han SJ, Nam SM, Kim TI, Kim EK, Seo KY. Meibomian gland dysfunction and tear cytokines after cataract surgery according to preoperative meibomian gland status. Clin Exp Ophthalmol. 2016;44(7):555–562.
14. Vu CHV, Kawashima M, Yamada M, et al; Dry Eye Cross-Sectional Study in Japan Study Group. Influence of meibomian gland dysfunction and friction-related disease on the severity of dry eye. Ophthalmology. 2018;125(8):1181–1188.
15. Ta H, McCann P, Xiao M, Lien T, Abbott K, Gregory DG, Qureshi R, Li T. Dry eye post-cataract surgery: a systematic review and meta-analysis. BMC Ophthalmol. 2025;25(1):18.
16. Ganesh S, et al. Topical cyclosporine (0.05%) for management of dry eyes in patients undergoing cataract surgery — a comparative study. Open Ophthalmol J. 2019;13:34–42.
17. Chen WT, Chen YY, Hung MC. Dry eye following femtosecond laser-assisted cataract surgery: a meta-analysis. J Clin Med. 2022;11(21):6228.

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ORIGINAL ARTICLE

COVID-19 Vaccine Hesitancy Among Parents of Children Aged Between 15 Years and 18 Years: A Cross Sectional Study

V. Sudha,[1,*] V. Nagavalli,[2] K. Sevvanthi[3] and R.K. Sreekannathal[4]
[1]*Professor, JR Medical College and Hospital, Affiliated to BHIER (Bharath Institute of Higher Education and Research), Tindivanam, Tamilnadu*
[2]*Senior Resident, JR Medical College and Hospital, Affiliated to BHIER (Bharath Institute of Higher Education and Research), Tindivanam, Tamilnadu*
[3]*Lecturer Cum Statistician, Aarupadai Veedu Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Kirumampakkam, Puducherry*
[4]*Aarupadai Veedu Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Kirumampakkam, Puducherry*

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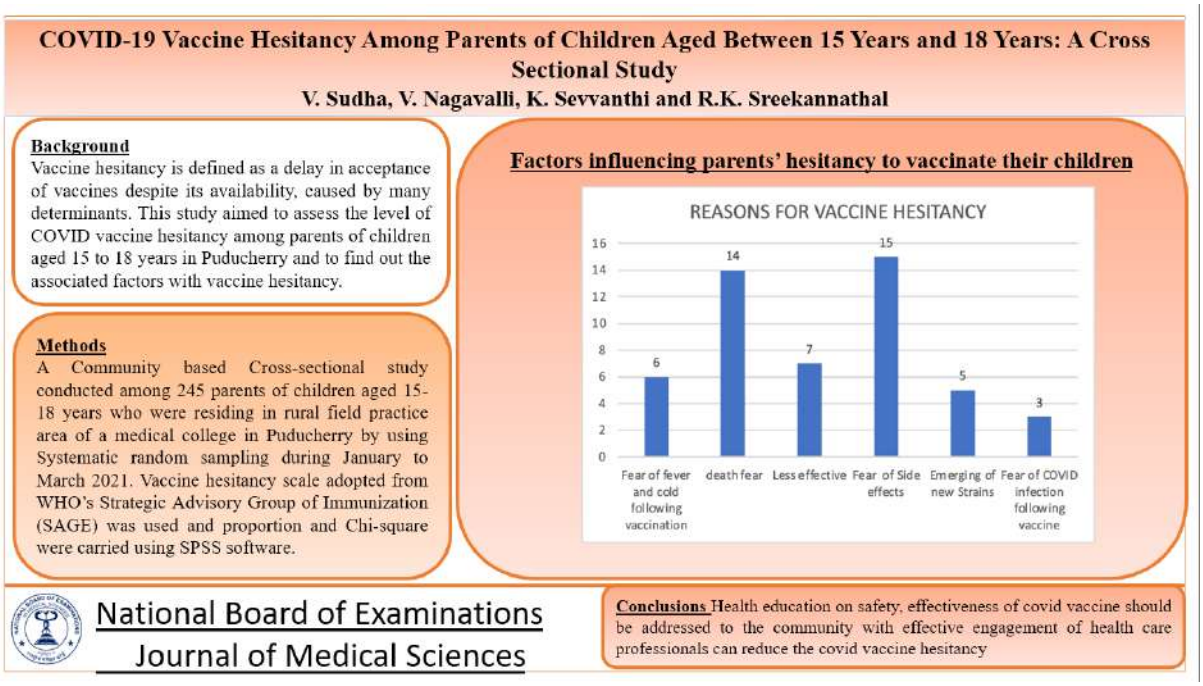
Abstract

Background and Objectives: Vaccine hesitancy is defined as a delay in acceptance of vaccines despite its availability, caused by many determinants. This study aimed to assess the level of COVID vaccine hesitancy among parents of children aged 15 to 18 years in Puducherry and to find out the associated factors with vaccine hesitancy. **Materials and Methods:** A Community based Cross-sectional study conducted among 245 parents of children aged 15- 18 years who were residing in rural field practice area of a medical college in Puducherry by using Systematic random sampling during January to March 2021. Vaccine hesitancy scale adopted from WHO's Strategic Advisory Group of Immunization (SAGE) was used and proportion and Chi-square were carried using SPSS software. **Results:** The mean age of the participants were 48 years with standard deviation of 7.3. Of the overall participants,159 (64.6%) were females and 87 (35.4%) were males. Around 20.3% of parents had hesitation in vaccinating their children. Higher proportion of the parents mentioned the fear of death and side effects are the reasons for not vaccinating their children. **Conclusions:** Health education on safety, effectiveness of covid vaccine should be addressed to the community with effective engagement of health care professionals can reduce the covid vaccine hesitancy.

Keywords: COVID 19, Vaccine hesitancy, Parents, Children, Vaccine hesitancy scale

*Corresponding Author: V. Sudha
Email: aswinsharwin@gmail.com

Graphical Abstract



Introduction

The novel Corona Virus disease 2019 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co V-2) has led to increasing causes and death rates, and constrained the health care system worldwide [1]. According to World Health Organization (WHO), around 135.05 million positive cases and 2.91 million deaths were reported. To prevent further spread, precautions like maintaining 1 meter distance from others, wearing mask, cleaning hands with alcohol-based sanitizers advises has been provided by Ministry of Health and Family Welfare [2–4].

In order to control the pandemic and to help to enhance the immune system an effective and safe vaccination development is expected to save countless lives. In April 2020, the World Health Organization issued a statement: "Immunization saves millions of lives every year and it is widely recognized as one of the World's most successful and cost-effective health interventions". Vaccines has reduced mortality and morbidity of several preventable diseases 2–3 million every year [5]. Despite the benefits there is still a chance of developing adverse effects like pain at the site of injection, fever, myalgia, dizziness and other life- threatening allergic reactions. In India, three vaccines were granted for emergency use of authorization by Central Drug Standard Control Organization (CDSCO), viz., Covidsheild, Covaxin is known as vaccine hesitancy, resulting the priority groups as they are at higher risk (Health care and frontline workers, Persons over 60 years of age, 45 to 59 years with comorbid conditions, Populations above 45 years, and all eligible citizens above 18 years completed their vaccine schedule and on 3rd January, 2022 it has been announced that age group between 15–18 year children are eligible for vaccination schedule [6]. In case of

young generation, parent's hesitancy towards vaccinations plays a major role. "A complex and context-specific delay in acceptance or refusal of vaccination despite availability influenced by factors such as communication, context, complacency, convenience and confidence (5C) in delay or refusal of vaccination is known as vaccine hesitancy [7–9]. From parents' perspective, hesitancy in vaccinating their children may arises from various factors such as, lack of awareness, education, religious beliefs, adverse effects, sociology-economic condition and so on. Therefore, reaching the parents of the above age group who remain hesitant to be vaccinated is important to control the outbreak.

Materials and Methods

Study design

Cross-Sectional Study

Study population

Parents of children aged between 15 years and 18 years

Sample size

The sample size of 245 was calculated using the formula $4pq/d^2$, with the expected prevalence of vaccine hesitancy as 42% which was obtained from a survey conducted in Jan 2021 [10] and with the absolute precision of 6%.

Sampling Technique

Systemic random sampling.

In a rural field practice area, 1452 households were initially listed. The sampling interval was calculated and sample size was 245. First household was selected randomly by lottery method and every 6th household was selected. If eligible participant was not available or the door was closed, the adjacent house with eligible participant were selected.

Selection criteria

Parent of children aged between 15 years and 18 years who residing in the rural field practice area for more than 6 months.

Study tool

Vaccine hesitancy scale (VHS), adopted from WHO's Strategic Advisory Group of Immunization (SAGE)

Statistical tool

Data were analyzed using SPSS version 29. Categorical variables were summarized as frequently and percentage. Continuous variables were summarized with mean + standard deviation. Chi-square test was performed to assess the association between socio-demographic variables and hesitancy. P value less than 0.05 was considered as statistically significant throughout the study.

Results

A systematic sample of 246 parents, who residing in the rural field practice area of a tertiary care hospital were included in this study. The mean age of the participants were 48 years with standard deviation of 7.3. Of the overall participants,159 (64.6%) were females and 87 (35.4%) were males. Most of the parents were daily labors (41.1%) and 95.5%. living with their spouse (Table 1).

Table1. Distribution of study participants based on Socio-demographic details

Demographic characteristics		Frequency	Percent %
Age	<40	29	11.8
	40-50	136	55.3
	50-60	72	29.3
	>60	9	3.7
Education	Illiterate	17	6.9
	Primary school	33	13.4
	Middle school	75	30.5
	High school	39	15.9
	Higher secondary school	20	8.1
	Graduate	38	15.4
	Post graduate	24	9.8
Religion	Hindu	12	5
	Muslim	5	2
	Christian	229	93
Occupation	Unemployed	4	1.6
	Housewife	95	38.6
	Daily labour	101	41.1
	Health care workers	5	2
	Professional	41	16.7
Marital Status	Living with spouse	235	95.5
	Separated	1	0.4
	Widowed	10	4.1

Parental Hesitancy on Vaccination

Table 2 shows percentages of vaccine hesitancy among parents, around 20.3% of parents had hesitation in vaccinating their children. About 90.2% of them thought vaccine can protect and only 9.8% thought vaccine cannot protect their children. About 85% of parents accepting all the recommended COVID 19 vaccines to their children. This study showed that 4.1% of the parents refused to get vaccination.

Table 2. Distribution of responses of the Vaccine hesitancy scale (VHS) by the study participants

Parental Hesitancy			
Characteristics		Frequency	Percentage %
Do you think vaccine can protect children from covid 19?	Yes	222	90.2
	No	24	9.8
Do you think that most parents like to have their children vaccinated with all the recommended vaccine for COVID 19?	Yes	209	85.0
	No	37	15.0
Have you ever been hesitant to get a vaccination for you children?	Yes	50	20.3
	No	196	79.7
Have you ever refused a vaccination for your child?	Yes	10	4.1
	No	236	95.9
Has, distance, timing of clinic, time needed to get to clinic or wait at clinic, and / or costs in getting to clinic prevented your children immunized?	Yes	7	2.8
	No	239	97.2
Are there other pressures in your life that you from getting your children immunized on time?	Yes	5	2
	No	241	98
Are there any reasons you can think of why children should not be vaccinated?	Yes	24	9.8
	No	222	90.2
Have you ever received any negative information about vaccinations?	Yes	134	54.5
	No	112	45.5
Do leaders in your community support vaccinations for infants and children?	Yes	228	92.7
	No	18	7.3

Parental Perception

Table 3 shows the details on the parents' perception on vaccination. Among the 246 parents 135 (54.9%) strongly agreed that the COVID 19 vaccination was important for their child's health and only 24 (5.8%) were disagreed. Around 126 (51.2%) of the parents were strongly agreed that COVID 19 vaccines were effective. 13.4% were strongly agreed that their child did not need vaccine and 38.6% were concerned on the serious side effects of the vaccine.

Table 4 shows the details on the association of vaccine hesitancy and different demographic variables. Age, gender and education had statistical association with Vaccine hesitancy, since the P value less than 0.05.

Table 3. Distribution of responses based on parent's perception on COVID vaccine

Parent's perception on COVID 19 Vaccine	Strongly disagree n (%)	Disagree N (%)	Agree N (%)	Strongly agree n (%)
Important for child's health	12 (4.9)	12 (4.9)	87(35.4)	135 (54.9)
Effective	9 (3.7)	15 (6.1)	96 (39.0)	126 (51.2)
Follow doctor's recommendation in vaccination	14 (5.7)	42 (17.1)	102 (41.5)	88 (35.8)
Best way to protect from COVID 19	16 (6.5)	25 (10.2)	108 (43.9)	97 (39.4)
Received reliable information about the vaccine	9 (3.7)	6 (2.4)	76 (30.9)	155 (63.0)
Vaccinating children is important for the health of others	14 (5.7)	19 (7.7)	96 (39)	117 (47.6)
Child does not need vaccine	88 (35.8)	99 (40.2)	26 (10.6)	33 (13.4)
New vaccines have more risks	64 (26)	94 (38.2)	40 (16.3)	48 (19.5)
Concerned about side effects of vaccine	58 (23.6)	23 (9.3)	70 (28.5)	95 (38.6)

Table 4. Association Between Demographic Variables and Vaccine Hesitancy

		Vaccine hesitancy		Total (n=246)	Chi-square value	P value
		Yes (n=50)	No (n=196)			
Age	<40	11	18	29	15.11	0.001*
	40-50	16	120	136		
	50-60	20	52	72		
	>60	3	6	9		
Sex	Male	10	77	87	6.482	0.01*
	Female	40	119	159		
Religion	Hindu	43	185	228	4.819	0.09
	Muslim	3	3	6		
	Christian	4	8	12		
Education	Illiterate	7	10	17	22.115	0.001*
	Primary school	12	21	33		
	Middle school	13	62	75		
	High school	5	34	39		
	Higher secondary school	8	12	20		
	Graduate	3	35	38		
	Post graduate	2	22	24		
Occupation	Unemployed	2	2	4	2.366	0.669
	Housewife	20	75	95		
	Daily labour	19	82	101		

	Health care workers	1	4	5		
	Professional	8	33	41		
Marital status	Living with spouse	50	185	235	2.937	0.230
	Separated	0	1	1		
	Widowed	0	10	10		

The reasons mentioned for not vaccinating their children is given in Figure 1. Higher proportion of the parents had the fear of death and side effects.

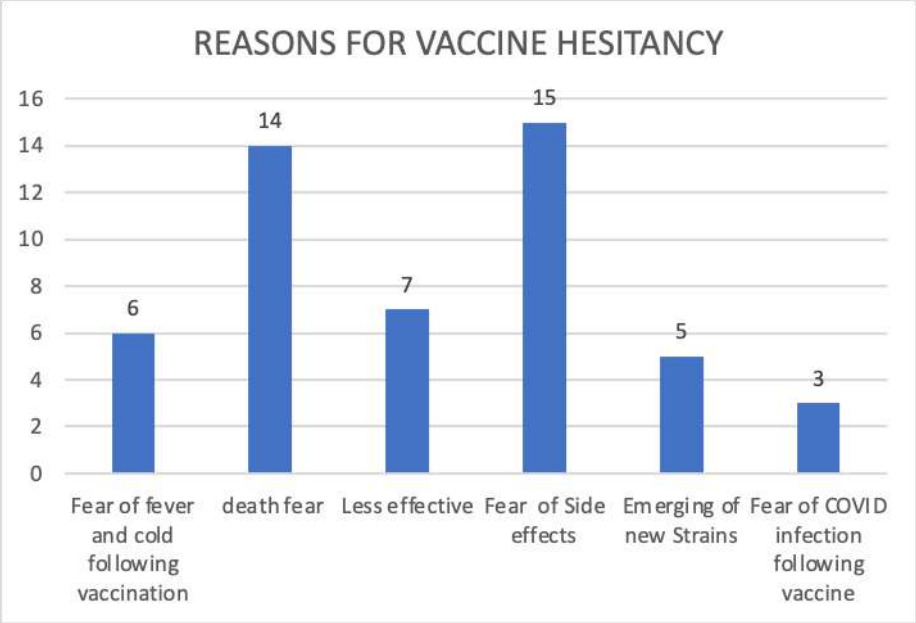


Figure 1. Factors influencing parents' hesitancy to vaccinate their children.

Discussion

The most effective way of prevention and to reduce the burden of COVID-19 pandemic is vaccination. In our cross-sectional study on COVID-19 vaccine hesitancy among parents of children aged 15–18 years, we found that one fifth of the participants were hesitant to have their children vaccinated against COVID-19, while lesser prevalence of vaccine hesitancy was observed in the studies conducted by Bagateli et al. [11] (2.8%), Hopfer et al. [12] (11%), Kadam et al. [13] (3.3%), Bonuk et al. [14] (10%). On the other hand, the higher prevalence of vaccine hesitancy was seen in the study conducted by Ali et al (45%) [15], Xu et al.

[16] (67.4%), Al-Qerem et al. [17] (48.4%) and Ruiz et al. [18] (78.8%).

In our study female participants were more (65%) than the male participants (35%) similar results were seen in Temsah et al. [19] (65%). On contrary, Male participants were more in study conducted by Abedin et al. [20] in Bangladesh. The higher rate of female participants was seen in Hopfer et al. [12] (98%) and Bagateli et al. [11] (85%), studies conducted in Brazil and Saudi Arabia respectively.

In this study, nearly 75% of the study participants were higher secondary below as their educational status which was similar to Danabal et al. [21] (79.7%) study. The education level of our participants hesitancy rate of parents in higher secondary education and below showed 74.4%. A study conducted by Xu et al. [22] in China showed hesitancy rate of 57.8% in parents with education status of higher secondary and below. A study Wang et al. [23] study in China showed hesitancy rate of 30.5% in parents with education status of higher secondary and below Danabal et al. [21] study in Tamil Nadu observed hesitancy rate of 79.7% in parents with education status of higher secondary and below. On the contrary, Delgado et al. [24] conducted a study among Mexican population showed hesitancy rate of 11.3% in parents with education status of higher secondary and below.

The study done by Ali et al. [15], McElfish et al. [25], Bagateli et al. [11] in relation with age of the parents and hesitancy towards COVID vaccination showed significance whereas, the study done by Ebrahimi et al. [26] was not significant which was similar to our study.

The study done by Danabal et al. [21], Ebrahim et al. [26], in relationship with sex of the parents and hesitancy towards COVID vaccination were found to be significant while the study conducted by McElfish et al. [25], Ali Met Al. [15], Bagatali et al. [11] found no significance which was similar to our study results. The study done by Danabal et al. [21] in relation with occupation of the parent and vaccine hesitancy found to be significant where in contrast to our study. The study conducted by Temsah et al. [19], Ali et al. [15], Bagateli et al. [11] found no significance which was similar to our study which also carried no significancy.

When we assessed the reasons for hesitancy, regarding fear of death USAID found only 5% whereas our study it was 28%. In comparison with the reason regarding less effective against COVID-19 vaccination study conducted by Fisher et al. [27],[27] in United States shows 20%, sage journals conducted national wide says 9.2%, Bonuck et al. [14], reported 48% and UNICEF observed 21% whereas our study showed 14%. In comparison with the reason regarding an unknown illness after years USAID showed 19% whereas our study shows 6%. We found that 10% of our educated parents said strains keep changing and there won't be use of the old vaccine. In comparison with the reason regarding concern about the side effects/safety, Celia Fisher et al. [27], in United States reported 33%, Hyunju Lee et al. [28], in Korea reported 90.4% Bonuck et al. [14] at statewide DD networks reported 88.7%, Sage journals national wide reported 56.5%, Kitro et al. [29] conducted study in Thailand reported 75.9% whereas in our study it was 24%. In comparison with the reason regarding the fear of getting infected from COVID-19 vaccine Bonuck et al. [14] conducted statewide DD Networks reported 18.8% whereas in our study it was only 6%.

Conclusion

Nearly one fifth of the study participants were hesitant to vaccinate their children. Various sociodemographic factors had direct and indirect effects towards vaccination among study participants. Health education on safety, effectiveness of covid vaccine should be addressed to the community with effective engagement of health care professionals can reduce the covid vaccine hesitancy.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

No funding was received for conducting this study.

Authors' Contributions

Conceptualization: VS; Methodology: VN; Formal Analysis: KS; Data Collection: SK Writing—Original Draft Preparation: VS and SK; Writing—Review and Editing: VS. All authors have read and approved the final version of the manuscript and agree to its publication.

Informed Consent

Written informed consent was obtained before starting the data collection from the participants privacy were maintained and respected.

Ethical Approval

Approval for conducting this study was obtained from the Institutional Ethical committee (IHEC No: AV/IEC/2022/058), this project was considered to have less than minimal risk.

References

1. Johns Hopkins Coronavirus Resource Centre. COVID-19 Map. Available from: https://coronavirus.jbu.edu/map.html (Accessed on January 31st, 2022).
2. Liu M, Cheng SZ, Xu KW, Yang Y, Zhu QT, Zhang H, Yang DY, Cheng SY, Xiao H, Wang JW, Yao HR. Use of personal protective equipment against coronavirus disease 2019 by healthcare professionals in Wuhan, China: cross sectional study. Bmj. 2020 Jun 10;369.
3. Park CL, Russell BS, Fendrich M, Finkelstein-Fox L, Hutchison M, Becker J. Americans' COVID-19 stress, coping, and adherence to CDC guidelines. Journal of general internal medicine. 2020 Aug;35(8):2296-303.
4. Shah K, Kamrai D, Mekala H, Mann B, Desai K, Patel RS. Focus on mental health during the coronavirus (COVID-19) pandemic: applying learnings from the past outbreaks. Cureus. 2020 Mar 25;12(3).
5. World Health Organisation Immunization Coverage. Available Online: http://www.who.int/news-room/fact-sheets/detail/immunization-coverage [(Accessed on 14th January 2022)].
6. India's COVID-19 Vaccine Guidelines. Available from: https://www.mohfw.gov.in/covid_vaccination/vaccination/index.html (accessed, January 31st, 2022).
7. Feleszko W, Lewulis P, Czarnecki A, Waszkiewicz P. Flattening the curve of COVID-19 vaccine rejection—an international overview. Vaccines. 2021 Jan;9(1):44.
8. Olson O, Berry C, Kumar N. Addressing parental vaccine hesitancy towards childhood vaccines in the United States: a systematic literature review of communication interventions and strategies. Vaccines. 2020 Dec;8(4):590.

9. Shapiro GK, Tatar O, Dube E, Amsel R, Knauper B, Naz A, Perez S, Rosberger Z. The vaccine hesitancy scale: Psychometric properties and validation. Vaccine. 2018 Jan 29;36(5):660-7.
10. Covid-19 vaccine hesitancy: Trends across states, over time https://www.ideasforindia.in/topics/governance/covid-19-vaccine-hesitancy-trends-across-states-over-time.html (Accessed on January, 31st 2022)
11. Bagateli LE, Saeki EY, Fadda M, Agostoni C, Marchisio P, Milani GP. COVID-19 Vaccine Hesitancy among Parents of Children and Adolescents Living in Brazil. Vaccines (Basel). 2021 Sep 30;9(10):1115. doi: 10.3390/vaccines9101115.
12. Hopfer S, Fields EJ, Ramirez M, Long SN, Huszti HC, Gombosev A, Boden-Albala B, Sorkin DH, Cooper DM. Adolescent COVID-19 Vaccine Decision-Making among Parents in Southern California. Int J Environ Res Public Health. 2022 Apr 1;19(7):4212. doi: 10.3390/ijerph19074212.
13. Kadam KS, Himanshi, Uttarwar P. Covid-19 Vaccine Hesitancy for Children in Parents: A Cross-Sectional Survey Among Healthcare Professionals in India. Indian J Psychiatry. 2022 Mar;64(Suppl 3):S565. doi: 10.4103/0019-5545.341630.
14. Bonuck K, Iadarola S, Gao Q, Siegel JF. COVID-19 Vaccines for Children with Developmental Disabilities: Survey of New York State Parents' Willingness and Concerns. J Dev Behav Pediatr. 2022 Dec 1;43(9):521-528. doi: 10.1097/DBP.0000000000001113.
15. Ali M, Ahmed S, Bonna AS, Sarkar AS, Islam MA, Urmi TA, Proma TS. Parental coronavirus disease vaccine hesitancy for children in Bangladesh: a cross-sectional study. F1000Res. 2022 Jan 25;11:90. doi: 10.12688/f1000research.76181.2.
16. Xu Y, Xu D, Luo L, Ma F, Wang P, Li H, Li Q, Wei L, Diao J, Liu Y, Zhang W, Zheng X. A Cross-Sectional Survey on COVID-19 Vaccine Hesitancy Among Parents From Shandong vs. Zhejiang. Front Public Health. 2021 Nov 5;9:779720. doi: 10.3389/fpubh.2021.779720.
17. Al-Qerem W, Al Bawab AQ, Hammad A, Jaber T, Khdair SI, Kalloush H, Ling J, Mosleh R. Parents' attitudes, knowledge and practice towards vaccinating their children against COVID-19: a cross-sectional study. Hum Vaccin Immunother. 2022 Nov 30;18(5):2044257. doi: 10.1080/21645515.2022.2044257.
18. Ruiz JB, Bell RA. Parental COVID-19 Vaccine Hesitancy in the United States. Public Health Rep. 2022 Nov-Dec;137(6):1162-1169. doi: 10.1177/00333549221114346.
19. Temsah MH, Alhuzaimi AN, Aljamaan F, Bahkali F, Al-Eyadhy A, Alrabiaah A, Alhaboob A, Bashiri FA, Alshaer A, Temsah O, Bassrawi R, Alshahrani F, Chaiah Y, Alaraj A, Assiri RA, Jamal A, Batais MA, Saddik B, Halwani R, Alzamil F, Memish ZA, Barry M, Al-Subaie S, Al-Tawfiq JA, Alhasan K. Parental Attitudes and Hesitancy About COVID-19 vs. Routine Childhood Vaccinations: A National Survey. Front Public Health. 2021 Oct 13;9:752323. doi: 10.3389/fpubh.2021.752323.
20. Abedin M, Islam MA, Rahman FN, Reza HM, Hossain MZ, Hossain MA, Arefin A, Hossain A. Willingness to vaccinate against COVID-19 among Bangladeshi adults: Understanding the strategies to optimize vaccination coverage. PLoS One. 2021 Apr 27;16(4):e0250495. doi: 10.1371/journal.pone.0250495.

21. Danabal KGM, Magesh SS, Saravanan S, Gopichandran V. Attitude towards COVID 19 vaccines and vaccine hesitancy in urban and rural communities in Tamil Nadu, India - a community based survey. BMC Health Serv Res. 2021 Sep 21;21(1):994. doi: 10.1186/s12913-021-07037-4.
22. Xu Y, Zhang R, Zhou Z, Fan J, Liang J, Cai L, Peng L, Ren F, Lin W. Parental psychological distress and attitudes towards COVID-19 vaccination: A cross-sectional survey in Shenzhen, China. J Affect Disord. 2021 Sep 1;292:552-558. doi: 10.1016/j.jad.2021.06.003.
23. Wang Q, Xiu S, Yang L, Han Y, Cui T, Shi N, Liu M, Yi Y, Liu C, Wang X, Yang G, Ji L, Zhou W, Jin H, Zhen S, Lin L. Changes in Parental Attitudes Toward COVID-19 Vaccination and Routine Childhood Vaccination During the COVID-19 Pandemic: Repeated Cross-sectional Survey Study. JMIR Public Health Surveill. 2022 May 13;8(5):e33235. doi: 10.2196/33235.
24. Delgado-Gallegos JL, Padilla-Rivas GR, Gastelum-Arias LJ, Zuñiga-Violante E, Avilés-Rodríguez G, Arellanos-Soto D, Franco-Villareal H, Garza-Treviño EN, Cosío-León MdlÁ, Romo-Cardenas GS, et al. Parent's Perspective towards Child COVID-19 Vaccination: An Online Cross-Sectional Study in Mexico. International Journal of Environmental Research and Public Health. 2022; 19(1):290. https://doi.org/10.3390/ijerph19010290
25. McElfish PA, Willis DE, Shah SK, Bryant-Moore K, Rojo MO, Selig JP. Sociodemographic determinants of COVID-19 vaccine hesitancy, fear of infection, and protection self-efficacy. Journal of primary care & community health. 2021 Aug;12:21501327211040746
26. Ebrahimi OV, Johnson MS, Ebling S, Amundsen OM, Halsøy Ø, Hoffart A, Skjerdingstad N, Johnson SU. Risk, trust, and flawed assumptions: vaccine hesitancy during the COVID-19 pandemic. Frontiers in Public Health. 2021 Jul 1;9:700213
27. Fisher, C.B.; Bragard, E.; Jaber, R.; Gray, A. COVID-19 Vaccine Hesitancy among Parents of Children under Five Years in the United States. Vaccines 2022, 10, 1313. https://doi.org/10.3390/vaccines10081313
28. Cho HK, Lee H, Choe YJ, Kim S, Seo S, Moon J, Choi EH, Kwon GY, Shin JY, Choi SY, Jeong MJ, You M. Parental concerns about COVID-19 vaccine safety and hesitancy in Korea: implications for vaccine communication. Epidemiol Health. 2022;45:e2023004. doi: 10.4178/epih.e2023004.
29. Kitro A, Sirikul W, Dilokkhamaruk E, Sumitmoh G, Pasirayut S, Wongcharoen A, Panumasvivat J, Ongprasert K, Sapbamrer R. COVID-19 vaccine hesitancy and influential factors among Thai parents and guardians to vaccinate their children. Vaccine X. 2022 Aug;11:100182. doi: 10.1016/j.jvacx.2022.100182.

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ORIGINAL ARTICLE

A Retrospective Study on the Association between Academic Performance of Students in High School and First-Year Medical College: A Quantitative Analysis

Kavitha Ukkirapandian,[1,*] U. Karthika Priyadharhini,[2,3] Punita Pushpanathan,[1] Deepika Chandrasekaran[1] and Muthulakshmi Rangasmy[1]

[1]*Department of Physiology, Meenakshi Medical College Hospital & Research Institute, MAHER University, Kancheepuram*
[2]*MHPE Scholar, Institute of Health Profession Education, Sri Balaji Vidyapeeth, Pondicherry*
[3]*Assistant professor, Department of Physiology, Indira Gandhi Medical College & Research Institute, Pondicherry*

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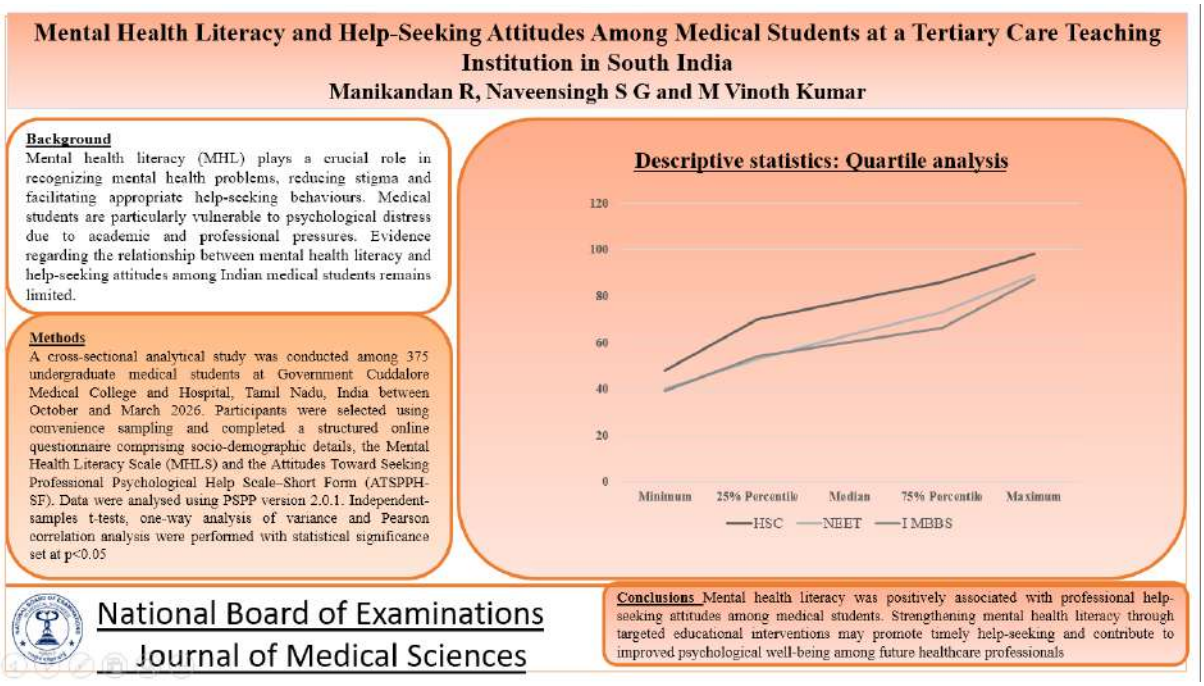
Abstract

Background: Getting into medical college is a highly competitive process; aspirants are focused mainly on attaining the eligibility criteria. Students who clear higher secondary exams (HSC) and qualify for the National Eligibility cum-Entrance Test (NEET) are getting admitted into medical colleges in India. The hypothetical question is: can we predict the academic performance of students in medicine by their school attainments? **Aim:** This study was done to identify the association between academic performance of students in high school and first-year medical college by doing quantitative analysis. Academic data of MBBS students who have recently appeared for first year university exams was collected retrospectively. Their academic data, which includes HSC, NEET-UG, and I-year MBBS university marks, were analysed. Descriptive statistics and odds ratios were done. **Results:** Students who score above average in the NEET exam are 3.25 times (OR-3.25) likely to score >60% in the first-year MBBS exam, at the same time, 67% of students who failed in the first-year MBBS university exam belonged to the below-average category in NEET. 83% of students who failed in the first-year MBBS exam have scored less than average marks in higher secondary school. **Conclusion:** The academic performance of students in both HSC and NEET can be considered in predicting their performance in medical college and to train the students effectively from the beginning itself.

Key words: National Eligibility cum-Entrance Test, Higher secondary exams (HSC), academic performance, higher education, university marks, medical students

*Corresponding Author: Kavitha Ukkirapandian
Email: kavikrish.u@gmail.com

Graphical Abstract



Introduction

Admission criteria for medical colleges vary worldwide. Many medical schools rely heavily on student's high school grades in their admission process along with premedical entrance exams [1]. Research studies have sought to clarify admissions criteria that will predict success in medical, dental, and doctoral programs [2]. In India, the admission criteria were varied from time to time.

Entrance examinations and eligible criteria are generally set high in order to select the best students as doctors. The National Eligibility-cum-Entrance Test (NEET) was implemented by the Government of India in the year 2019 as a common entrance test. Particularly in India, medical college admissions are completely based on NEET examination scores, and the syllabus for the NEET exam includes Physics, Chemistry, and Biology subjects of higher secondary school. Students who are really good at studies are expected to perform well in higher secondary school board exams also, though credentials are not given for HSC marks to enter into medical colleges.

In reality, students are trained to score maximum marks in entrance exams mainly by clearing structure based multiple-choice questionnaires. Students who are capable of getting coaching from the standard institutes are scoring more than others. This increases the diversity of students, which was evidenced by the exponential growth of coaching institutes and repeaters in NEET by getting training throughout the year to fit into selection criteria [2]. The hypothetical questions are that the students who entered into medical colleges,

Do all the eligible students academically perform well in medicine?

Can we predict the academic performance of students in medicine by their school attainments?

Hence, this study was undertaken to identify the association between the

academic performance of students in high school and medical college.

Materials and Methods

This retrospective study was conducted after obtaining ethical clearance from the Institutional Ethics Committee of Meenakshi Medical College Hospital & Research Institute (MMCH & RI). The Institutional Review Board certification number for this study is MMCH&RI IEC/FACULTY/04/OCT/23.

Permission was obtained from the administrative head to collect data from the institute's administrative office. The method of convenient sampling was employed. It is a single-centred study. The study population consisted of MBBS students who had recently passed the first-year MBBS university examination. Out of 250 students, 247 appeared for the exam, making the final sample size 247 students.

Data Collection

Higher secondary mark sheets and NEET score percentages, which were submitted during admission, were obtained from the admin office. The consolidated percentage of higher secondary school board examination marks in major subjects-Physics, Chemistry, and Biology (PCB)-was recorded. Similarly, the percentage of marks obtained in the NEET examination was collected. The first-year MBBS university marks were obtained from the university office with proper approval, and the total percentage of marks obtained in the first-year MBBS university exam was calculated.

Grouping Criteria

For statistical analysis, students were categorized into two groups based on their average percentage of marks within each academic performance parameter-Higher Secondary (HSC), NEET, and First-Year MBBS.

Above Average: Students who scored above the calculated average percentage.

Below Average: Students who scored below the calculated average percentage.

Statistical Analysis

The data was analysed using GraphPad Prism 8. Q-Q (quantile-quantile plot) plot was generated, which is a visual tool used to compare probability distributions. Descriptive statistics, including mean, median, and quartile analysis, were conducted. Based on these, students were categorized into above-average and below-average groups for HSC, NEET, and first-year MBBS scores. The odds ratio (OR) was calculated to determine the association between different academic performance variables (Figure 1).

Results

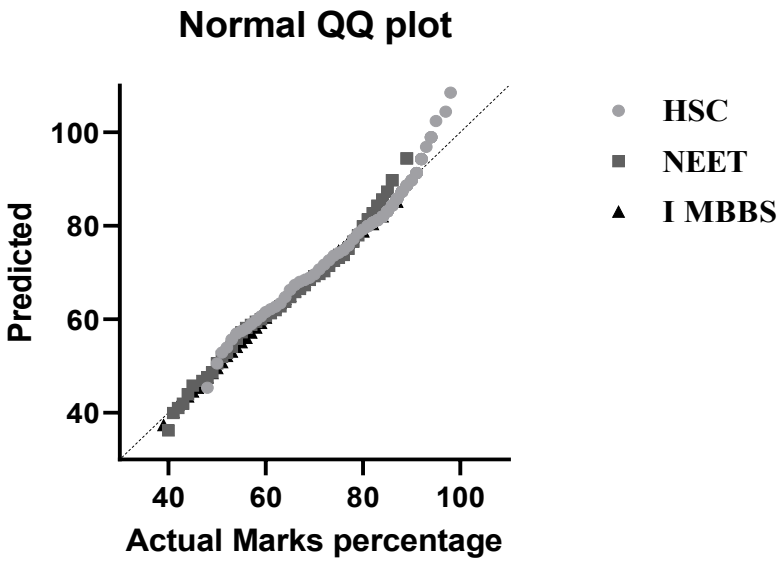


Figure 1. Q-Q plot between marks percentage distribution in HSC, NEET and I MBBS university exam

HSC: Higher secondary school marks percentage; NEET: UG Medical entrance exam marks percentage; I MBBS: First-year MBBS university exam marks percentage

The Q-Q plot showed that the percentage of Marks distribution in HSC and NEET was not distributed normally, whereas 1st-year MBBS university marks have shown normal distribution (Figure 1).

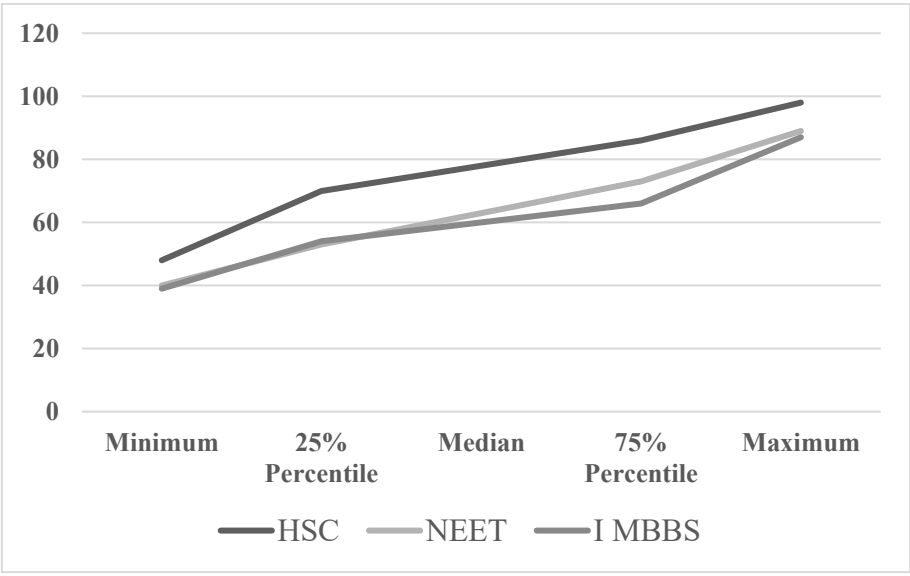


Figure 2. Descriptive statistics- Quartile analysis

Minimum and maximum marks percentages in both NEET and the first-year MBBS university exam were similar, whereas the HSC marks percentage was higher than both, which showed the level of difficulty of all three exams (Figure 2).

Table 1. Odds ratio between NEET and I year MBBS marks percentage

Odds Ratio 3.25	NEET >60	NEET<60
I MBBS >60	85 (60%)	33 (31%)
I MBBS <60	57 ((40%)	72 (69%)
Total	142	105
P value (alpha=0.01)	<0.0001****	

NEET >60: Number of students who scored more than 60% in NEET (above average)
NEET <60: Number of students who scored less than 60% in NEET (below average)
I MBBS >60: Number of students who scored more than 60% in I year MBBS university exam
I MBBS <60: Number of students who scored less than 60% in I year MBBS university exam

Odds ratios >3 indicate strong positive association that students who scored >60% in the NEET exam are also able to score >60% in the first- year MBBS university exam (Table 1).

Table 2. Odds ratio between Higher secondary and I MBBS marks percentage

Odds Ratio 1.81	HSC >77	HSC<77	Total
I MBBS >60	71	47	118
I MBBS <60	59	71	130
Total	130	118	248
P value	0.02*		

HSC >77: Number of students who scored more than 77% in HSC (above average)
HSC <77: Number of students who scored less than 77% in HSC (below average)
I MBBS >60: Number of students who scored more than 60% in I year MBBS university exam
I MBBS <60: Number of students who scored less than 60% in I year MBBS university exam

Odds ratios >1 indicate positive association that students who scored >77% in the HSC exam are also able to score >60% in the first-year MBBS university exam (Table 2).

Table 3. Odds ratio between number of pass and fail with NEET marks percentage

Odds Ratio 3.146	Pass	Fail	Total
NEET>60%	129	12 (23%)	141
NEET<60%	82	24 (67%)	106
Total	211	36	247
P value	0.0039****		

OR>1 indicates a strong true positive. P value is significant ****. Students who scored >60% in NEET have a high chance to get through the exam (Table 3).

Table 4. Odds ratio between number of pass and fail with HSC marks percentage

Odds Ratio 0.18	Pass	Fail	Total
HSC >77%	140 (65%)	5 (16%)	145
HSC<77%	76 (35%)	26 (83%)	102
Total	216	31	247
P value (alpha=0.01)	0.0002****		

OR <1 it strongly identifies the true negative. Students who scored less than the average marks (<77%) were more likely to fail in the first-year MBBS exam (Table 4).

Discussion

In this study, the mean, minimum, and maximum marks percentages of the NEET and first-year MBBS university exams were similar. The average percentages of NEET and first-year MBBS university exams were also 60%. But the average percentage of HSC is 77%. This data showed that aspirants of medicine really score better in HSC, though credentials have not been given to enter into medical college. Besides, the similar median value of NEET and I MBBS may indicate that the difficulty level of both exams was more similar than HSC.

Students who score above average in the NEET exam are 3.25 times (OR-3.75) likely to score >60% in the first-year MBBS exam. At the same time, 67% of students who failed the first-year MBBS university exam belonged to the below-average category in NEET. These results in the current study claim that the level of difficulty in both the NEET and the IMBBS medical exams was similar.

Though no scientific studies have been conducted in India on NEET and medical college performance, as general international studies are available that sought their countries admission criteria for medical education. Studies done in the US and Portugal demonstrated that entrance exams used to determine admission to universities, such as the American College Testing (ACT) and Scholastic Aptitude Test (SAT), are considered to be the most accurate indicators of a student's performance in higher education [3, 4].

When comparing HSC marks with first-year MBBS to evaluate student's academic performance, OR = 1.79 indicates students who score more than average (>77%) in HSC were 1.79 times more likely to score more than average in I MBBS. At the same time, 83% of students who failed the first-year MBBS exam have scored less than average marks in higher secondary school. These results were supported by the findings of Silva P. et al. (2020), who claimed that high school grades can predict the dropouts/failures in university exams, though they cannot predict the overall performance of students in university [5]. A study that looked at the relationship between different entrance requirements and academic achievement at medical colleges in Pakistan found that MBBS professional exam scores and HSC scores had a slight correlation, whereas entrance exam scores showed no correlation at all [6-8]. In a recent study done in the Philippines, it was recommended that the pre-entry grades (HSC) of the applicants are to be included in evaluating and ranking the candidates for admission [9].

The majority of research studies conducted worldwide have stated that the HSC marks percentage, in conjunction with the medical entrance exam, is an important admission criterion that improves students' performance at the higher secondary school level [10].

To our knowledge, in India this is the first study to report the correlation between higher secondary marks and NEET marks percentage with first-year MBBS academic performance in university exams.

Limitations: Being a single-centred study, these findings cannot be generalized as a whole. In the future, a multi-centre study can be done to check the reliability. There are many factors including socioeconomic status, Physiological factors and study habits as confounders- we add these aspects in future studies.

Conclusion

By having this knowledge that poor performers in HSC are expected to be slow learners in medical college, teachers can allocate resources accurately with effective predictions that train the students from the beginning itself. Small group teaching or extra classes can be conducted separately to enhance their academic performance without further delay.

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institute which were instrumental in the successful completion of this work.

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. Davies TA, Miller MB, Moore VA, Kaye EA. Predicting professional school performance with a unique lens: are there other cognitive predictors? BMC Med Educ. 2020 Jan 15;20(1):14. doi: 10.1186/s12909-020-1930-2.
2. Park HY, Berkowitz O, Symes K, Dasgupta S. The art and science of selecting graduate students in the biomedical sciences: Performance in doctoral study of the foundational sciences. PLoS One. 2018 Apr 3;13(4):e0193901. doi: 10.1371/journal.pone.0193901.
3. Baron J, Norman MF. SATs, achievement tests, and high-school class rank as predictors of college performance. Educational and Psychological Measurement. 1992 Dec;52(4):1047–55. https://doi.org/10.1177/0013164492052004029.
4. Ferrão M, Almeida L. Differential effect of university entrance score on first-year students' academic performance in Portugal. Assessment & Evaluation in Higher Education. 2019 May 19;44(4):610–22. https://doi.org/10.1080/02602938.2018.1525602
5. Silva, P. L., Nunes, L. C., Seabra, C., Balcao Reis, A., & Alves, M. (2020). Student selection and performance in higher education: admission exams vs. high school scores. Education Economics, 28(5), 437–454. https://doi.org/10.1080/09645292.2020.1782846
6. Iftikhar S, Cheema KM, Aziz I: MBBS admission criteria as predictor of academic performance in a medical college of Pakistan. Pak J Med Sci. 2023, 39:1706–1710. https://doi.org/10.12669/pjms.39.6.6839
7. Qazi MA, Anwar J, Moffat M. Predictive Ability and Stakeholders' Perceptions of the Selection Tools for MBBS in Women Medical College: A Mixed Methods Study. J Ayub Med Coll Abbottabad. 2020 Jan-Mar;32(1):78–82.
8. Ali R, Ali SK, Afzal A: Predictive validity of a uniform entrance test for the health professionals. Pak J Med Sci. 2019, 35:330–336. 10.12669/pjms.35.2.334
9. Montalbo, Agnes Fernandez and Evangelista, Yolanda P. and Bernal, Merlene M., Admission Test as Predictor of Student Performance in Political Science and Psychology Students of Rizal Technological University (August 2018). Asia Pacific Journal of Multidisciplinary Research, Vol. 6, No. 3, August 2018, https://ssrn.com/abstract=3533808

10. Al-Qahtani MF, Alanzi TM. Comparisons of the predictive values of admission criteria for academic achievement among undergraduate students of health and non-health science professions: a longitudinal cohort study. Psychol Res Behav Manag. 2018 Dec 19;12:1–6.

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ORIGINAL ARTICLE

ELABELA as a Predictive Biomarker in Pre-Eclampsia: A Comparative Study of Early-Onset and Late-Onset Variants

M. Aishwarya Vaishnavi,[1,*] S. Prakash[1] and T. Uma[2]

[1]*Assistant Professor, Department of Biochemistry, Government Medical College Krishnagiri, Tamilnadu*
[2]*Associate Professor, Department of Biochemistry, Government Chengalpattu Medical College, Tamilnadu*

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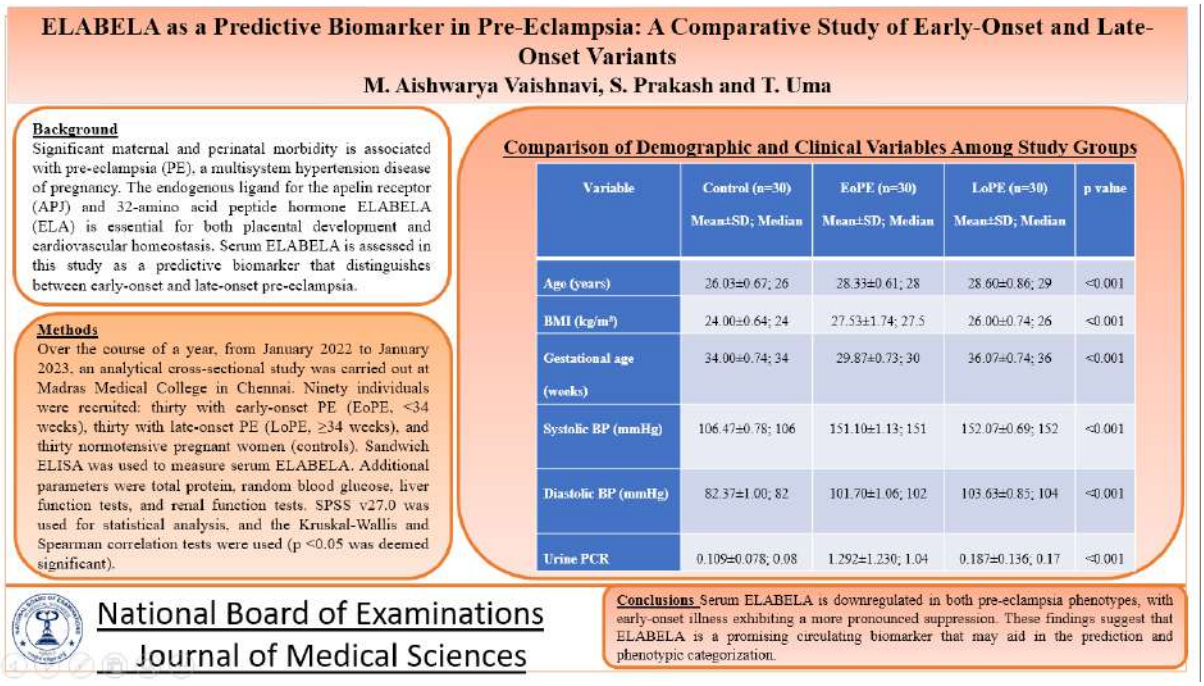
Abstract

Background: Significant maternal and perinatal morbidity is associated with pre-eclampsia (PE), a multisystem hypertension disease of pregnancy. The endogenous ligand for the apelin receptor (APJ) and 32-amino acid peptide hormone ELABELA (ELA) is essential for both placental development and cardiovascular homeostasis. Serum ELABELA is assessed in this study as a predictive biomarker that distinguishes between early-onset and late-onset pre-eclampsia. **Methods:** Over the course of a year, from January 2022 to January 2023, an analytical cross-sectional study was carried out at Madras Medical College in Chennai. Ninety individuals were recruited: thirty with early-onset PE (EoPE, <34 weeks), thirty with late-onset PE (LoPE, ≥34 weeks), and thirty normotensive pregnant women (controls). Sandwich ELISA was used to measure serum ELABELA. Additional parameters were total protein, random blood glucose, liver function tests, and renal function tests. SPSS v27.0 was used for statistical analysis, and the Kruskal-Wallis and Spearman correlation tests were used ($p < 0.05$ was deemed significant). **Results:** EoPE (7.0 ± 0.584 pg/mL) and LoPE (11.5 ± 0.290 pg/mL) had significantly lower mean serum ELABELA than controls (18.0 ± 0.585 pg/mL) ($p = <0.001$). Serum creatinine ($r = –0.695$) and urea ($r = –0.447$) showed significant negative associations with ELABELA, while total protein ($r = +0.557$) showed a significant positive relationship.
Conclusion: Serum ELABELA is downregulated in both pre-eclampsia phenotypes, with early-onset illness exhibiting a more pronounced suppression. These findings suggest that ELABELA is a promising circulating biomarker that may aid in the prediction and phenotypic categorisation of pre-eclampsia, warranting further evaluation in longitudinal studies.

Keywords: Pre-eclampsia, ELABELA, Apelin receptor, Biomarker, Early-onset pre-eclampsia, Late-onset pre-eclampsia, Hypertensive disorders of pregnancy

*Corresponding Author: M. Aishwarya Vaishnavi
Email: aishvaish93@gmail.com

Graphical Abstract



Introduction

A pregnancy-specific condition known as pre-eclampsia (PE) is characterised by new-onset hypertension (≥140/90 mmHg) after 20 weeks of gestation, together with uteroplacental insufficiency or maternal organ dysfunction. It continues to be a major cause of maternal and perinatal morbidity and mortality, accounting for 14% of maternal deaths worldwide, and complicates roughly 2–7% of pregnancies internationally [1]. The urgent need for trustworthy prognostic biomarkers and a better comprehension of its pathogenesis is highlighted by the fact that, despite significant advancements in perinatal care, the only effective treatment is still delivery [2].

According to the two-stage concept of PE, the failure of spiral artery remodelling and deficient trophoblast invasion cause placental hypoperfusion (stage 1), which in turn causes systemic maternal endothelial dysfunction (stage 2). The pathophysiology, severity, and prognosis of early-onset (EoPE; delivery before 34 weeks) and late-onset (LoPE; delivery at or after 34 weeks) variants of PE differ significantly. LoPE is more often linked to maternal metabolic and cardiovascular comorbidities; EoPE is characterised by severe placental malperfusion, foetal development restriction, and increased cardiovascular risk in later life [3].

The 32-amino acid peptide hormone ELABELA (ELA), also known as Apela or Toddler, serves as an endogenous ligand for the G protein-coupled apelin receptor (APJ). Villous cytotrophoblasts and syncytiotrophoblasts express ELA, which has angiogenic, anti-apoptotic, vasodilatory, and cardiorenal regulatory effects. Binding of ELA to APJ activates downstream PI3K/Akt-eNOS signalling, promoting nitric oxide generation, trophoblast invasion, and endothelial function, while disruption of this axis is linked to increased

oxidative stress and impaired vascular homeostasis [18]. Exogenous ELA injection reverses the PE-like phenotype that ELA-knockout animals develop, which includes hypertension, proteinuria, and glomerular endotheliosis. This suggests that ELA plays a crucial protective function in preserving maternal-placental vascular homeostasis [4-6].

Human data on ELA in PE is still scarce and occasionally contradictory. In order to establish ELABELA as a phenotype-specific predictive biomarker in PE, the current study was planned to detect serum ELABELA levels in EoPE, LoPE, and normotensive controls and to assess its correlations with recognised biochemical indicators.

Materials and Methods

Study Design and Setting

The Institute of Biochemistry and the Institute of Obstetrics and Gynaecology, Madras Medical College, and Rajiv Gandhi Government General Hospital, Chennai, were the sites of this one-year (January 2022–January 2023) analytical cross-sectional hospital-based study. Before the event began, the Institutional Ethics Committee gave its approval, and each participant provided signed informed consent.

Study Population and Grouping

Ninety pregnant women between the ages of twenty and forty were divided into three groups of thirty: Pre-eclampsia with gestational age less than 34 weeks is classified as Group A (EoPE); pre-eclampsia with gestational age greater than 34 weeks is classified as Group B (LoPE); Pregnant women with normotension who were matched for gestational age and maternal age made up Group C (Control).

The ISSHP criteria (new-onset hypertension ≥140/90 mmHg after 20 weeks with proteinuria or organ failure) were used to diagnose PE [7]. Only women with singleton pregnancies were included in the study. Pre-existing chronic hypertension, diabetes mellitus, hyperuricaemia, renal illness, cardiovascular disease, and multiple (twin or higher-order) pregnancies were among the exclusion criteria. A formal a priori sample size calculation was not performed; a convenience sample of 30 participants per group was recruited over the one-year study period, a group size comparable to that used in other analytical studies of ELABELA in early- and late-onset pre-eclampsia [8].

Sample Collection and Laboratory Analysis

Under aseptic conditions, five millilitres of fasting venous blood were drawn from the antecubital vein. Centrifugation was used to separate the serum (3000 RPM, 15 minutes). For ELABELA estimate, one millilitre of serum was kept at -20°C. On the same day, routine biochemical measures were examined. To estimate the protein-creatinine ratio (PCR), spot urine was collected.

A commercially available sandwich ELISA kit (optical density read at 450 nm; standard curve range 100–3200 pg/mL) was used to quantify serum ELABELA. Random blood glucose (Hexokinase), urea (urease-GLDH kinetic method), creatinine (kinetic Jaffé method, IDMS-traceable), uric acid (uricase-PAP), AST and ALT (modified IFCC method), and total protein (Biuret method) were among the additional assays. Urine creatinine was measured

using the Jaffé method and urine protein using the sulphosalicylic acid method.

Statistical Analysis

Data were analysed using SPSS version 27.0. Results are expressed as mean ± SD and median. Between-group comparisons were performed using the Kruskal-Wallis test. Spearman rank correlation was used to assess relationships between serum ELABELA and biochemical variables. A p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

There was a statistically significant age difference across the groups, with the mean age of participants being 28.33 years in EoPE, 28.60 years in LoPE, and 26.03 years in controls (p=<0.001). EoPE had the highest mean BMI (27.53 kg/m^2), followed by LoPE (26.00 kg/m2) and controls (24.00 kg/m2) (p = <0.001). For EoPE and LoPE, the mean gestational age was 29.87 and 36.07 weeks, respectively (p = <0.001). Key clinical and demographic factors are summarised in Table 1.

Table 1. Comparison of Demographic and Clinical Variables Among Study Groups

Variable	Control (n=30) Mean±SD; Median	EoPE (n=30) Mean±SD; Median	LoPE (n=30) Mean±SD; Median	p value
Age (years)	26.03±0.67; 26	28.33±0.61; 28	28.60±0.86; 29	<0.001
BMI (kg/m²)	24.00±0.64; 24	27.53±1.74; 27.5	26.00±0.74; 26	<0.001
Gestational age (weeks)	34.00±0.74; 34	29.87±0.73; 30	36.07±0.74; 36	<0.001
Systolic BP (mmHg)	106.47±0.78; 106	151.10±1.13; 151	152.07±0.69; 152	<0.001
Diastolic BP (mmHg)	82.37±1.00; 82	101.70±1.06; 102	103.63±0.85; 104	<0.001
Urine PCR	0.109±0.078; 0.08	1.292±1.230; 1.04	0.187±0.136; 0.17	<0.001

EoPE = Early-onset pre-eclampsia; LoPE = Late-onset pre-eclampsia; BP = blood pressure; PCR = protein-creatinine ratio. Kruskal-Wallis test.

Biochemical Parameters

Mean random blood glucose was 92.73 mg/dL in EoPE and 107.40 mg/dL in LoPE compared to 87.60 mg/dL in controls (p=<0.001). Liver enzymes (AST and ALT) were considerably higher in both PE groups: in EoPE, AST was 26.57 IU/L and ALT was 24.87 IU/L; in LoPE, AST was 34.47 IU/L and ALT was 30.20 IU/L, compared to 23.53 IU/L and 16.60 IU/L respectively in controls (p=<0.001). Serum urea and creatinine were within normal limits across

all groups, while statistically significant inter-group differences were found. Total protein was considerably reduced in EoPE (5.20 g/dL) compared to controls (6.75 g/dL) and LoPE (6.81 g/dL) (p=<0.001). Table 2 provides the biochemical data.

Table 2. Comparison of Biochemical Parameters Among Study Groups

Parameter	Control	EoPE	LoPE	p value
Random blood glucose (mg/dL)	87.60±4.87	92.73±4.32	107.40±11.92	<0.001
AST (IU/L)	23.53±0.97	26.57±0.86	34.47±2.62	<0.001
ALT (IU/L)	16.60±0.50	24.87±0.73	30.20±1.30	<0.001
Urea (mg/dL)	25.20±0.55	26.00±0.64	25.47±0.94	<0.001
Creatinine (mg/dL)	0.64±0.03	0.75±0.01	0.75±0.02	<0.001
Total protein (g/dL)	6.75±0.13	5.20±0.36	6.81±0.12	<0.001

Values are Mean±SD. Kruskal-Wallis test. EoPE = Early-onset pre-eclampsia; LoPE = Late-onset pre-eclampsia.

Serum ELABELA Levels

In comparison to controls, serum ELABELA was considerably downregulated in both PE groups. In EoPE, LoPE, and controls, the mean serum ELABELA concentration was 7.0 ± 0.584 pg/mL (median 7), 11.5 ± 0.290 pg/mL (median 11.6), and 18.0 ± 0.585 pg/mL (median 18) (p=<0.001). A gradient of suppression with more severe placental illness was indicated by the decreased ELABELA levels in EoPE compared to LoPE (Table 3).

Table 3. Comparison of Serum ELABELA Among Study Groups

Variable	Control (n=30)	EoPE (n=30)	LoPE (n=30)	p value
Serum ELABELA (pg/mL) Mean ± SD; Median	18.0 ± 0.585; 18	7.0 ± 0.584; 7	11.5 ± 0.290; 11.6	<0.001

Kruskal-Wallis test. EoPE = Early-onset pre-eclampsia; LoPE = Late-onset pre-eclampsia.

Correlation of Serum ELABELA with Biochemical Parameters

Serum ELABELA showed a medium negative correlation with urea (r = –0.447, p <0.001) and a significant large negative correlation with creatinine (r = –0.695, p <0.001), according to Spearman correlation analysis. The whole correlation matrix is shown in Table 4.

Table 4. Spearman Correlation of Serum ELABELA with Biochemical Variables (n=90)

Biochemical Variable	Correlation Coefficient (r)	p value
Serum creatinine	–0.695	<0.001
Serum urea	–0.447	<0.001
Total protein	+0.557	<0.001

Correlation significant at 0.01 level (2-tailed).

Discussion

Serum ELABELA is markedly downregulated in both early-onset and late-onset pre-eclampsia, with the degree of suppression being more noticeable in EoPE, according to this study. These results support and add to the increasing amount of data linking the ELA-APJ axis to the pathophysiology of pregnancy-related hypertension diseases.

Placental angiogenesis, trophoblast invasion, nitric oxide-mediated vasodilatation, and cardiorenal fluid balance are all significantly influenced by the ELA-APJ system. Through paracrine effects on foetal endothelial cells and systemic effects on maternal vasculature, ELA—which is mostly expressed in villous cytotrophoblasts and syncytiotrophoblasts—promotes spiral artery remodelling and placental perfusion. Proteinuria, glomerular endotheliosis, and systemic hypertension are PE-like characteristics that appear in ELA-knockout mice and are reversible with exogenous ELA injection [6].

The different pathophysiology of the two phenotypes is consistent with our observation that EoPE had lower ELABELA than LoPE. Early placental malperfusion and more severe placental insufficiency, when disruption of ELA-mediated trophoblast invasion and angiogenesis would be most prominent, are the main causes of EoPE, and these differences are compounded by distinct patterns of innate immune activation reported between early- and late-onset disease [9]. According to Panaitescu et al., EoPE had lower ELABELA plasma concentrations than LoPE, which is in line with the higher cardiovascular impairment seen in early-onset illness [10]. This phenotype-specific gradient is corroborated by Amer Ali et al., who reported significantly lower serum Elabela in EoPE than in LoPE and healthy controls, with a cut-off value showing high sensitivity and specificity for distinguishing EoPE [8]. Zhou et al. similarly found reduced ELA levels, together with decreased placental ELA and APJ expression, in late-onset PE, and demonstrated in vitro that ELA promotes trophoblast invasion and proliferation through APJ signalling [11]. Yang et al., using an independent cohort and an immunochromatographic assay, confirmed markedly lower serum ELABELA in late-onset PE compared with normotensive pregnancy [12]. Khan et al. reported a parallel reduction in both apelin and ELABELA in preeclamptic women, suggesting that suppression of the wider apelinergic (apelin-ELA-APJ) axis, rather

than ELABELA alone, may accompany the disorder [13]. Most recently, Wang et al. showed that placental ELA was specifically reduced in early-onset preeclampsia and that silencing ELA impaired trophoblast invasion and migration via the MEK/ERK signalling pathway, providing direct mechanistic support for a phenotype-specific role of ELA in EoPE [14].

These findings are, however, not universal. A systematic review of the human apelinergic axis in preeclampsia by Georgiadou et al. similarly concluded that circulating ELABELA findings in early-onset disease are inconsistent across studies and that late-onset findings remain inconclusive [15]. Ma et al. measured first-trimester (10–14 week) serum ELA in a nested case-control cohort and found levels statistically unchanged between women who later developed gestational hypertension or PE and matched controls [16]. Similarly, Ozgen et al. reported no significant difference in first-trimester ELA between women who subsequently developed late-onset PE and those who remained normotensive [17].

A plausible explanation for this discrepancy is the timing of sampling relative to disease onset: ELABELA suppression may be a downstream consequence of established placental malperfusion and syncytiotrophoblast stress rather than an early antecedent change detectable before clinical disease is manifest. Consistent with this interpretation, studies reporting reduced ELABELA, including the present one, sampled at or after clinical diagnosis of PE, whereas the studies reporting unchanged levels sampled in the first trimester, well before disease onset. Differences in assay methodology (in-house ELISA kits with differing epitope specificity and reference ranges) and population characteristics may also contribute to the discrepant findings, and this should be considered when comparing absolute ELABELA concentrations across studies.

The well-documented glomerular endotheliosis brought on by sFLT1-mediated VEGF antagonism is consistent with the substantial negative association of ELABELA with serum creatinine ($r = –0.695$) and urea ($r = –0.447$), which indicates contemporaneous decline of renal function in pre-eclampsia. Although these correlations reached statistical significance, urea and creatinine values remained within normal clinical reference ranges across all groups; the observed differences are therefore of limited clinical importance and are best interpreted as a subclinical biochemical trend accompanying ELABELA suppression rather than evidence of overt renal impairment. On the other hand, the hypoproteinemia seen in EoPE—possibly as a result of increased urine protein loss and hemodilution—may be reflected in the positive association with total protein ($r = +0.557$), which reflects ELABELA suppression in this group.

Mechanistically, experimental evidence indicates that lower ELA levels may weaken APJ signalling, which can lead to decreased PI3K/Akt-eNOS activity, reduced trophoblast invasion, increased reactive oxygen species (consistent with the broader role of apelin/APJ disruption in vascular oxidative stress [18], impaired nitric oxide generation, and placental hypoxia, all of which are hallmarks of pre-eclampsia. As the present study is cross-sectional in design, it can demonstrate association but not causation; the observed correlations should not be interpreted as

evidence that ELABELA suppression directly causes these downstream changes in this cohort, and the intensity and phenotype of placental injury may, at most, be reflected in rather than caused by the degree of ELA suppression. Longitudinal studies with serial sampling are required to establish temporality and causal direction.

A further point relevant to prediction is the graded pattern seen across the three groups in this study: serum ELABELA fell progressively from controls (18.0 pg/mL) to LoPE (11.5 pg/mL) to EoPE (7.0 pg/mL) (Table 3), tracking the transition from normotensive pregnancy to increasingly severe disease. If this decline also occurs sequentially within the same pregnancy as it moves from a normotensive state toward pre-eclampsia—something only a longitudinal, serially-sampled design can confirm—a falling ELABELA trajectory, rather than a single threshold value, could serve as an antenatal warning sign that pre-eclampsia is developing. This would be consistent with the cut-off-based approach already demonstrated by Amer Ali et al., who showed that a low serum Elabela value predicted EoPE with 96.7% sensitivity and 93.3% specificity (8). These findings suggest that serum ELABELA may have a function in PE as a phenotype-stratifying biomarker. ELABELA may be useful in characterising the degree of vascular and placental damage throughout the PE spectrum, in contrast to sFLT1/PGF, which was mainly developed for early-onset illness prediction and ruling out PE [19]. Before clinical translation, however, validation in larger prospective, multi-centric cohorts with serial measures throughout gestational ages is crucial, alongside evaluation of whether ELABELA-informed risk stratification can meaningfully strengthen existing preventive strategies for pre-eclampsia [20].

Conclusion

In comparison to normotensive pregnancy, serum ELABELA is markedly suppressed in both early-onset and late-onset pre-eclampsia, with the early-onset phenotype showing the largest suppression. ELABELA's integration into the pathophysiological network of PE is seen in its correlation pattern with renal and metabolic markers. These findings support ELABELA as a promising circulating biomarker for the prediction and phenotypic categorisation of pre-eclampsia, though longitudinal studies are required to confirm its predictive value, as a causal or predictive role cannot be firmly established from a cross-sectional design. To ascertain its clinical relevance, more prospective, longitudinal trials with serial ELABELA readings, bigger sample sizes, and first-trimester screening cohorts are necessary.

Limitations

The cross-sectional design of this study prevents temporal assessment of ELABELA throughout gestation; the sample size is small (n=90); figures showing correlations could not be included in this manuscript; and the study was carried out at a single tertiary center in South India, which may limit generalisability.

Statements and Declarations

Ethics Approval

Ethical approval received from the Institutional Ethics Committee of Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

Informed Consent

Written informed consent was obtained from all participants.

Funding

No external funding was received for this study.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

MAV Design of the study, literature search, data acquisition, manuscript writing and review. SP Literature search, Data analysis, Manuscript review and editing. TU Conceptualisation, manuscript review and editing. MAV acted as the corresponding author for this study.

References

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1–7. DOI: 10.1016/j.ejogrb.2013.05.005
2. Steegers EA, et al. Pre-eclampsia. Lancet. 2010;376(9741):631–44. DOI: 10.1016/S0140-6736(10)60279-6
3. Brown MA, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2018;13:291–310. DOI: 10.1016/j.preghy.2018.05.004
4. Sharma M, Prabhavalkar KS, Bhatt LK. Elabela Peptide: An Emerging Target in Therapeutics. Curr Drug Targets. 2022;23(13):1304–18. DOI: 10.2174/1389450123666220826160123
5. Liet B, Nys N, Siegfried G. Elabela/toddler: New peptide with a promising future in cancer diagnostic and therapy. Biochim Biophys Acta Mol Cell Res. 2021;1868(4):119065. DOI: 10.1016/j.bbamcr.2021.119065
6. Ho L, van Dijk M, Chye STJ, et al. ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice. Science. 2017;357(6352):707–13. DOI: 10.1126/science.aam6607
7. Magee LA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2022;27:148–69. DOI: 10.1016/j.preghy.2021.10.008
8. Amer Ali E, Nori W, Salman AF, Al-Rawi TSS, Hameed BH, Al-Ani RM. Elabela is a reliable biomarker for predicting early onset preeclampsia: A comparative study. World J Clin Cases. 2023;11(17):3993–4002. DOI: 10.12998/wjcc.v11.i17.3993
9. Aneman I, Pienaar D, Suvakov S, et al. Mechanisms of Key Innate Immune Cells in Early- and Late-Onset Preeclampsia. Front Immunol. 2020;11:1864. DOI: 10.3389/fimmu.2020.01864
10. Panaitescu B, Romero R, Tarca AL, et al. ELABELA plasma concentrations are reduced in women with late-onset preeclampsia. J Matern Fetal Neonatal Med. 2020;33(5):753–62.

11. Zhou L, Sun H, Cheng R, Fan X, Lai S, Deng C. ELABELA, as a potential diagnostic biomarker of preeclampsia, regulates abnormally shallow placentation via APJ. Am J Physiol Endocrinol Metab. 2019;316(5):E773–81. DOI: 10.1152/ajpendo.00383.2018
12. Yang N, Liu K, Zhang W, et al. Predicting late-onset preeclampsia by detecting ELABELA content using an immunochromatographic colloidal gold test strip. J Clin Hypertens (Greenwich). 2023;25(10):932–42. DOI: 10.1111/jch.14724
13. Khan H, Uraneb S, Mushtaq R, Bano F. Effect of serum apelin and elabela levels in pregnancies complicated with preeclampsia in association to BMI, CRP and parity. Pak J Pharm Sci. 2023;36(3):749–53.
14. Wang L, Wang X, He N, Yang L, Zou Y, Weng Z, Guo L. ELABELA targets the MEK/ERK axis to enhance trophoblast invasion in early-onset preeclampsia. Sci Rep. 2025;15(1):29357. DOI: 10.1038/s41598-025-15533-4
15. Georgiadou D, Afink GB, van Dijk M. The apelinergic-axis in human preeclamptic pregnancies: A systematic review. Pregnancy Hypertens. 2019;17:148–157. DOI: 10.1016/j.preghy.2019.06.002
16. Ma S, Guo C, Zhang J, Long S, Tan H, You Y. Association between ELABELA Serum Concentrations in First Trimester and Pregnancy-Induced Hypertension. Biomed Res Int. 2020;2020:2051701. DOI: 10.1155/2020/2051701
17. Ozgen G, Aydin GA, Ayvaci H. Predictive Role of First-trimester ELABELA Levels for Late-onset Preeclampsia. J Coll Physicians Surg Pak. 2021;31(8):916–20. DOI: 10.29271/jcpsp.2021.08.916
18. Zhou Q, Cao J, Chen L. Apelin/APJ system: A novel therapeutic target for oxidative stress-related inflammatory diseases (Review). Int J Mol Med. 2016;37(5):1159–69. DOI: 10.3892/ijmm.2016.2544
19. Zeisler H, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374(1):13–22. DOI: 10.1056/NEJMoa1414838
20. Rahnemaei FA, Fashami MA, Abdi F, Abbasi M. Factors effective in the prevention of Preeclampsia: A systematic review. Taiwan J Obstet Gynecol. 2020;59(2):173–82. DOI: 10.1016/j.tjog.2020.01.003

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ORIGINAL ARTICLE

Effectiveness, Safety, and Quality of Life among Patients with Moderate to Severe Acne on Oral Doxycycline versus Oral Azithromycin with Add-on Topical Retinoids: A Prospective Observational Study in a Tertiary Care Centre

Arjun Gowda T S,[1,*] Nagabushan H,[1] Deepadarshan K[2] and Chandan N G[1]

[1]*Department of Pharmacology, Mandya Institute of Medical Sciences (MIMS), Mandya, Karnataka, India*
[2]*Department of Dermatology, Mandya Institute of Medical Sciences (MIMS), Mandya, Karnataka, India*

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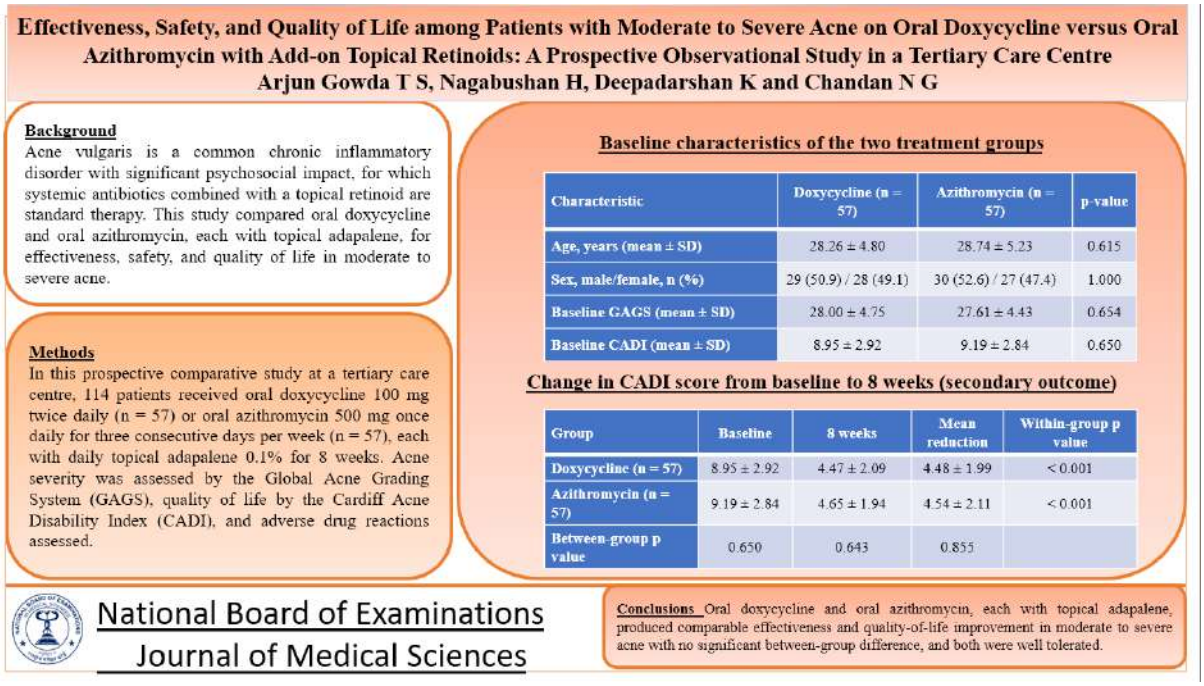
Abstract

Background: Acne vulgaris is a common chronic inflammatory disorder with significant psychosocial impact, for which systemic antibiotics combined with a topical retinoid are standard therapy. This study compared oral doxycycline and oral azithromycin, each with topical adapalene, for effectiveness, safety, and quality of life in moderate to severe acne. **Methods:** In this prospective comparative study at a tertiary care centre, 114 patients received oral doxycycline 100 mg twice daily (n = 57) or oral azithromycin 500 mg once daily for three consecutive days per week (n = 57), each with daily topical adapalene 0.1% for 8 weeks. Acne severity was assessed by the Global Acne Grading System (GAGS), quality of life by the Cardiff Acne Disability Index (CADI), and adverse drug reactions assessed. **Results:** Significant reductions in GAGS scores (doxycycline 28.00 to 9.93; azithromycin 27.61 to 10.07; $p < 0.001$) and CADI scores (doxycycline 8.95 to 4.47; azithromycin 9.19 to 4.65; $p < 0.001$) were seen in both groups, with no significant between-group difference in GAGS ($p = 0.438$) or CADI ($p = 0.855$) reduction. Adverse drug reactions were mild, self-limiting, and related to gastrointestinal tract, with no significant difference between groups (doxycycline 12.3%, azithromycin 7.0%; $p = 0.53$). **Conclusion:** Oral doxycycline and oral azithromycin, each with topical adapalene, produced comparable effectiveness and quality-of-life improvement in moderate to severe acne with no significant between-group difference, and both were well tolerated. The choice between them can be individualised.

Keywords: Acne vulgaris, Doxycycline, Azithromycin, Adapalene, Quality of life, Global Acne Grading System

*Corresponding Author: Arjun Gowda T S
Email: arjuntsgowda@gmail.com

Graphical Abstract



Introduction

Acne vulgaris is a chronic inflammatory disorder which involves the pilosebaceous unit. It is clinically characterised by comedones, papules, pustules, nodules, and scarring in more severe cases [1,2]. It is among the most common conditions in dermatological practice, ranking among the three problems most frequently encountered in primary and secondary care. It typically begins around 12 to 14 years of age and affects the majority of adolescents and young adults of both sexes [1]. Although the condition is not life-threatening, it can impose a substantial physical and psychosocial burden which includes poor self-image, depression, anxiety, and sometimes, permanent disfiguring or scarring [1,2]. Its aetiology is multifactorial and the pathogenic factors involved are follicular hyperkeratinization, colonization by Cutibacterium acnes (formerly Propionibacterium acnes), increased sebum production, and a complex inflammatory response [2,3].

A reliable grading of acne severity is needed for guiding treatment decisions, monitoring response to therapy, and also to enable comparison across studies. The Global Acne Grading System (GAGS) is a reliable, easy-to-use tool that is widely applied for this purpose [4]. The GAGS classifies acne by scores as mild (1–18), moderate (19–30), severe (31–38), or very severe (>39). It is simple, accurate, and reproducible, with low inter- and intra-rater variability [5].

Topical adapalene 0.1% has a positive influence on quality of life and is effective when used alone or in combination [6]. Systemic antibiotics are combined with topical retinoids to limit bacterial resistance in treatment of moderate to severe acne [7]. Efficacy, adverse-effect profile, and resistance considerations guide the choice of antibiotics. The most commonly used

systemic antibiotics are doxycycline and azithromycin.

Doxycycline acts by inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit and also has anti-inflammatory effects, including inhibition of chemotaxis and metalloproteinase activity. However, it is associated with gastrointestinal disturbance, phototoxicity and is contraindicated in pregnancy [2]. Azithromycin binds to the 50S ribosomal subunit and, due to its extensive tissue distribution with a long elimination half-life of approximately three days, it can be administered in intermittent "pulse" regimens. This shortens treatment and improves patient compliance, with a favourable tolerability profile [8,9].

The disease-specific quality-of-life scales are used to capture the patient's experience because the impact of acne extends beyond visible lesions. The Cardiff Acne Disability Index (CADI) is a short questionnaire that has been developed for teenagers and adults. It has an established validity, internal consistency, reliability, and responsiveness to modification [10]. The CADI's measure of quality-of-life impairment corresponds with clinical severity and has a correlation with the GAGS score, thereby highlighting the importance of evaluating both severity and quality of life simultaneously [11].

The results from previous studies directly comparing the two antibiotics remain inconsistent. A meta-analysis found azithromycin pulse therapy equivalent in efficacy to daily doxycycline in moderate to severe acne, with fewer adverse-event discontinuations [12]. Some studies favour doxycycline for overall lesion clearance [13], whereas several reports found azithromycin to be comparable or modestly superior with a favourable safety profile [9,14,15]. Majority of the studies have assessed the antibiotics alone, without the topical retinoid. Few studies have simultaneously assessed safety and patient-reported quality of life in the same cohort, which is crucial for a disorder whose burden is as much psychological as physical [1,9,15].

Additional real-world evidence directly comparing these regimens is needed to support individualised treatment selection [1]. The choice between the two antibiotics may therefore be guided by dosing convenience, tolerability, contraindications, and antibiotic stewardship [2,8]. This study was therefore conducted to compare oral doxycycline and oral azithromycin, each with an add-on topical retinoid to evaluate effectiveness, safety, and quality of life simultaneously in a tertiary care setting.

Aims and Objectives

The primary objective of this study was to compare the clinical effectiveness of oral doxycycline and oral azithromycin with an add-on topical retinoid for each, in patients with moderate to severe acne vulgaris.

The secondary objectives were to compare the safety between the two regimens and to evaluate patient's quality of life.

Materials and Methods

This was a prospective, observational, comparative study conducted in the Departments of Pharmacology and Dermatology at Mandya Institute of Medical Sciences (MIMS), Mandya, India. The study was conducted from February 2026 to June 2026, after approval from the Institutional Ethics Committee. Adults aged 18 years or older

of either sex with a clinical diagnosis of moderate to severe acne vulgaris, graded using the GAGS, who provided informed consent were eligible for inclusion. Patients were divided into two groups, group A received oral doxycycline 100 mg twice daily and group B received oral azithromycin 500 mg once daily for three consecutive days per week with an add-on daily topical adapalene 0.1% gel for each. Patients with mild acne not requiring systemic antibiotics, pregnant or lactating women, and patients who were on hormonal therapy or contraceptives were excluded. The sample size of 114 (57 per group) was calculated using the formula for the comparison of two means, taking a 5% level of significance, 80% power, and an expected between-group difference of 1.63 in mean GAGS reduction derived from a previous comparative study [14].

At enrolment, sociodemographic details, clinical history, and treatment history were recorded on a semi-structured proforma, and baseline acne severity and quality of life were assessed using the GAGS and the CADI. Both scales were used at the end of eight weeks, and any adverse drug reactions spontaneously reported by patients during the treatment period were documented. The severity of each reaction was graded using the Modified Hartwig and Siegel scale [16], and its causal association with the study drug was assessed using the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) causality assessment scale [17]. The change in GAGS score from baseline to eight weeks served as the primary outcome, while the change in CADI score and the nature and frequency of adverse drug reactions were the secondary outcomes.

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS version 31. Categorical variables such as sex were assessed as frequencies and percentages, and continuous variables such as age, GAGS score, and CADI score as mean ± standard deviation. The changes within each group were assessed using the paired t-test and the changes between the two groups using the unpaired t-test. The frequency of adverse drug reactions between the two groups was assessed using Fisher's exact test. A p-value of < 0.05 was considered statistically significant. Analysis of covariance (ANCOVA), with the baseline score as a covariate, was used to compare eight-week GAGS and CADI scores between groups, yielding adjusted mean differences with 95% confidence intervals.

Results

Baseline characteristics of the study population

A total of 121 patients were enrolled with 114 patients completing the study and 7 were lost to follow-up. The overall mean age was 28.5 ± 5.0 years (range 18–42 years), and the two groups were comparable in age (doxycycline group 28.2 ± 4.8 years vs azithromycin group 28.7 ± 5.2 years; $p = 0.615$). The sex distribution was also similar, with males comprising 29 (50.9%) of the doxycycline group and 30 (52.6%) of the azithromycin group ($p = 1.000$). At baseline, acne severity and quality-of-life scores did not differ significantly between the groups, confirming that the two groups were comparable (baseline GAGS $p = 0.654$; baseline CADI $p = 0.650$) (Table 1).

Table 1. Baseline characteristics of the two treatment groups

Characteristic	Doxycycline (n = 57)	Azithromycin (n = 57)	p-value
Age, years (mean ± SD)	28.26 ± 4.80	28.74 ± 5.23	0.615
Sex, male/female, n (%)	29 (50.9) / 28 (49.1)	30 (52.6) / 27 (47.4)	1.000
Baseline GAGS (mean ± SD)	28.00 ± 4.75	27.61 ± 4.43	0.654
Baseline CADI (mean ± SD)	8.95 ± 2.92	9.19 ± 2.84	0.650

Effect on acne severity

The mean GAGS score significantly decreased in both groups between baseline and eight weeks. The score decreased from 28.00 ± 4.75 to 9.93 ± 2.88 in the doxycycline group and from 27.61 ± 4.43 to 10.07 ± 2.16 in the azithromycin group. The reductions of scores within each group were statistically significant ($p < 0.001$). The mean reduction in GAGS score was 18.07 ± 3.80 with doxycycline and 17.54 ± 3.41 with azithromycin. The between-group difference in GAGS reduction was not statistically significant (mean difference 0.53; 95% CI −0.81 to 1.87; $p = 0.438$). Eight-week GAGS scores were also comparable between the two groups ($p = 0.769$). After adjustment for baseline severity using ANCOVA, the between-group difference at eight weeks remained non-significant (adjusted mean difference −0.27; 95% CI −1.02 to 0.47; $p = 0.468$) (Table 2).

Table 2. Change in GAGS score from baseline to 8 weeks

Group	Baseline	8 weeks	Mean reduction	Within-group p value
Doxycycline (n = 57)	28.00 ± 4.75	9.93 ± 2.88	18.07 ± 3.80	< 0.001
Azithromycin (n = 57)	27.61 ± 4.43	10.07 ± 2.16	17.54 ± 3.41	< 0.001
Between-group p value	0.654	0.769	0.438	

GAGS, Global Acne Grading System

Effect on quality of life

The patients' quality of life, measured by the CADI, improved significantly in both groups. The mean CADI score decreased from 8.95 ± 2.92 to 4.47 ± 2.09 in the doxycycline group and from 9.19 ± 2.84 to 4.65 ± 1.94 in the azithromycin group. The reduction of scores within the group was statistically significant ($p < 0.001$). The mean reduction in CADI scores was 4.48 ± 1.99 with doxycycline and 4.54 ± 2.11 with azithromycin, a difference that was not statistically significant between the groups (mean difference −0.07; 95% CI −0.83 to 0.69; $p = 0.855$). After adjustment for the baseline CADI score using ANCOVA, the between-group difference at eight weeks remained non-significant (adjusted mean difference −0.05; 95% CI −0.59 to 0.48; $p = 0.840$) (Table 3).

Table 3. Change in CADI score from baseline to 8 weeks (secondary outcome)

Group	Baseline	8 weeks	Mean reduction	Within-group p value
Doxycycline (n = 57)	8.95 ± 2.92	4.47 ± 2.09	4.48 ± 1.99	< 0.001
Azithromycin (n = 57)	9.19 ± 2.84	4.65 ± 1.94	4.54 ± 2.11	< 0.001
Between-group p value	0.650	0.643	0.855	

CADI, Cardiff Acne Disability Index

Adverse drug reactions

Adverse drug reactions were infrequent, self-limiting, and related to gastrointestinal tract in both groups, and none required discontinuation of treatment. As shown in Table 4, reactions were reported in 7 of 57 patients (12.3%) receiving doxycycline and in 4 of 57 patients (7.0%) receiving azithromycin. In the doxycycline group these comprised epigastric pain in 4 patients and nausea in 3 patients, whereas in the azithromycin group they comprised diarrhoea in 2 patients and nausea in 2 patients. All reactions resolved spontaneously without specific treatment. All reactions were graded as mild on the Modified Hartwig and Siegel severity scale, and their causal relationship to the study drug was categorised as "possible" on the WHO–UMC causality assessment scale. The difference in the overall frequency of adverse drug reactions between the two groups was not statistically significant (p = 0.53).

Table 4. Adverse drug reactions by group

Adverse reaction	Doxycycline (n = 57)	Azithromycin (n = 57)
Epigastric pain	4	0
Nausea	3	2
Diarrhoea	0	2
Total, n (%)	7 (12.3)	4 (7.0)

Discussion

This is a prospective, observational, comparative study which was conducted in a tertiary care setting to compare oral doxycycline and oral azithromycin, each combined with an add-on topical adapalene, in patients with moderate to severe acne vulgaris. Both groups showed significant and comparable reductions in acne severity. There was no statistically significant difference between the groups. This is in agreement with the meta-analysis by Kim et al., which concluded that azithromycin pulse therapy is equivalent to daily doxycycline in moderate to severe acne [12], and also with Ahsan et al. and Gurung et al., who reported the two drugs to be similarly efficacious [9,18]. Conversely, some studies have found that azithromycin has a better efficacy than doxycycline, an earlier onset of action, or fewer adverse effects with pulse therapy [14,19,20]. These discrepancies are most likely due to differences in study design,

dosing schedules, concomitant topical therapy, outcome measures, and follow-up duration. In our study, both groups received topical adapalene, in keeping with the principle that retinoids form the core of acne therapy and should be used in combination with systemic antibiotics [2,6,7]. Therefore, the present results should thus be interpreted as a comparison of two systemic antibiotics with add-on daily topical adapalene rather than of the antibiotics in isolation.

Adverse drug reactions were related to gastrointestinal tract and were less frequent with azithromycin than with doxycycline, but this difference was not statistically significant. A tolerability advantage for azithromycin has been reported in several comparative studies [8,9,12,19]. The higher frequency of adverse drug reactions in the doxycycline group, comprising nausea and epigastric pain, is consistent with the recognised potential of doxycycline to cause gastrointestinal disturbance [2].

The patient's quality of life which was assessed with the CADI scale showed significant improvement in both groups. This corresponded with the clinical response and reflects the close relationship between acne severity and quality-of-life impairment reported previously [11]. A similar concurrent improvement in quality of life was reported by Mekala et al., who evaluated it alongside efficacy and safety in a comparison of the two antibiotics [15]. The baseline quality-of-life impairment observed in the patients is consistent with the findings of Pradhan et al., who reported that acne impairs self-image and quality of life among patients attending a dermatology outpatient department [21]. As the burden of acne is as much psychological as physical [1], the finding that both regimens relieve this burden equally is clinically meaningful. This supports the inclusion of patient-reported outcomes, rather than lesion-based measures alone, in the assessment of acne therapy. In summary, these findings suggest that, when systemic antibiotics were combined with topical adapalene, the choice of systemic antibiotic has limited influence on the overall clinical and quality-of-life response in moderate to severe acne vulgaris.

Limitations

The study was conducted at a single centre using convenience sampling, which may limit generalisability. The eight-week duration with a single end-of-treatment assessment precludes conclusions about relapse and the durability of the quality-of-life benefit.

Conclusions

In moderate to severe acne vulgaris, oral doxycycline and oral azithromycin, each combined with topical adapalene, produced comparable improvements in acne severity and quality of life, with no statistically significant difference between them, and both were well tolerated. Therefore, the choice between the two regimens can be individualised on the basis of tolerability, dosing convenience, contraindications, and antibiotic stewardship. Larger randomised trials with longer follow-up are needed to confirm these findings and to assess relapse and the durability of the quality-of-life benefit.

Statements and Declarations

Conflicts of Interest

The authors declare that they do not have conflict of interest.

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References

1. Mahmood NF, Shipman AR. The age-old problem of acne. Int J Womens Dermatol. 2017;3(1):71–76.
2. Reynolds RV, Yeung H, Cheng CE, Cook-Bolden F, Desai SR, Druby KM, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2024;90(5):1006.e1–1006.e30.
3. US Food and Drug Administration, Center for Drug Evaluation and Research. Acne vulgaris: establishing effectiveness of drugs intended for treatment: guidance for industry. Silver Spring (MD): FDA; 2018.
4. Alsulaimani H, Kokandi A, Khawandanh S, Hamad R. Severity of acne vulgaris: comparison of two assessment methods. Clin Cosmet Investig Dermatol. 2020;13:711–716.
5. Bae IH, Kwak JH, Na CH, Kim MS, Shin BS, Choi H. A comprehensive review of the acne grading scale in 2023. Ann Dermatol. 2024;36(2):65–73.
6. Parikh NR, Sood SV, Rana D, Chaudhary R, Malhotra SD. Evaluation of adapalene alone versus combination therapy of adapalene with benzoyl peroxide and adapalene with clindamycin in treatment of acne vulgaris: a prospective, observational study. Int J Res Dermatol. 2019;5(4):831–838.
7. Madnani N, Saraswat A, Nott A, Jakhar D, Gupta LK, Kohli M, et al. PRACT-India: practical recommendations on acne care and medical treatment in India—a modified Delphi consensus. Antibiotics (Basel). 2025;14(8):844.
8. Sadhana C, Muthiah NS. Azithromycin pulse therapy with oral doxycycline in the treatment of acne vulgaris, a randomized group study. J Pharm Res Int. 2021;33(23B):1–9.
9. Ahsan M, Ranjan R, Chandra S, Mayank K. Comparison of efficacy and safety of oral azithromycin and oral doxycycline in acne vulgaris. Int J Basic Clin Pharmacol. 2019;8(5):913–917.
10. Abdelrazik YT, Ali FM, Salek MS, Finlay AY. Clinical experience and psychometric properties of the Cardiff Acne Disability Index (CADI). Br J Dermatol. 2021;185(4):711–724.
11. Madhuri VAV, Reddy N, Kunjaram G, Thomas J. Clinico-demographical profile and correlation of Cardiff Acne Disability Index score (CADI) and Global Acne Grading System score (GAGS) in patients with acne vulgaris in a tertiary health care centre. IJCED. 2025;11(1):114–120.
12. Kim JE, Park AY, Lee SY, Park YL, Whang KU, Kim HJ. Comparison of the efficacy of azithromycin versus doxycycline in acne vulgaris: a meta-analysis of randomized controlled trials. Ann Dermatol. 2018;30(4):417–426.
13. Zaman S, Sumsuzzoha SM, Sattar MA, Das AK. Efficacy of azithromycin and doxycycline in the treatment of acne vulgaris: a single center study in Bangladesh. Sch J Appl Med Sci. 2022;10(12):2216–2220.
14. Raees T, Ali A, Ahmed S, Tayyab M, Munir A, Lodhi S. Unmasking acne: azithromycin edges out doxycycline

in randomized trial at a tertiary care centre. J Islamabad Med Dental Coll. 2024;13(2):257–264.

15. Mekala P, Somani R, Pingali U, Panditharadhyula VS, Khan I. Evaluation of efficacy and safety of azithromycin and doxycycline in treatment of acne vulgaris with different levels of serum testosterone: a prospective, randomized, controlled, cost-effective, comparative study. Asian J Pharm Clin Res. 2024;17(12):181–185.
16. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49(9):2229–2232.
17. World Health Organization–Uppsala Monitoring Centre. The use of the WHO–UMC system for standardised case causality assessment. Uppsala: The Uppsala Monitoring Centre; 2013.
18. Gurung S, Patil N, Rao K, Chaudhary G, Nazeer M, Varghese GM, et al. A comparative study on efficacy of azithromycin and doxycycline in the treatment of acne vulgaris at a tertiary care centre. Biomed Pharmacol J. 2020;13(3):1451–1455.
19. Kishore Kumar V. A comparative study on the efficacy and safety of oral azithromycin pulse versus doxycycline daily in the treatment of acne vulgaris. J Evid Based Med Healthc. 2017;4(90):5410–5413.
20. Sultan N, Dar M, Rehman Z. To compare the clinical effectiveness of azithromycin vs doxycycline on the first follow-up visit of acne vulgaris patients. J Dermatol Cosmetol. 2020;4(3):72–76.
21. Pradhan M, Jha CB, Rai D. The impact of acne on the quality of life of patients attending the dermatology outpatient department at Nobel Medical College Teaching Hospital. J Nobel Med Coll. 2018;7(1):45–49.

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ORIGINAL ARTICLE

Immunohistochemical Expression of Vascular Endothelial Growth Factor in Invasive Breast Carcinoma and Its Correlation with Clinicopathological Parameters

B Senthil,[1,*] P Gowri[2] and G Veera Raghavan[2]

[1]*Assistant Professor, Department of Pathology, Government Krishnagiri Medical College and Hospital, Krishnagiri, Tamilnadu*
[2]*Assistant Professor, Department of Pathology, Government Kilpauk Medical College and Hospital, Chennai, Tamilnadu*

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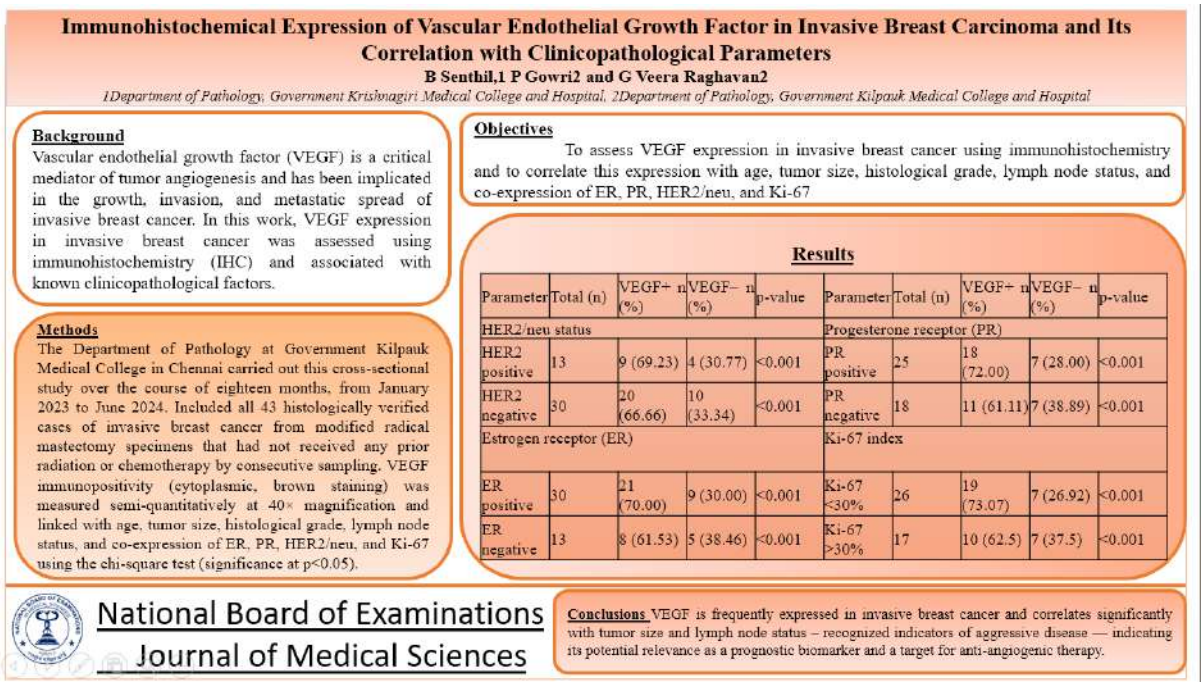
Abstract

Background: Vascular endothelial growth factor (VEGF) is a critical mediator of tumor angiogenesis and has been implicated in the growth, invasion, and metastatic spread of invasive breast cancer. In this work, VEGF expression in invasive breast cancer was assessed using immunohistochemistry (IHC) and associated with known clinicopathological factors. **Methods:** The Department of Pathology at Government Kilpauk Medical College in Chennai carried out this cross-sectional study over the course of eighteen months, from January 2023 to June 2024. Included all 43 histologically verified cases of invasive breast cancer from modified radical mastectomy specimens that had not received any prior radiation or chemotherapy by consecutive sampling. VEGF immunopositivity (cytoplasmic, brown staining) was measured semi-quantitatively at 40× magnification and linked with age, tumor size, histological grade, lymph node status, and co-expression of ER, PR, HER2/neu, and Ki-67 using the chi-square test (significance at $p<0.05$). **Results:** VEGF positive was reported in 29/43 instances (67.44%; $p<0.001$). Positivity increased with advancing age (100% in 61–70 years) and bigger tumor size (100% in tumors >5 cm; $p<0.001$), and was substantially linked with lymph node status and HER2/neu, ER, and PR co-expression (all $p<0.001$). VEGF expression and histological grade did not significantly correlate ($p>0.05$). **Conclusion:** VEGF is frequently expressed in invasive breast cancer and correlates significantly with tumor size and lymph node status – recognized indicators of aggressive disease — indicating its potential relevance as a prognostic biomarker and a target for anti-angiogenic therapy.

Keywords: Vascular endothelial growth factor, Invasive breast carcinoma, Immunohistochemistry, Angiogenesis, Prognostic marker

*Corresponding Author: B Senthil
Email: drsenthil03@gmail.com

Graphical Abstract



Introduction

Breast carcinoma is the most frequent malignancy among women globally and accounts for nearly one-fourth of all female cancers [1]. Hematogenous metastasis and tumor growth beyond a few millimeters depend on tumor angiogenesis, which is the creation of new blood vessels from pre-existing vasculature [2]. This process is primarily driven by vascular endothelial growth factor (VEGF), which is found on chromosome 6p12. VEGF enhances vascular permeability, stimulates endothelial proliferation, and accelerates extracellular matrix disintegration, all of which enable tumor invasion [3].

An increasing body of evidence links VEGF expression to conventional prognostic factors in breast cancer, including tumor size, histological grade, lymph node status, and hormone receptor (ER/PR) and HER2/neu status, however findings across studies remain inconsistent. Characterizing VEGF expression and its clinicopathological correlates in a local population is important for both diagnosis and treatment because of its prominent role in the angiogenic cascade and its development as a target for anti-angiogenic therapy.

The purpose of this study was to assess VEGF expression in invasive breast cancer using immunohistochemistry and to correlate this expression with age, tumor size, histological grade, lymph node status, and co-expression of ER, PR, HER2/neu, and Ki-67.

Materials and Methods

Study design and setting

This cross-sectional study was conducted in the Department of Pathology, Government Kilpauk Medical College, Chennai, over a period of 18 months (January 2023 to June 2024).

Study population

Histologically confirmed invasive breast carcinoma (NOS) from modified radical mastectomy (MRM) specimens. Cases that had received chemotherapy or radiotherapy prior to surgery, excision/tru-cut biopsies, and poorly fixed specimens were excluded.

Sample size and Sampling technique

Universal sampling was employed. All 43 cases of histologically confirmed invasive breast carcinoma that fulfilled the predefined inclusion and exclusion criteria during the study period (January 2023 to June 2024) were consecutive included in the study.

Methods

Specimens were fixed in 10% formalin, processed, and paraffin-embedded; 4 µm sections were mounted on silanized slides and stained with haematoxylin and eosin. Clinicopathological parameters — age, tumor size, focality, histological type and grade, lymph node status, lymphovascular and perineural invasion — were recorded, along with IHC status for ER, PR, HER2/neu, and Ki-67. VEGF immunohistochemistry was performed on representative blocks; immunopositivity was cytoplasmic and brown, assessed as the percentage of positive cells among 100 malignant cells at 40× magnification, and scored using a standardized 0–4+ scale. [3] After antigen retrieval and incubation with the primary antibody, immunoreactivity was visualized using a DAB detection system. Appropriate positive and negative controls were included in each staining run to ensure staining quality.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using appropriate statistical software. Associations between VEGF expression and clinicopathological variables were primarily assessed using the Chi-square test. The assumptions for the Chi-square test were verified prior to analysis. Where expected cell counts were less than five, Fisher's exact test was used as appropriate**.** A *p*-value of <0.05 was considered statistically significant.

Results

Of the 43 cases of invasive breast carcinoma studied, VEGF positive expression was observed in 29 cases (67.44%) and negative expression in 14 cases (32.56%) (Table 1).

Table 1. Overall VEGF expression in invasive breast carcinoma (n=43)

Total cases (n)	VEGF positive n (%)	VEGF negative n (%)
43	29 (67.44%)	14 (32.56%)

VEGF positive exhibited a growing tendency with advancing age, from 66.66% in the 31–40-year group to 100% in the 61–70-year group. Positivity also increased with tumor size, reaching 100% in tumors larger than 5 cm (T3), compared with 62.85–66.67% in smaller tumors (all $p<0.001$). No statistically significant correlation was discovered between VEGF expression and histological grade ($p>0.05$), but Grade I tumors showed the highest positive (100%). VEGF expression was

substantially linked with lymph node status, HER2/neu status, ER status, PR status, and Ki-67 index (all p<0.001), with a consistently greater proportion of VEGF positivity across both positive and negative subgroups of each marker (Table 2).

Table 2. Correlation of VEGF expression with clinicopathological parameters

Parameter	Total (n)	VEGF+ n (%)	VEGF– n (%)	p-value
Age (years)				
31–40	3	2 (66.66)	1 (33.34)	<0.05*
41–50	14	8 (57.14)	6 (42.86)	
51–60	22	15 (68.18)	7 (31.82)	
61–70	4	4 (100.00)	0 (0.00)	
Tumor size				
T1 (≤2 cm)	3	2 (66.67)	1 (33.33)	<0.001*
T2 (2–5 cm)	35	22 (62.85)	13 (37.15)	
T3 (>5 cm)	5	5 (100.00)	0 (0.00)	
Tumor grade				
Grade I	3	3 (100.00)	0 (0.00)	>0.05*
Grade II	29	19 (65.52)	10 (34.48)	
Grade III	11	7 (63.64)	4 (36.36)	
Lymph node status				
LN positive	24	16 (66.66)	8 (33.33)	<0.001*
LN negative	19	13 (68.42)	6 (31.57)	
HER2/neu status				
HER2 positive	13	9 (69.23)	4 (30.77)	<0.001*
HER2 negative	30	20 (66.66)	10 (33.34)	
Estrogen receptor (ER)				
ER positive	30	21 (70.00)	9 (30.00)	<0.001*
ER negative	13	8 (61.53)	5 (38.46)	
Progesterone receptor (PR)				
PR positive	25	18 (72.00)	7 (28.00)	<0.001*
PR negative	18	11 (61.11)	7 (38.89)	
Ki-67 index				
Ki-67 <30%	26	19 (73.07)	7 (26.92)	<0.001*
Ki-67 >30%	17	10 (62.5)	7 (37.5)	

*p-value<0.05-Statistically significant

Discussion

Tumor angiogenesis, progression, and metastasis are all significantly influenced by VEGF, and its expression has been connected to known prognostic factors in breast cancer, including tumor size, tumor grade, lymph node status, and hormone receptor and HER2 status. The conclusion that VEGF expression is common in invasive breast cancer is supported by the fact that 67.44% of patients in the current investigation had VEGF positivity, which is similar to the 59.62% positivity reported by Almumen et al. [3].

In contrast to the results of A. Pa et al., who found no correlation between chronological age and VEGF levels, VEGF positive rose with age in this cohort, reaching 100% in the 61–70-year group, suggesting a potential age-related trend in angiogenic activity. A substantial positive connection was also seen between tumor size and VEGF expression, with all tumors larger than 5 cm showing positivity — a trend largely comparable with Almumen et al., who also reported the highest VEGF positivity in the largest tumor-size category [3]. This lends credence to the idea that tumor growth is accompanied by an increase in angiogenic drive.

In contrast, no significant association was found between VEGF expression and histological grade in this study, in agreement with the view that other biological factors may more strongly influence VEGF expression in invasive ductal carcinoma than grade alone; this differs from Shera et al., who reported increasing VEGF levels with higher tumor grade and stage [7].

VEGF expression was substantially related with lymph node status, being high in both LN-positive (66.66%) and LN-negative (68.42%) groups, demonstrating that VEGF elevation is not confined to node-positive illness alone. Similarly, high VEGF positivity was observed across both HER2/neu-positive and -negative groups, comparable to the findings of Jannat Shakila et al. and Almumen et al. [3,8]. Co-expression analysis with hormone receptors showed higher VEGF positivity in both ER-positive (70%) and PR-positive (72%) cases, in keeping with the findings of Jannat Shakila et al. and Konecny et al., although Almumen et al. reported the reverse trend (higher positivity in ER-negative tumors), indicating that this relationship may vary across populations [3,8,9]. VEGF positivity was also higher in tumors with lower Ki-67 proliferation index (<30%), suggesting VEGF up-regulation may occur independent of proliferative activity in this group.

Although statistically significant associations were observed between VEGF expression and certain clinicopathological parameters, including lymph node status and HER2/neu expression, the absolute differences in VEGF positivity between some comparison groups were relatively small. Therefore, these findings should be interpreted with caution, as statistical significance does not necessarily equate to clinical significance. Larger studies with adequate statistical power and longitudinal follow-up are required to determine the true clinical relevance and prognostic impact of these associations.

Collectively, these data reaffirm VEGF as a marker intimately connected to tumor volume and nodal involvement — both established indications of aggressive illness — but its relationship with grade and proliferation markers is more variable among studies.

Conclusion

VEGF expression was observed in a majority of invasive breast carcinoma cases and demonstrated significant associations with tumor size, lymph node status, and selected clinicopathological parameters. These findings support the potential role of VEGF as a biomarker of tumor angiogenesis and disease aggressiveness in invasive breast carcinoma. Further large-scale prospective studies are warranted to validate these observations and to better define the prognostic and therapeutic relevance of VEGF expression in routine clinical practice.

Limitations

This study has certain limitations that should be considered while interpreting the findings. First, it was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the results to other populations. Second, the cross-sectional study design precludes assessment of temporal relationships and does not permit evaluation of the prognostic significance of VEGF expression with respect to disease recurrence, disease-free survival, or overall survival. Third, owing to the limited sample size, multivariable analysis was not performed; therefore, the independent prognostic value of VEGF after adjusting for potential confounding clinicopathological variables could not be established. Finally, VEGF immunohistochemical staining was not evaluated by a single pathologist, and inter-observer variability was not assessed, which may have introduced observer-related bias despite the use of standardized scoring criteria. Future multicentric studies with larger cohorts, longitudinal follow-up, and multivariable analyses are warranted to validate these findings.

Authors' Contributions

BS has contributed to the conceptualization and definition of the intellectual content of the manuscript, design of the study and Manuscript preparation. PG contributed to the literature search, manuscript editing, and manuscript review. GVR contributed towards data acquisition Statistical analysis, Manuscript review and editing. BS will act as the corresponding author of the manuscript.

Data availability statement

The datasets generated and analysed in this study are available from the corresponding author on reasonable request. They are not publicly shared because they contain sensitive information that could indirectly identify participants.

Ethical Approval

This study has been approved by the Institution Ethics Committee Ref.No: ECR/1385/Inst/TN/2020

Informed Consent

Written informed consent was obtained from all participants after explaining the study procedures, potential risks and benefits. Consent covered both participation and publication of anonymised findings, with assurance of confidentiality and data privacy.

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. Singhal H, Gohel MS, Kaur K, Thomson S. Breast cancer evaluation. eMedicine. 2008:2–10.
2. Folkman J. The role of angiogenesis in tumor growth. Semin Cancer Biol. 1992;3(2):65-71.
3. Almumen M. Immunohistochemical VEGF levels in relation to other pathological parameters of breast carcinoma. J Cancer Ther. 2015;6(9):811–20. doi:10.4236/jct.2015.69089.
4. Nuka S, Devarakonda KK. Immunohistochemical VEGF levels and its relationship with tumor grade in breast carcinomas. J Cancer Dis. 2023.
5. Ribatti D, Nico B, Ruggieri S, Tamma R, Simone G, Mangia A. Angiogenesis and antiangiogenesis in triple-negative breast cancer. Transl Oncol. 2016;9(5):453–7. doi:10.1016/j.tranon.2016.07.002.
6. Pa A, et al. VEGF-A as individual prognostic factor in invasive breast carcinoma. Rom J Morphol Embryol. 2008;49(3):303–8.
7. Shera S, et al. VEGF levels in cancer of breast. Int J Adv Res. 2019;7(10):897–901. doi:10.21474/ijar01/9905.
8. Jannat S, Ahmed M, Syeed S, Khatun H, Afroze N. VEGF levels in breast carcinoma and its link with levels of estrogen receptors, progesterone receptors and HER-2/neu and molecular subtypes. Ann Int Med Dent Res. 2023;9(3):65–73. doi:10.53339/aimdr.2023.9.3.9.
9. Konecny GE, Meng YG, Untch M, Wang HJ, Bauerfeind I, Epstein M, et al. Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients. Clin Cancer Res. 2004;10(5):1706–16. doi:10.1158/1078-0432.ccr-0951-3.

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ORIGINAL ARTICLE

Characteristics of Google Scholar Classic Papers (2006) in Orthopaedic Medicine and Surgery: A Bibliometric Analysis

Raju Vaishya,[1] Abhishek Vaish,[1] Luise Schäfer[2] and Filippo Migliorini[3,4,5,*]

[1]*Department of Orthopaedics and Joint Replacement Surgery, Indraprastha Apollo Hospitals, New Delhi, India*
[2]*Department of Orthopaedic and Trauma Surgery, Eifelklinik St. Brigida, Simmerath, Germany*
[3]*Department of Trauma and Reconstructive Surgery, University Hospital of Halle, Martin-Luther University Halle-Wittenberg, 06097 Halle (Saale), Germany*
[4]*Department of Orthopedics and Trauma Surgery, Academic Hospital of Bolzano (SABES-ASDAA), 39100 Bolzano, Italy*
[5]*Department of Life Sciences, Health, and Health Professions, Link Campus University, 00165 Rome, Italy*

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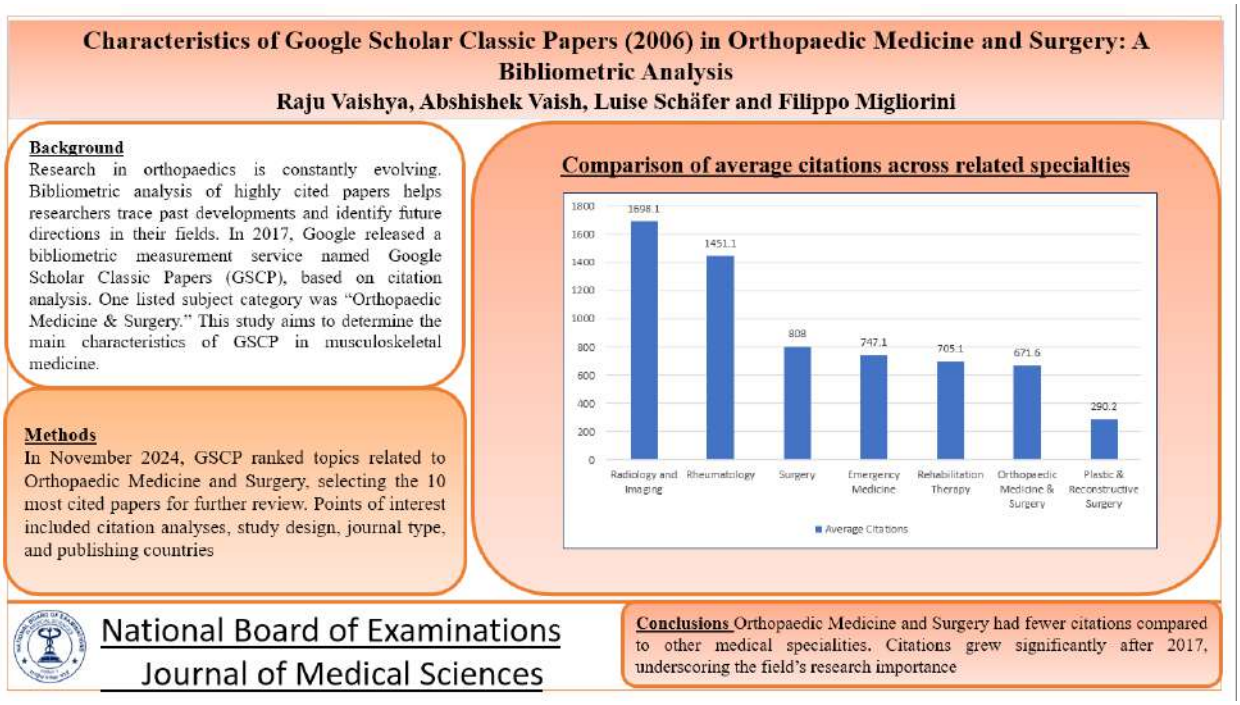
Abstract

Purpose: Research in orthopaedics is constantly evolving. Bibliometric analysis of highly cited papers helps researchers trace past developments and identify future directions in their fields. In 2017, Google released a bibliometric measurement service named Google Scholar Classic Papers (GSCP), based on citation analysis. One listed subject category was "Orthopaedic Medicine & Surgery." This study aims to determine the main characteristics of GSCP in musculoskeletal medicine. **Methods**: In November 2024, GSCP ranked topics related to Orthopaedic Medicine and Surgery, selecting the 10 most cited papers for further review. Points of interest included citation analyses, study design, journal type, and publishing countries. **Results**: Six categories emerged. Radiology & Imaging and Rheumatology ranked highest, with average citations of 1,698.1 and 1,451.1, respectively. Orthopaedic Medicine & Surgery and Plastic & Reconstructive Surgery averaged 671.6 and 290.2 citations. Citations for classic Orthopaedic papers ranged from 518 to 884 (2006-2016) and increased between 2017 and 2024 (858 to 1,423). The 10 most cited papers were published in high-impact journals, with 80% originating in the USA, and 39.1% of authors also based there. **Conclusion**: Orthopaedic Medicine and Surgery had fewer citations compared to other medical specialities. Citations grew significantly after 2017, underscoring the field's research importance. **Level of evidence:** IV

Keywords: Classic Papers, Highly Cited Papers, Orthopaedic, Research, Google Scholar

*Corresponding Author: Filippo Migliorini
Email: filippo.migliorini@uk-halle.de

Graphical Abstract



Introduction

Orthopaedics is one of the most important surgical disciplines and has grown in importance with the ageing population worldwide [1-6]. Over time, a large number of subspecialties have emerged and evolved in clinical practice, basic science, and research [7-10]. Bibliometric methods are a widely used tool to visualise the literature of a scientific field and aim to identify research priorities and future developments in different specialities [11,12]. Citation analysis is one of the widely used indicators for assessing research trends and the impact of published scientific literature in a particular scientific field [13,14]. In this context, publications with a particularly high number of citations are repeatedly identified and analysed [15-18]. Bibliometric analysis of highly cited articles helps researchers efficiently identify the history of developments and future directions of a research field [19,20]. In 2017, Google released an advanced bibliometric measurement service named Google Scholar Classic Papers (GSCP), based on citation analysis 2017 [21]. One of the subject categories listed by GSCP is "Orthopaedic Medicine & Surgery" [22,23].

Related to the significant advances in this research field over recent decades, the present study aimed to identify the primary characteristics of the GSCP in the field of musculoskeletal medicine, based on citation analyses, study design, journal type, and country of publication.

Methods

In November 2024, a bibliometric analysis was conducted using the "Classic Papers" service provided by Google Scholar, an online platform designed to highlight influential research articles that have demonstrated sustained academic impact over time. This tool, accessible via https://scholar.googleblog.com/2017/06/classic-papers-articles-that-have-stood.html (last accessed in November 2024), compiles lists of the most cited scholarly

articles published in 2006, organised by discipline. The purpose of the present analysis was to assess the relative citation impact and academic relevance of research within the broader field of health and medical sciences, with a particular focus on Orthopaedic Medicine and Surgery and its related subspecialties.

The first step involved identifying and retrieving data related to the predefined categories of interest, as defined by Google Scholar. For each subject area, the citation range (minimum to maximum number of citations) and the average number of citations per article were extracted to establish a comparative ranking across various disciplines (Table 1). This provided insight into the overall scholarly visibility and long-term impact of orthopaedic research relative to other medical fields.

Subsequently, the top 10 most cited papers in the category of Orthopaedic Medicine and Surgery, all originally published in 2006, were selected for in-depth analysis. These landmark articles were manually curated and examined to identify their complete bibliographic details, including journal source, authorship, and institutional affiliation. Citation data were collected both from the 2016 Google Scholar Classic Papers listing and updated with figures from 2024, offering a longitudinal perspective on the citation trajectory of each publication (Table 2).

In addition to citation counts, the analysis considered key qualitative features of each study, such as the study design (e.g., randomised controlled trial, observational cohort, or basic science study), type of journal (general medical vs. speciality-specific), and country of origin of the corresponding author. This contextual evaluation aimed to identify common characteristics among high-impact publications and to explore potential patterns related to research methodology, editorial visibility, and geographic distribution (Table 3). The results of this investigation provide a snapshot of what constitutes influential orthopaedic literature and offer insights into the elements that may contribute to the enduring academic success of a scientific publication.

Results

Six related subject areas within the speciality of Orthopaedic Medicine and Surgery were identified. The research topics covered in these papers pertained to common musculoskeletal issues (i.e. orthopaedics, traumatology, rheumatology, physiotherapy). Over the decade from 2006 to 2016, the specialities of Radiology and Imaging and Rheumatology garnered the most citations, with average citation counts of 1,698.1 and 1,451.1, respectively. In contrast, the fields of Orthopaedic Medicine and Surgery and Plastic and Reconstructive Surgery had lower averages of 671.6 and 290.2 citations (Table 1 and Figure 1).

Table 1. Comparative Citations of the Top 10 GSCPs of Orthopaedic Medicine & Surgery and its allied specialities in 10 years (2006 to 2016)

Rank	Speciality	Range of Citations	Average Citations
1	Radiology & Imaging	812 - 3381	1,698.1
2	Rheumatology	706 - 2956	1,451.1
3	Surgery	542 - 1145	808.0
4	Emergency Medicine	298 - 2235	747.1
5	Rehabilitation Therapy	313 - 2613	705.2
6	Orthopaedic Medicine & Surgery	518 - 884	671.6
7	Plastic & Reconstructive Surgery	224 - 397	290.2

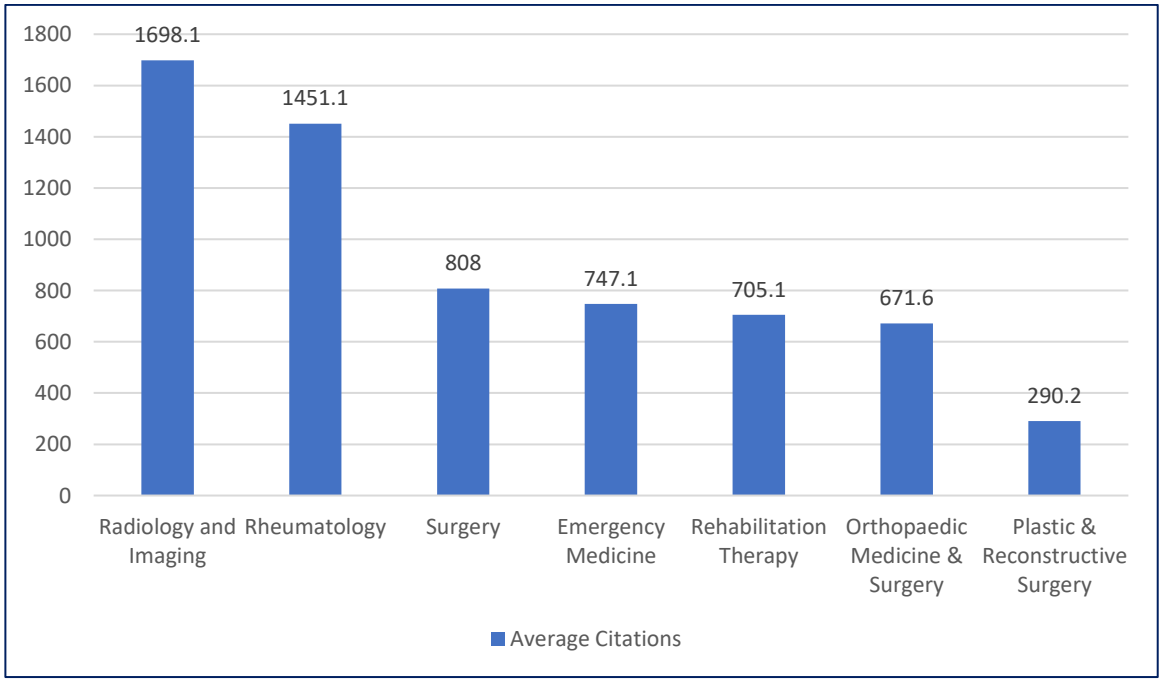


Figure 1. Comparison of average citations across related specialties

The top 10 GSCPs of the speciality of Orthopaedic Medicine and Surgery published in 2006 [22] are listed in Table 2. The total number of citations received by these classic papers in their first 10 years of publication (2006-2016) ranged from 518 to 884. These papers continued to receive substantially more citations over the next six years (2017-2024), with a range of 858 to 1,423 (Figure 2).

Table 2. Top 10 GSCPs of Orthopaedic Medicine and Surgery in 2006, with the total number of citations in 2016 and 2024

Rank	Publications	Citations (2016)	Citations (2024)
1	Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, Abdu WA, Hilibrand AS, Boden SD, Deyo RA. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. JAMA 2006 Nov 22;296(20):2441-50.	884	1,423
2	Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. American Journal of Sports Medicine 2006 Nov; 34(11):1774-8.	831	1,224
3	Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates: estimates from US national surveys, 2002. Spine. 2006 Nov 1;31(23):2724-7.	777	1,406
4	Nancollas GH, Tang R, Phipps RJ, Henneman Z, Gulde S, Wu W, Mangood A, Russell RG, Ebetino FH. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone. 2006 May 1;38(5):617-27.	710	1,080
5	Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, Silverman S. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clinic Proceedings 2006 Aug 1 (Vol. 81, No. 8, pp. 1013-1022).	660	858
6	Frankle M, Siegal S, Pupello D, Saleem A, Mighell M, Vasey M. The reverse shoulder prosthesis for glenohumeral arthritis associated with severe rotator cuff deficiency. J Bone Joint Surg-Am.2006; 5:697-705.	618	1,030

7	Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, Herkowitz H, Fischgrund J, Cammisa FP, Albert T, Deyo RA. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA 2006 Nov 22; 296(20):2451-9.	603	937
8	Boileau P, Villalba M, Héry JY, Balg F, Ahrens P, Neyton L. Risk factors for recurrence of shoulder instability after arthroscopic Bankart repair. J Bone Joint Surg-Am 2006 Aug 1;88(8):1755-63.	560	1,110
9	Boileau P, Watkinson D, Hatzidakis AM, Hovorka I. Neer Award 2005: The Grammont reverse shoulder prosthesis: results in cuff tear arthritis, fracture sequelae, and revision arthroplasty. Journal of Shoulder and Elbow Surgery. 2006 Sep 1;15(5):527-40.	555	1,112
10	Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA. The demographic and morphological features of rotator cuff disease: a comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg-Am 2006 Aug 1;88(8):1699-704.	518	1,086

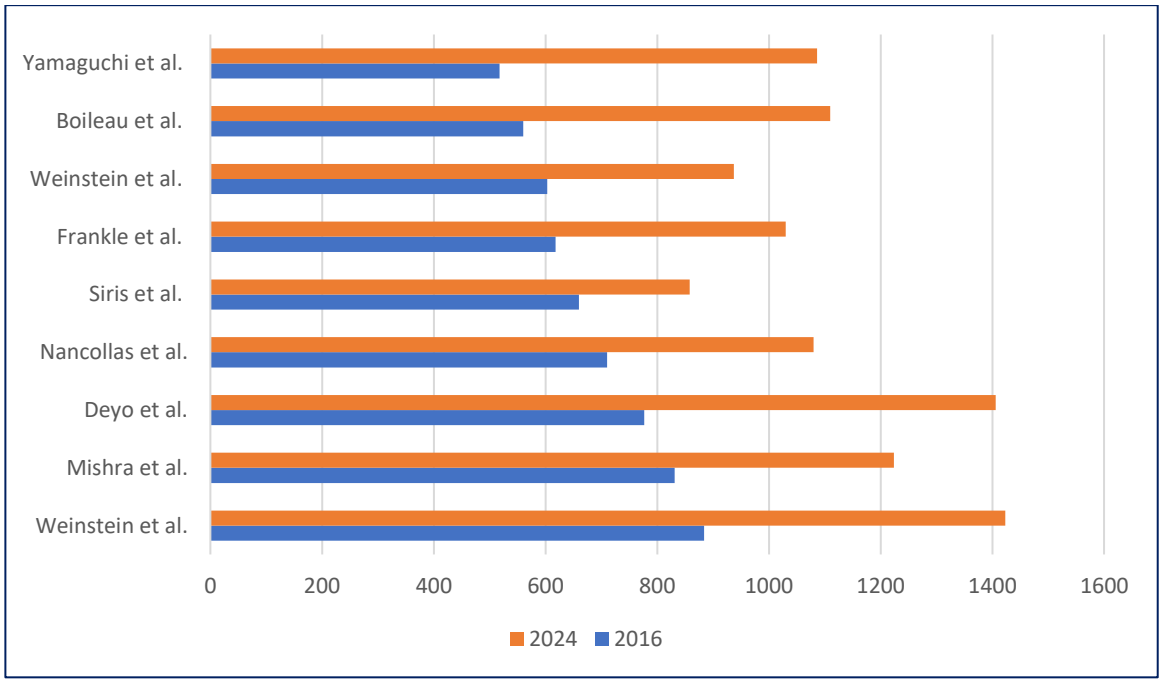


Figure 2. Citation growth of the Top 10 Classic Papers (2016 vs 2024)

Of the top 10 GSCPs of Orthopaedic Medicine and Surgery, nine reported clinical experience, and one was a clinical review. Most of them were comparative studies; one was designed as a cohort study. Two of the clinical trials had a prospective study design, and one was a randomised controlled trial (RCT). Research topics dealing with spinal complaints and diseases of the shoulder were both reported four times. Two techniques related to the shoulder are described in the clinical methods of prosthetic joint surgery. Basic research was the subject of two publications dealing with the effect of bisphosphonates on bone, and only one study reported on chronic tendinosis of the elbow. All publications were published in high-impact journals. In detail, the Journal of Bone and Joint Surgery American volume (JBJS (Am), N = 3), Journal of the American Medical Association (JAMA, N = 2), The American Journal of Sports Medicine (AJSM, N = 1), Bone (N = 1), Spine (N = 1), Mayo Clinic Proceedings (MCP, N = 1), and the Journal of Shoulder & Elbow Surgery (JSES, N = 1) (Figure 3).

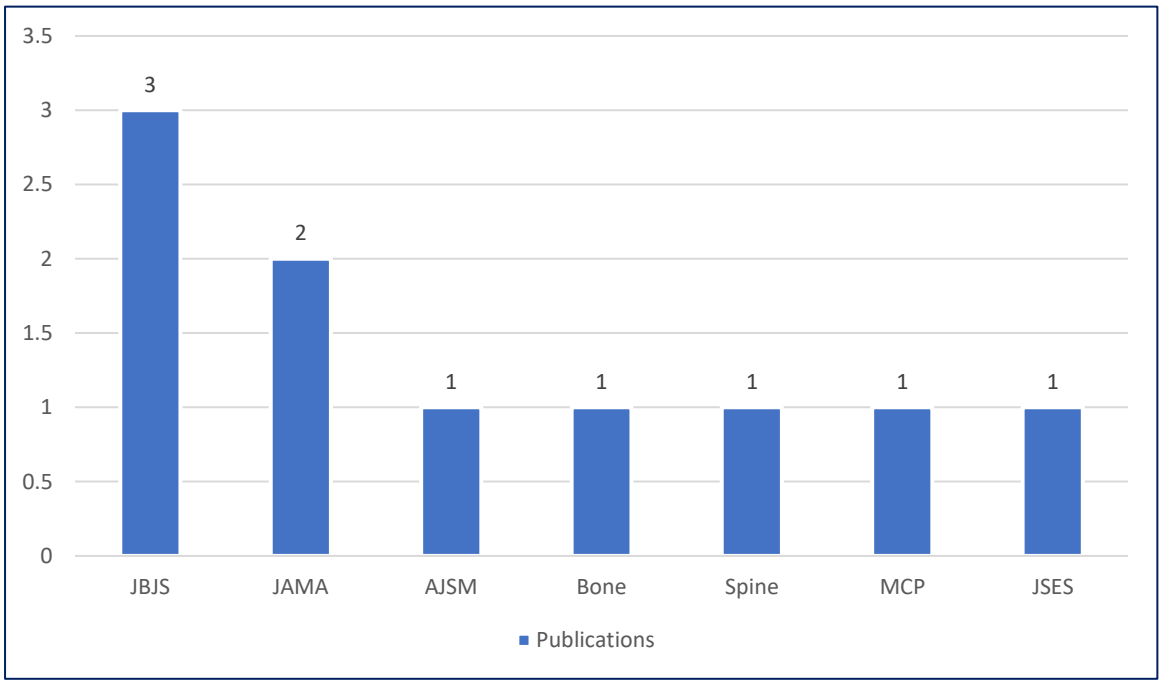


Figure 3. A bar chart showing the journals publishing the classic papers in Orthopaedics

(JBJS-Journal of bone and Joint Surgery; JAMA-Journal of American Medical Association; AJSm-American Journal of Soirts Medicine; MCP-Mayo clinic Proceedings; JSES-Journal of Shoulder and Elbow Surgery)

The United States was the country of publication in 80% (8 of 10) of the studies, and in terms of total authors and co-authors, 39.1% (9 of 23) were also from the United States. The generalities of the top 10 GSCPs of Orthopaedic Medicine & Surgery in 2006 are shown in Table 3.

Table 3. Generalities of the top 10 GSCPs of Orthopaedic Medicine & Surgery in 2006

Rank	Author, year	Journal	Study design	Country	Research questions
1	Weinstein et al., 2006 [24]	JAMA	RCT	USA	Lumbar disk herniation
2	Mishra et al., 2006 [25]	Am J Sports Med	Cohort study	USA	Chronic elbow tendinosis
3	Deo et al., 2006 [26]	Spine	Review	USA	Back pain
4	Nancollas et al., 2006 [27]	Bone	Comparative study	USA	Bisphosphonates on bone
5	Siris et al., 2006 [28]	Mayo Clin Proc	Comparative study	USA	Adherence to bisphosphonate therapy/vertebral and nonvertebral fractures
6	Frankle et al., 2006 [29]	J Bone Joint Surg Am		USA	Reverse Shoulder prosthesis
7	Weinstein et al., 2006 [30]	JAMA	Prospective	USA	Lumbar disk herniation
8	Boileau et al., 2006 [31]	J Bone Joint Surg Am	Prospective	France	Shoulder instability after Arthroscopic Bankart repair
9	Boileau et al., 2006 [32]	J Shoulder Elbow Surg	Comparative study	France	Reverse shoulder prosthesis
10	Yamaguchi et al., 2006 [33]	J Bone Joint Surg Am	Comparative study	USA	Shoulder rotator cuff disease

Discussion

Bibliometric research is an established method of measuring scientific output based on a statistical analysis of publications in a particular sector [11,12]. In the medical field, this type of research aims explicitly to follow up on medical developments, identify knowledge gaps, and provide guidelines for future scientific research [20,19]. Additionally, the evaluation of bibliometrics enables researchers to measure, assess, and evaluate their personal publication output and scientific performance [34,35]. Medical journals employ the same measures to define their impact and attract a greater number of high-quality authors based on their level of influence [36,37]. Moreover, bibliometric studies play an important role in identifying research characteristics of numerous medical fields [38-42].

A variety of different bibliometric indicators are available to collect, analyse, and measure data on a wide range of scientific aspects, and subsequently produce rankings for researchers, institutions, and universities worldwide [43,44]. The scope of bibliometric methods includes studies of publication patterns, bibliographic referencing, bibliographic linkage, and citation analysis [45,46]. In health science disciplines, citation studies are a widely used bibliometric method [47,48]. While the number of publications measures output, the number of citations measures scientific impact based on the number of references to a given previous publication [49-51]. As academic interest in the subject of excellent research increases, attention is increasingly drawn to papers in specific journals or fields that exhibit an unusually high proportion of all citations, known as classic papers [52-55]. Highly cited papers (HCPs) provide evidence and information about research trends and scientific advances in a particular field and are considered central to research [56-58]. As early as 1967, Garfield published a list of the 50 most cited articles and used the term “classics” for the first time to refer to the investigations he listed [59,60]. A classic paper is characterised by the fact that it has been judged to be of high and outstanding quality over an extended period and thus serves as a model for further research [61].

The widespread use of citation analysis in academia, by creating an electronic citation index called Web of Science (WoS), was enabled by Garfield in 1964 [62,63]. In 2004, Google Scholar, among other databases, revolutionised the way scholarly publications are searched, retrieved, and accessed, opening new possibilities in bibliometric measurement [51,64]. Before the emergence of Google Scholar and Scopus, in late 2004, WoS was the only citation-tracking provider for many years [65]. Given the differences in WoS, Scopus, and Google Scholar, a comparison of citations on Google Scholar, Scopus, and Web of Science indicates that citations of papers on Google Scholar are significantly higher than those on Scopus and WoS [66,67]. The abundance of citations in Google Scholar is primarily caused by the fact that Google Scholar automatically detects and indexes publications within the Web environment. At the same time, Scopus and WoS have their policies for selecting journals [68,69]. The lowest number of citations that classic papers have achieved is reported as 410 by Google Scholar, 262 by Scopus, and 212 by WoS [70]. Therefore, an author, to publish an article of the quality of a classical paper, should receive more than 200-400 citations for this article [71]. Additionally, it is worth

noting that citation rates vary across different disciplines. In an orthopaedic subspecialty with fewer researchers, the number of citations that led to determining a publication as classic may be lower than in a larger field of orthopaedics [71,72,60].

In June 2017, Google introduced a new service named Google Scholar Classic Papers (GSCP), one of the most advanced citation indices [21]. It concerns the top 10 most cited English-language original research articles published in 2006 across 252 subject categories, according to data available in Google Scholar as of May 2017 [23]. Eligible criteria for inclusion in the GSCP list include publishing in 2006 and reporting original research written in English in the form of journal articles, articles deposited in repositories, or conference proceedings [21]. Review articles, introductory articles, editorials, guides, commentaries, etc., are explicitly excluded [21]. Furthermore, they must be among the top 10 most cited documents in their respective category and have received at least 20 citations [21].

One of the subject categories listed by GSCP is "Orthopaedic Medicine & Surgery" [22,23]. According to the main findings of the present study, the speciality of Orthopaedic Medicine and Surgery was among the least cited, with a citation average of 671.6. The related specialities of Orthopaedic Medicine and Surgery, which published articles on topics of general interest and common health problems, were cited more frequently than the specialised surgical specialities, such as Orthopaedics and Plastic Surgery. Specifically, Orthopaedic Medicine and Surgery received a total of 518 to 884 citations in the first 10 years of publication (2006-2016). In the following six years (2017-2024), the number of citations increased significantly (from 858 to 1,423), confirming its great importance for research. In a recent study, Vaishya et al. found that medical journals have higher journal-level metrics than Surgical and Orthopaedic journals, given a larger interest in common health-related issues published in medical journals [73].

Given the long-term visibility after publication, classic papers in orthopaedics have made long-lasting and game-changing contributions to clinical practice and research [71]. They highlight the topics that have had the most impact on clinical practice, provide the impetus to evaluate practical standards, and recognise key advances and significant developments in orthopaedics [74,75]. The research topics of the evaluated GSCP encompass spinal complaints [24,26,28,30], diseases of the shoulder [29,31-33], the effect of bisphosphonates on bones [27,28], and chronic tendinosis of the elbow [25].

Although criticism of the impact factor (IF) is widespread today, and many scientists and editors refrain from basing the success of individual articles on journal prominence, it remains of great importance to scientific authors, especially when deciding where to submit a manuscript [76,77]. In general, journals with a higher IF are deemed more reputable than those with a lower IF [78,79]. Since all publications listed in the GSCP have appeared in high-impact journals, the results of the current study also reflect the findings regarding the relevance of the IF of previous studies.

The majority of the GSCPs evaluated in the present study originated from the United States [24-30,32,33], with France [32] being the only other representative. The ranking, compiled by the Institute for Scientific Information

(ISI), includes a total of 20 scientific disciplines and reports that the United States has traditionally led the rankings in the output of publications in all these 20 disciplines [80]. This is thought to be largely influenced by the number of orthopaedic surgeons in the United States, their wealth, and their overall scientific output compared to other countries [81]. As a consequence, it is not unexpected that the United States accounts for 80% (8 of 10) of the GSCP assessed in this study. Evaluation of the total authors and co-authors of the GSCP in Orthopaedic Medicine and Surgery revealed that 39.1% (9 of 23) of the authors were from the United States. Therefore, it can be deduced that collaboration with American authors can positively influence the achievement of high-quality HCPs.

In 2010, Kelly et al. [74] and Lefaivre et al. [75] published an analysis of the top 100 HCPs in orthopaedics. Both articles generated a list based on the frequency of the publications cited in specific orthopaedic journals and produced a top 100 list with minor variations. Kelly et al. [74] examined data from the ISI's Science Citation Index (SCI) from 1945 to 2008. They emphasised the importance of the English language and the journal's IF [74]. Furthermore, they highlighted the challenge of deriving a qualitative evaluation using citation analyses, which, however, does not diminish the influence of highly cited papers on the history and development of orthopaedics [74]. Lefaivre et al. [75] searched the SCI for citations to articles published in any of the 49 journals in the subject category "Orthopaedics". They concluded that authors aiming to write a highly cited article in an orthopaedic surgery journal will be favoured by the language of publication, source journal, country of origin, and the introduction of a classification scheme or outcome tool [75]. Although the source and number of publications examined differ from those used in the present investigation, the main findings are consistent.

Bibliometric data are not without limitations [82,83]. Scientific performance, especially the quality of research, cannot be expressed by facts and figures alone. For this reason, it is essential to consider several indicators in bibliometric analysis, ideally determined within the respective discipline and in consultation with the scientist concerned [84-88]. The number of publications and citations does not automatically guarantee the quality of research output or scientific performance [89,88]. Citations are often biased [90,91]. It is reported that the authors read less than 20% of the cited papers, and 3% to 60% (mean, >20%) of the citations are erroneous [71]. A rating system based on citations is, therefore, equally complex to apply without restrictions. The recent publication by Orduna-Malea et al. [92] highlighted several methodological concerns of the GSCP service. By comparing a total of 2,515 datasets, they identified concerns related to the thematic classification of documents and the use of homogeneous visualisation of thresholds regardless of the discipline [92]. In addition, the authors highlight that the lack of transparency is a methodological problem, as Google Scholar does not explain in detail how the product was developed [92]. Given these limitations, the results of the present study should not be interpreted without caution.

Conclusion

The speciality of Orthopaedic Medicine and Surgery was among the least cited. Its related specialities (such as

Radiology and Imaging, Rheumatology, etc.) published articles on topics of general interest and common health problems more frequently than the specialised surgical fields (like Orthopaedics and Plastic Surgery). Specifically, Orthopaedic Medicine and Surgery received a total of 518 to 884 citations in the first 10 years of publication (2006-2016). In the subsequent six years (2017-2024), the number of citations increased significantly (from 858 to 1,423), confirming its importance for research.

Statements and Declarations

Competing interests

The authors declare that they have any competing interests in this article.

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Consent to Participate

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Ethical approval

This study complies with ethical standards.

Consent to publish

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available throughout the manuscript.

References

1. Bell CS, Jackson RW What's New in Orthopaedic Surgery? A Review of Major Breakthroughs and Advances in Orthopaedics. In: Baylor University Medical Center Proceedings, 1999. vol 2. Taylor & Francis, pp 121–125
2. Migliorini F, Giorgino R, Hildebrand F, Spiezia F, Peretti GM, Alessandri-Bonetti M, Eschweiler J, Maffulli N (2021) Fragility Fractures: Risk Factors and Management in the Elderly. Medicina (Kaunas) 57 (10). doi:10.3390/medicina57101119
3. Fucs P, Scarlat MM (2017) Pediatric Orthopaedics - from Kirschner wires to titanium. Int Orthop 41 (12):2429–2431. doi:10.1007/s00264-017-3677-x
4. Migliorini F, Tingart M, Maffulli N (2020) Progress with stem cell therapies for tendon tissue regeneration. Expert Opin Biol Ther 20 (11):1373–1379. doi:10.1080/14712598.2020.1786532
5. Barahona M, de Los Santos D, Diaz N, Barrientos C, Infante CA (2021) Trends in Orthopedic Surgery in Chile: Analysis Between 2004 and 2020. Cureus 13 (5):e15080. doi:10.7759/cureus.15080
6. Zhi X, Cui J, Gu Z, Cao L, Weng W, Li Q, Chen X, Su J (2016) Orthopedics research output from China, USA, UK, Japan, Germany and France: A 10-year survey of the literature. Orthop Traumatol Surg Res 102 (7):939–945. doi:10.1016/j.otsr.2016.05.005
7. Rodeo SA, Sugiguchi F, Fortier LA, Cunningham ME, Maher S (2014) What's new in orthopaedic research. J Bone Joint Surg Am 96 (23):2015–2019. doi:10.2106/JBJS.N.01001
8. Ninomiya JT, Dean JC, Incavo SJ (2015) What's New in Hip Replacement. J Bone Joint Surg Am

97 (18):1543–1551. doi:10.2106/JBJS.O.00526
9. Greenstein AS, Gorczyca JT (2019) Orthopedic Surgery and the Geriatric Patient. Clin Geriatr Med 35 (1):65–92. doi:10.1016/j.cger.2018.08.007
10. Vaish A, Migliorini F, Vaishya R (2023) Artificial intelligence in foot and ankle surgery: current concepts. Orthopadie (Heidelb). doi:10.1007/s00132-023-04426-x
11. Mejia C, Wu M, Zhang Y, Kajikawa Y (2021) Exploring Topics in Bibliometric Research Through Citation Networks and Semantic Analysis. Front Res Metr Anal 6:742311. doi:10.3389/frma.2021.742311
12. Thompson DF, Walker CK (2015) A descriptive and historical review of bibliometrics with applications to medical sciences. Pharmacotherapy 35 (6):551–559. doi:10.1002/phar.1586
13. Malhotra K, Saeed O, Goyal N, Katsanos AH, Tsivgoulis G (2018) Top-100 Highest-Cited Original Articles in Ischemic Stroke: A Bibliometric Analysis. World Neurosurg 111:e649–e660. doi:10.1016/j.wneu.2017.12.140
14. Franceschini M, Boffa A, Andriolo L, Di Martino A, Zaffagnini S, Filardo G (2022) The 50 most-cited clinical articles in cartilage surgery research: a bibliometric analysis. Knee Surg Sports Traumatol Arthrosc 30 (6):1901–1914. doi:10.1007/s00167-021-06834-y
15. Namdari S, Baldwin K, Kovatch K, Huffman GR, Glaser D (2012) Fifty most cited articles in orthopedic shoulder surgery. Journal of shoulder and elbow surgery 21 (12):1796–1802
16. Nayar SK, Dein EJ, Spiker AM, Bernard JA, Zikria BA (2015) The top 100 cited articles in clinical orthopedic sports medicine. Am J Orthop (Belle Mead NJ) 44 (8):E252–E261
17. Jia Z, Ding F, Wu Y, He Q, Ruan D (2015) The 50 most-cited articles in orthopaedic surgery from Mainland China. Clinical Orthopaedics and Related Research® 473:2423–2430
18. Baldwin KD, Kovatch K, Namdari S, Sankar W, Flynn JM, Dormans JP (2012) The 50 most cited articles in pediatric orthopedic surgery. Journal of Pediatric Orthopaedics B 21 (5):463–468
19. Kumar M, George RJ, PS A (2023) Bibliometric analysis for medical research. Indian Journal of Psychological Medicine 45 (3):277–282
20. Szomszor M, Adams J, Fry R, Gebert C, Pendlebury DA, Potter RW, Rogers G (2021) Interpreting bibliometric data. Frontiers in Research Metrics and Analytics:30
21. Google Scholar blog - Classic Papers: Articles That Have Stood The Test of Time. Accessed last on 11th September 2023. https://scholar.googleblog.com/2017/06/classic-papers-articles-that-have-stood.html?m=1.
22. Google Scholar- Top 10 Classic papers. Last accessed on 13th September 2023. Orthopedic Medicine & Surgery. https://scholar.google.com/citations?view_op=list_classic_articles&hl=en&by=2006&vq=med_orthopedicmedicinesurgery.

23. Google Scholar. Classic Papers – Health and Medical Sciences. Last accessed on 13th September 2023. https://scholar.google.com/citations?view_op=list_classic_articles&hl=en&by=2006.
24. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, Abdu WA, Hilibrand AS, Boden SD, Deyo RA (2006) Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. Jama 296 (20):2441–2450
25. Mishra A, Pavelko T (2006) Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. The American journal of sports medicine 34 (11):1774–1778
26. Deyo RA, Mirza SK, Martin BI (2006) Back pain prevalence and visit rates: estimates from US national surveys, 2002. Spine 31 (23):2724–2727
27. Nancollas GH, Tang R, Phipps RJ, Henneman Z, Gulde S, Wu W, Mangood A, Russell RG, Ebetino FH (2006) Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone 38 (5):617–627. doi:10.1016/j.bone.2005.05.003
28. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, Silverman S (2006) Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 81 (8):1013–1022. doi:10.4065/81.8.1013
29. Frankle M, Siegal S, Pupello D, Saleem A, Mighell M, Vasey M (2005) The Reverse Shoulder Prosthesis for glenohumeral arthritis associated with severe rotator cuff deficiency. A minimum two-year follow-up study of sixty patients. J Bone Joint Surg Am 87 (8):1697–1705. doi:10.2106/JBJS.D.02813
30. Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, Herkowitz H, Fischgrund J, Cammisa FP, Albert T, Deyo RA (2006) Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA 296 (20):2451–2459. doi:10.1001/jama.296.20.2451
31. Boileau P, Villalba M, Hery JY, Balg F, Ahrens P, Neyton L (2006) Risk factors for recurrence of shoulder instability after arthroscopic Bankart repair. J Bone Joint Surg Am 88 (8):1755–1763. doi:10.2106/JBJS.E.00817
32. Boileau P, Watkinson D, Hatzidakis AM, Hovorka I (2006) Neer Award 2005: The Grammont reverse shoulder prosthesis: results in cuff tear arthritis, fracture sequelae, and revision arthroplasty. J Shoulder Elbow Surg 15 (5):527–540. doi:10.1016/j.jse.2006.01.003
33. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA (2006) The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg Am 88 (8):1699–1704. doi:10.2106/JBJS.E.00835

34. Costas R, Van Leeuwen TN, Bordons M (2010) A bibliometric classificatory approach for the study and assessment of research performance at the individual level: The effects of age on productivity and impact. Journal of the American society for information science and technology 61 (8):1564–1581
35. Sandström E, Sandström U (2009) Meeting the micro-level challenges: Bibliometrics at the individual level. Proceedings ISSI
36. Garfield E (2006) The history and meaning of the journal impact factor. JAMA 295 (1):90–93. doi:10.1001/jama.295.1.90
37. Pendlebury DA (2009) The use and misuse of journal metrics and other citation indicators. Arch Immunol Ther Exp (Warsz) 57 (1):1–11. doi:10.1007/s00005-009-0008-y
38. Barbera J, Selverian S, Courington R, Mikhail C, Colvin A (2020) The Top 50 Most Influential Articles in Hip Arthroscopy. Arthroscopy 36 (3):716–722. doi:10.1016/j.arthro.2019.09.031
39. Karsli B, Tekin SB (2021) The Top 100 Most-Cited Articles on Ankle Arthroscopy: Bibliometric Analysis. J Foot Ankle Surg 60 (3):477–481. doi:10.1053/j.jfas.2020.08.028
40. Khatra O, Shadgan A, Taunton J, Pakravan A, Shadgan B (2021) A Bibliometric Analysis of the Top Cited Articles in Sports and Exercise Medicine. Orthop J Sports Med 9 (1):2325967120969902. doi:10.1177/2325967120969902
41. Mikhail CM, Schwartz JT, Barbera J, Selverian SR, Chen D (2020) The most influential papers in direct anterior approach to total hip arthroplasty. Arthroplast Today 6 (2):190–195. doi:10.1016/j.artd.2020.01.006
42. Vaishya R, Gupta BM, Mamdapur GMN, Vaish A, Migliorini F (2023) Scientometric analysis of highly cited papers on avascular necrosis of the femoral head from 1991 to 2022. Journal of Orthopaedics and Traumatology 24 (1):1–14
43. La Torre G, Sciarra I, Chiappetta M, Monteduro A (2017) [New bibliometric indicators for the scientific literature: an evolving panorama]. Clin Ter 168 (2):e65–e71. doi:10.7417/CT.2017.1985
44. Garner RM, Hirsch JA, Albuquerque FC, Fargen KM (2018) Bibliometric indices: defining academic productivity and citation rates of researchers, departments and journals. J Neurointerv Surg 10 (2):102–106. doi:10.1136/neurintsurg-2017-013265
45. Narin F, Hamilton KS (1996) Bibliometric performance measures. Scientometrics 36:293–310
46. Cooper ID (2015) Bibliometrics basics. J Med Libr Assoc 103 (4):217–218. doi:10.3163/1536-5050.103.4.013
47. Wallin JA (2005) Bibliometric methods: pitfalls and possibilities. Basic & clinical pharmacology & toxicology 97 (5):261–275
48. Moed HF (2009) New developments in the use of citation analysis in research evaluation. Arch Immunol Ther Exp (Warsz) 57 (1):13–18. doi:10.1007/s00005-009-0001-5
49. Suelzer EM, Jackson JL (2022) Measures of Impact for Journals, Articles, and Authors. J Gen Intern

Med 37 (7):1593–1597. doi:10.1007/s11606-022-07475-8
50. Cheek J, Garnham B, Quan J (2006) What's in a number? Issues in providing evidence of impact and quality of research(ers). Qual Health Res 16 (3):423–435. doi:10.1177/1049732305285701
51. Hicks D, Melkers J (2013) Bibliometrics as a tool for research evaluation. Handbook on the theory and practice of program evaluation:323–349
52. Kavanagh R, Kelly J, Kelly P, Moore D (2013) The 100 classic papers of pediatric orthopaedic surgery: a bibliometric analysis. JBJS 95 (18):e134
53. Huo Y-q, Pan X-h, Li Q-b, Wang X-q, Jiao X-j, Jia Z-w, Wang S-j (2015) Fifty top-cited classic papers in orthopedic elbow surgery: a bibliometric analysis. International Journal of Surgery 18:28–33.
54. Li Y, Xu G, Long X, Ho Y-S (2019) A bibliometric analysis of classic publications in web of science category of orthopedics. Journal of Orthopaedic Surgery and Research 14:1–11
55. Sun J, Guo Y, Scarlat MM, Lv G, Yang X-G, Hu Y-C (2018) Bibliometric study of the orthopaedic publications from China. International orthopaedics 42:461–468
56. Bornmann L (2014) How are excellent (highly cited) papers defined in bibliometrics? A quantitative analysis of the literature. Research Evaluation 23 (2):166–173
57. Aksnes DW, Sivertsen G (2004) The effect of highly cited papers on national citation indicators. Scientometrics 59 (2):213–224
58. Aksnes DW (2003) Characteristics of highly cited papers. Research evaluation 12 (3):159–170. doi:10.3152/147154403781776645
59. Garfield E (1976) Highly cited articles. 26. Some classic papers of late 19th and early 20th centuries. Inst Sci Inform Inc 3501 Market St, Philadelphia, PA 19104.
60. Garfield E (1977) Introducing citation classics-human side of scientific reports. Inst Sci Inform Inc 3501 Market St, Philadelphia, Pa 19104 USA.
61. Canale S (2010) In the top 100 classic articles, where's mine. AAOS Now:1-1
62. Garfield E (1964) "Science Citation Index"--A New Dimension in Indexing. Science 144 (3619):649–654. doi:10.1126/science.144.3619.649
63. Birkle C, Pendlebury DA, Schnell J, Adams J (2020) Web of Science as a data source for research on scientific and scholarly activity. Quantitative Science Studies 1 (1):363–376. doi:10.1162/qss_a_00018
64. Alonso S, Cabrerizo FJ, Herrera-Viedma EE, Herrera F (2009) h-Index: A review focused in its variants, computation and standardization for different scientific fields. J Informetrics 3:273–289
65. Bakkalbasi N, Bauer K, Glover J, Wang L (2006) Three options for citation tracking: Google Scholar, Scopus and Web of Science. Biomed Digit Libr 3:7. doi:10.1186/1742-5581-3-7
66. Kulkarni AV, Aziz B, Shams I, Busse JW (2009) Comparisons of citations

in Web of Science, Scopus, and Google Scholar for articles published in general medical journals. JAMA 302 (10):1092–1096. doi:10.1001/jama.2009.1307

67. Anker MS, Hadzibegovic S, Lena A, Haverkamp W (2019) The difference in referencing in Web of Science, Scopus, and Google Scholar. ESC Heart Fail 6 (6):1291–1312. doi:10.1002/ehf2.12583
68. Kulkarni AV, Aziz B, Shams I, Busse JW (2009) Comparisons of citations in Web of Science, Scopus, and Google Scholar for articles published in general medical journals. Jama 302 (10):1092–1096
69. Martín-Martín A, Orduna-Malea E, Thelwall M, López-Cózar ED (2018) Google Scholar, Web of Science, and Scopus: A systematic comparison of citations in 252 subject categories. Journal of informetrics 12 (4):1160–1177
70. Saberi MK, Ekhtiyari F (2018) Characteristics of classic papers of library and information science: a scientometric study. Library Philosophy and Practice:1
71. Mavrogenis AF, Quaile A, Scarlat MM (2020) Classic publications and scientometrics in orthopaedics. vol 44. Springer,
72. Jelicic Kadic A, Kovacevic T, Runjic E, Simicic Majce A, Markic J, Polic B, Mestrovic J, Puljak L (2020) Research methodology used in the 50 most cited articles in the field of pediatrics: types of studies that become citation classics. BMC Med Res Methodol 20 (1):60. doi:10.1186/s12874-020-00940-0
73. Jeyaraman M, Selvaraj P, Vaish A, Iyengar KP, Vaishya R (2023) Journal metrics of the top-ranked Orthopaedic, Medical, and Surgical journals - A cross-sectional, comparative study. Int Orthop. doi:10.1007/s00264-023-06010-6
74. Kelly JC, Glynn RW, O'Briain DE, Felle P, McCabe JP (2010) The 100 classic papers of orthopaedic surgery: a bibliometric analysis. J Bone Joint Surg Br 92 (10):1338–1343. doi:10.1302/0301-620X.92B10.24867
75. Lefaivre KA, Shadgan B, O'Brien PJ (2011) 100 most cited articles in orthopaedic surgery. Clin Orthop Relat Res 469 (5):1487–1497. doi:10.1007/s11999-010-1604-1
76. Seglen PO (1997) Why the impact factor of journals should not be used for evaluating research. BMJ 314 (7079):498–502. doi:10.1136/bmj.314.7079.497
77. Lankhorst GJ, Franchignoni F (2001) The 'impact factor'--an explanation and its application to rehabilitation journals. Clin Rehabil 15 (2):115–118. doi:10.1191/026921501676657944
78. Moverley R, Rankin KS, McNamara I, Davidson DJ, Reed M, Sprowson AP (2013) Impact factors of orthopaedic journals between 2000 and 2010: trends and comparisons with other surgical specialties. Int Orthop 37 (4):561–567. doi:10.1007/s00264-012-1769-1
79. Mohamed NS, Gwam CU, Etcheson JI, George NE, Piuzzi NS, Rosas S, Sohdi N, Sultan AA, Khlopas A, Delanois RE (2018) Impact factors of orthopaedic journals between 2010 and 2016: trends and comparisons with other surgical specialties. Ann

Transl Med 6 (7):114. doi:10.21037/atm.2018.03.02

80. Coppen A, Bailey J (2004) 20 most-cited countries in clinical medicine ranked by population size. Lancet 363 (9404):250. doi:10.1016/S0140-6736(03)15353-6
81. Man JP, Weinkauf JG, Tsang M, Sin JHDD (2004) Why do some countries publish more than others? An international comparison of research funding, English proficiency and publication output in highly ranked general medical journals. European journal of epidemiology 19:811–817
82. Belter CW (2015) Bibliometric indicators: opportunities and limits. J Med Libr Assoc 103 (4):219–221. doi:10.3163/1536-5050.103.4.014
83. Durieux V, Gevenois PA (2010) Bibliometric indicators: quality measurements of scientific publication. Radiology 255 (2):342–351. doi:10.1148/radiol.09090626
84. Joshi MA (2014) Bibliometric indicators for evaluating the quality of scientifc publications. J Contemp Dent Pract 15 (2):258–262. doi:10.5005/jp-journals-10024-1525
85. Mathur VP, Sharma A (2009) Impact factor and other standardized measures of journal citation: a perspective. Indian J Dent Res 20 (1):81–85. doi:10.4103/0970-9290.49072
86. Saxena A, Thawani V, Chakrabarty M, Gharpure K (2013) Scientific evaluation of the scholarly publications. J Pharmacol Pharmacother 4 (2):125–129. doi:10.4103/0976-500X.110894
87. Ioannidis JP, Klavans R, Boyack KW (2016) Multiple Citation Indicators and Their Composite across Scientific Disciplines. PLoS Biol 14 (7):e1002501. doi:10.1371/journal.pbio.1002501
88. Dougherty MR, Horne Z (2022) Citation counts and journal impact factors do not capture some indicators of research quality in the behavioural and brain sciences. R Soc Open Sci 9 (8):220334. doi:10.1098/rsos.220334
89. Teplitskiy M, Duede E, Menietti M, Lakhani KR (2022) How status of research papers affects the way they are read and cited. Research Policy 51 (4):104484
90. Clarke T (2003) Copied citations give impact factors a boost. Nature 423 (6938):373. doi:10.1038/423373a
91. Ball P (2002) Paper trail reveals references go unread by citing authors. Nature 420 (6916):594. doi:10.1038/420594a
92. Orduna-Malea E, Martín-Martín A, López-Cózar ED (2018) Classic papers: using Google Scholar to detect the highly-cited documents.

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ORIGINAL ARTICLE

Fix and Flap for Open Gustilo-Anderson Type II and III Tibial Fractures: A Prospective Observational Study of Anatomical and Functional Outcomes

Harri Vishnu M,[1] T. Thirumalaiswamy[2] and Senthil C[3,*]

[1]*Professor, Department of Orthopaedics, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Tamil Nadu*
[2]*Associate Professor, Department of General Surgery, Dhanalakshmi Srinivasan Medical College, Siruvachur, Tamil Nadu*
[3]*Postgraduate, Department of Orthopaedics, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Tamil Nadu*

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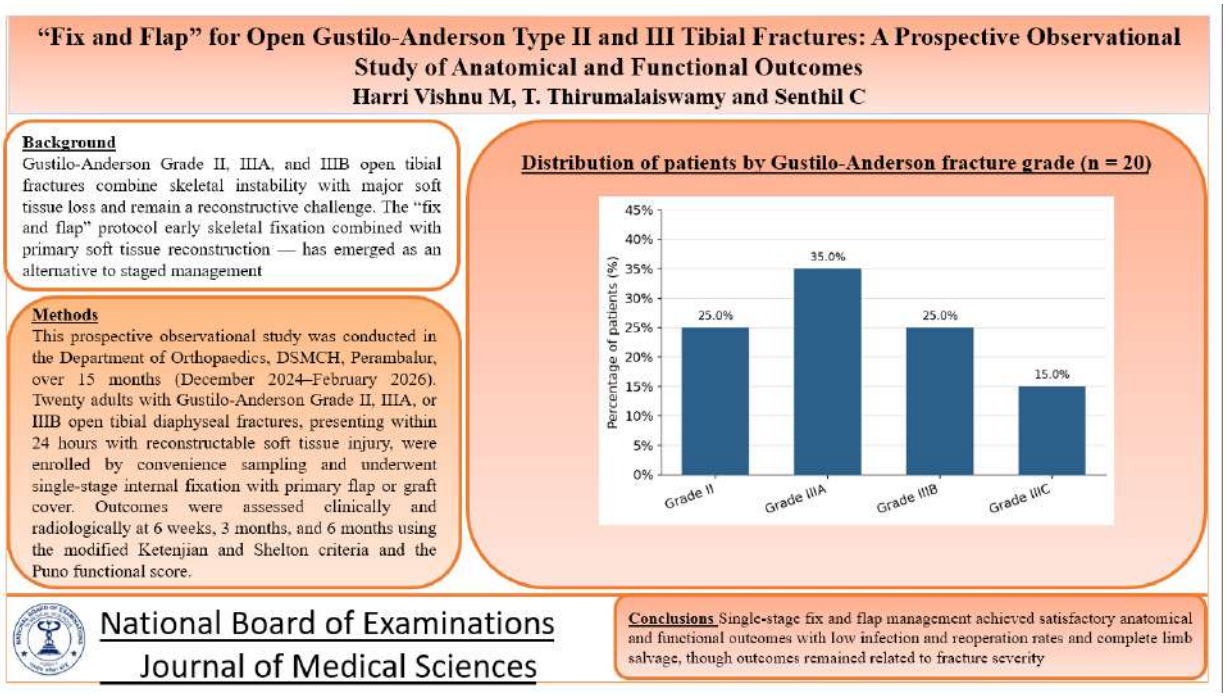
Abstract

Background: Gustilo-Anderson Grade II, IIIA, and IIIB open tibial fractures combine skeletal instability with major soft tissue loss and remain a reconstructive challenge. The "fix and flap" protocol early skeletal fixation combined with primary soft tissue reconstruction — has emerged as an alternative to staged management. **Materials and Methods:** This prospective observational study was conducted in the Department of Orthopaedics, DSMCH, Perambalur, over 15 months (December 2024–February 2026). Twenty adults with Gustilo-Anderson Grade II, IIIA, or IIIB open tibial diaphyseal fractures, presenting within 24 hours with reconstructable soft tissue injury, were enrolled by convenience sampling and underwent single-stage internal fixation with primary flap or graft cover. Outcomes were assessed clinically and radiologically at 6 weeks, 3 months, and 6 months using the modified Ketenjian and Shelton criteria and the Puno functional score. Data were analysed using IBM SPSS v26. **Results:** Mean age was 40.30±8.57 years; Grade IIIA fractures were most common (35%). Mean time to soft tissue cover was 47.45±12.58 hours and mean time to radiological union was 23.30±3.64 weeks. Fasciocutaneous flaps were used in 35% of patients. Complications occurred in 45% of patients (osteomyelitis 10%, deep infection 10%, restricted knee motion 10%, superficial infection 5%, nonunion 5%, delayed union 5%), and 10% required reoperation. At 6 weeks, 60% achieved full weight-bearing. Functional outcome was excellent in 20%, good in 30%, fair in 30%, and poor in 20% (80% satisfactory), with 100% limb salvage and no mortality. **Conclusion:** Single-stage fix and flap management achieved satisfactory anatomical and functional outcomes with low infection and reoperation rates and complete limb salvage, though outcomes remained related to fracture severity.

Keywords: Fix and flap, Gustilo-Anderson classification, open tibial fracture, soft tissue reconstruction, functional outcome

*Corresponding Author: Senthil C
Email: drcs28183@gmail.com

Graphical Abstract



Introduction

Open fractures of the tibia are among the most challenging injuries encountered in orthopaedic trauma practice. The tibia is the most frequently fractured long bone, and its subcutaneous anteromedial surface renders it particularly vulnerable to exposure following high-energy trauma such as road traffic accidents and falls from height [1]. The Gustilo-Anderson classification remains the most widely used system for grading the severity of open fractures and guiding management; Type II and Type III (IIIA and IIIB) injuries are characterised by extensive soft tissue loss, periosteal stripping, contamination, and occasionally segmental bone loss, and typically require a multidisciplinary approach for an optimal outcome [2].

Conventional management of open tibial fractures has followed a staged protocol — debridement, temporary external fixation, and delayed wound cover once the wound bed is considered clean [3]. This delay in soft tissue coverage has been associated with an increased risk of infection, nonunion, prolonged hospitalisation, and inferior functional recovery, particularly given the tibia's comparatively poor soft tissue envelope and vascularity [4].

Godina's work in the 1980s demonstrated that early microsurgical reconstruction, ideally within 72 hours of injury, reduced infection and nonunion rates compared with delayed coverage [5]. Building on this principle, Gopal et al. described the "fix and flap" protocol, combining definitive skeletal fixation with primary soft tissue reconstruction, usually within the first three days of injury, converting an open wound into a closed one at the earliest opportunity [6]. Single-stage combined orthopaedic and plastic surgical management — the "orthoplastic" approach — has since been associated with a reduced hospital stay and fewer

complications compared with staged protocols [7,8].

The timing of definitive coverage continues to be debated. Byrd et al. proposed a timing-based classification of acute (<72 hours), subacute (72 hours to 3 months), and chronic (>3 months) reconstruction, and reported superior outcomes with earlier intervention [9]. International guidelines now recommend that patients with severe open fractures be assessed jointly by orthopaedic and plastic surgical teams, ideally within 24 hours of injury, to enable coordinated single-stage management [7,10].

Despite growing evidence favouring the fix and flap approach, prospective outcome data from Indian tertiary care settings remain limited. This study was undertaken to evaluate the anatomical and functional outcomes of Gustilo-Anderson Grade II, IIIA, and IIIB open tibial fractures managed by early locking intramedullary nailing or plating combined with primary soft tissue reconstruction, and to document the methods of soft tissue reconstruction employed.

Materials and Methods

Study design, setting, and duration

This prospective observational study was conducted in the Department of Orthopaedics, Dhanalakshmi Srinivasan Medical College and Hospital (DSMCH), Perambalur, Tamil Nadu, India, over 15 months (December 2024 to February 2026), to assess the anatomical and functional outcomes of open Gustilo-Anderson Grade II and IIIA/IIIB tibial fractures managed by the fix and flap protocol — early skeletal stabilisation with locking intramedullary interlocking nailing or plating, combined with primary soft tissue reconstruction.

Study population Sample size and sampling

Study population included patients presenting with Tibial fractures. A formal sample size calculation was not performed, as this was an exploratory prospective observational study. All consecutive eligible patients fulfilling the inclusion and exclusion criteria and presenting during the predefined 15-month study period were included. Adults (>20 years) presenting within 24 hours of injury with high-grade open tibial diaphyseal fractures (Gustilo-Anderson Grade II, IIIA, or IIIB) and primarily reconstructable soft tissue injury were included. Patients with open growth plates, intra-articular extension into the proximal or distal tibia, Grade IIIC fractures with vascular compromise, grossly contaminated or non-reconstructable wounds, or those who declined consent were excluded. A total of 20 patients were enrolled by convenence sampling, representing the complete cohort available during the study period.

Ethical considerations

Institutional Ethics Committee approval was obtained prior to commencement of the study. Written informed consent was obtained from all participants (or their legal guardians, where applicable) after explaining the study objectives, procedures, risks, and benefits. Participation was voluntary, and confidentiality of patient data was maintained throughout.

Procedure and postoperative care

A semi-structured proforma was used to record sociodemographic data, mechanism and timing of injury, fracture classification, intraoperative findings, and postoperative outcomes. All patients

underwent initial debridement followed by internal fixation with a locking intramedullary nail or plate, as appropriate to the fracture pattern, with primary soft tissue cover provided in the same stage using local, regional, or free flaps, or split-thickness skin grafting, depending on the extent of the defect. Postoperatively, patients received broad-spectrum intravenous antibiotics, routine wound inspection and dressing, and early mobilisation and physiotherapy guided by fixation stability and flap healing. Follow-up clinical and radiological assessment was performed at 6 weeks, 3 months, and 6 months.

Outcome measures

Anatomical outcome was assessed by time to radiological union on serial radiographs and the occurrence of complications (infection, malunion, nonunion). Functional outcome was assessed using the Puno functional score and the modified Ketenjian and Shelton criteria (as modified by Yokoyama), incorporating pain, range of motion, strength, residual deformity, activities of daily living, and sensation.

Statistical analysis

Data were entered in Microsoft Excel and analysed using IBM SPSS version 26. Descriptive statistics (mean, standard deviation, frequency, percentage) summarised the data; the chi-square test was used for categorical variables and the paired t-test/Wilcoxon signed-rank test for pre- and post-intervention comparisons. A p-value <0.05 was considered statistically significant.

Results

Twenty patients with Gustilo-Anderson Grade II, IIIA, IIIB, or IIIC open tibial fractures were studied. The majority (60%) were aged 40–49 years (mean age 40.30±8.57 years), with an equal male:female distribution (10:10, 50% each). Left-hand dominance was present in 65% of patients, while the right limb was more frequently injured (60%). Self-fall (40%) was the leading mechanism of injury, followed by assault (35%) and road traffic accidents (25%). Associated injuries were present in 45% of patients, most commonly multiple fractures (44.4%). (Table 1)

Table 1. Sociodemographic and injury characteristics (n = 20)

Variable	Category	n	%
Age group (years)	20–29	4	20.0
	30–39	2	10.0
	40–49	12	60.0
	>49	2	10.0
Sex	Male	10	50.0
	Female	10	50.0
Affected side	Right	12	60.0
	Left	8	40.0

Variable	Category	n	%
Cause of injury	Self-fall	8	40.0
	Assault	7	35.0
	Road traffic accident	5	25.0
Associated injuries	Present	9	45.0
	Absent	11	55.0

Grade IIIA injuries were the most common (35%), followed by Grade II and Grade IIIB (25% each) and Grade IIIC (15%) (Figure 1). On AO/OTA classification, types 42-A2 and 43-B1 were most frequent (20% each), followed by 43-C1 (15%) (Table 2).

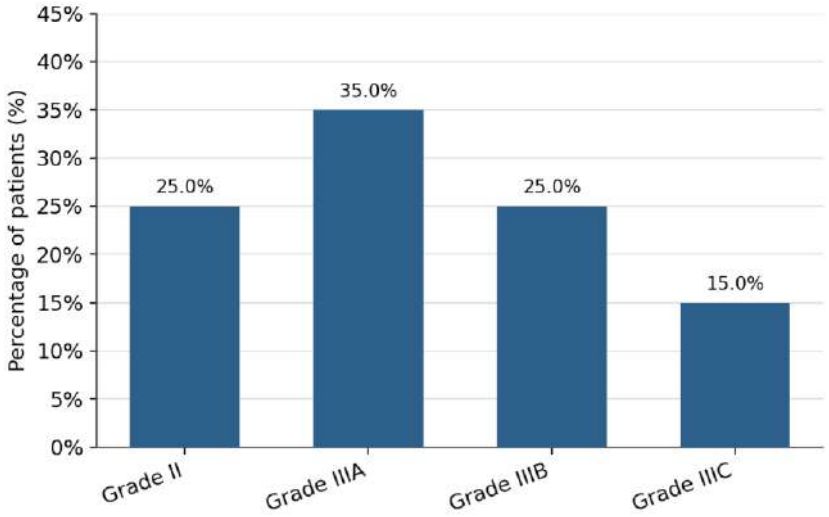


Figure 1. Distribution of patients by Gustilo-Anderson fracture grade (n = 20)

Table 2. AO/OTA fracture classification (n = 20)

AO/OTA type	n	%
42-A2	4	20.0
43-B1	4	20.0
43-C1	3	15.0
Other types (combined)	9	45.0

Fasciocutaneous flaps were the most frequently used method of soft tissue reconstruction (35%), followed by muscle pedicle flaps (25%); primary closure and split-thickness skin grafting each accounted for 20% (Figure 2). Soft tissue cover was achieved immediately (within 24 hours) in 35% of patients and early (within 72 hours) in a further 45%, with the mean time to cover being 47.45±12.58 hours (Table 3).

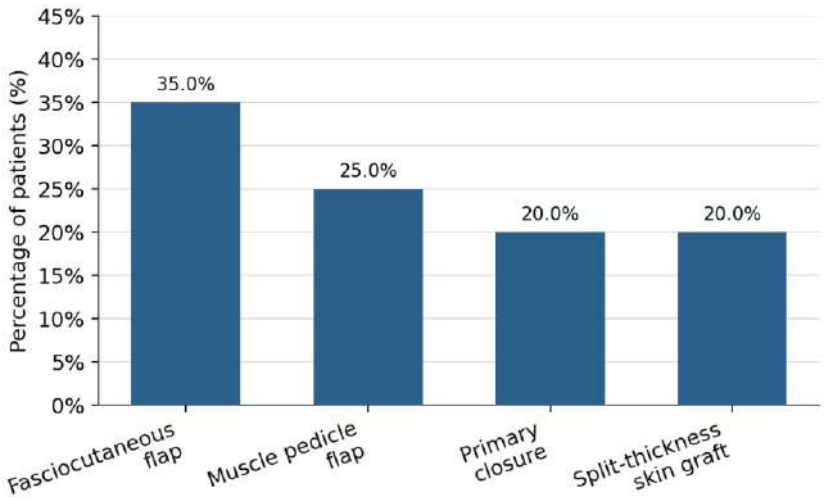


Figure 2. Method of soft tissue reconstruction (n = 20)

Table 3. Timing of soft tissue cover (n = 20)

Timing of cover	n	%
Immediate (<24 h)	7	35.0
Early (24–72 h)	9	45.0
Delayed (>72 h)	4	20.0

Fifty-five per cent of patients had no complications. Deep infection, osteomyelitis, and restricted knee motion each occurred in 10% of patients, while superficial infection, nonunion, and delayed union each occurred in 5% (Figure 3). Reoperation was required in 10% of patients (2 of 20). There were no mortality and no amputation in this series.

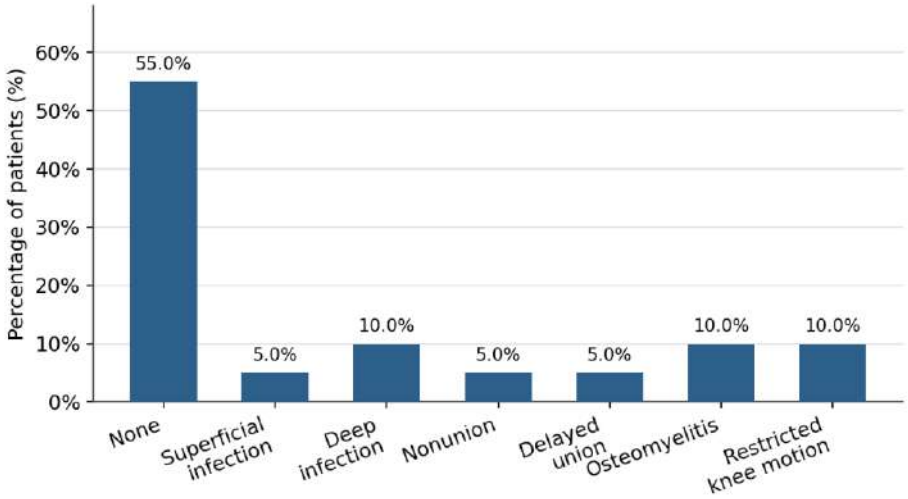


Figure 3. Postoperative complications (n = 20)

At 6 weeks, 60% of patients had achieved full weight-bearing, 15% partial weight-bearing, and 25% remained non-weight-bearing. Physiotherapy compliance was good in 55%, moderate in 30%, and poor in 15% of patients (Table 5). By the modified Ketenjian and Shelton criteria, functional outcome was excellent in 20%, good in 30%, fair in 30%, and poor in 20% of patients — an overall satisfactory (excellent/good/fair) outcome in 80% (Figure 4).

Table 5. Mobilisation and physiotherapy compliance at final follow-up (n = 20)

Variable	Category	n	%
Weight-bearing at 6 weeks	Full	12	60.0
	Partial	3	15.0
	None	5	25.0
Physiotherapy compliance	Good	11	55.0
	Moderate	6	30.0
	Poor	3	15.0

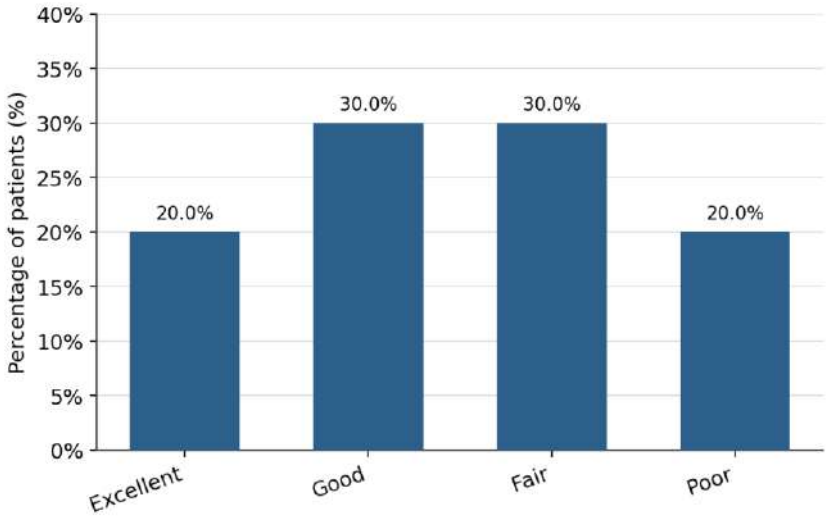


Figure 4. Functional outcome by the modified Ketenjian and Shelton criteria (n = 20)

The mean Injury Severity Score was 16.25±3.52 and the mean time to surgery was 12.30±5.59 hours. The mean time to radiological union was 23.30±3.64 weeks. The mean Puno functional score (of a maximum 30) was 15.55±3.93 (Table 6).

Table 6. Descriptive statistics of key clinical and functional variables (n = 20)

Variable	Mean ± SD
Age (years)	40.30 ± 8.57
Injury Severity Score	16.25 ± 3.52
Time to soft tissue cover (hours)	47.45 ± 12.58
Time to surgery (hours)	12.30 ± 5.59
Time to radiological union (weeks)	23.30 ± 3.64
Pain score	2.60 ± 1.67
Range of motion score	2.45 ± 1.79
Strength score	2.55 ± 1.54
Residual deformity score	2.95 ± 2.01
Activities of daily living score	2.75 ± 1.65
Sensation score	2.25 ± 1.94
Puno functional score (/30)	15.55 ± 3.93

On comparison across Gustilo-Anderson grades, Grade II fractures showed the shortest mean time to union (20.40±2.61 weeks) and the best activities-of-daily-living scores (3.60±1.67), while Grade IIIC fractures showed the lowest Puno functional score (12.67±3.79) despite the shortest flap timing (33.67±7.37 hours), reflecting greater intrinsic injury severity in this subgroup, yet none showed a statistical significance (Table 7).

Table 7. Clinical and functional profile across Gustilo-Anderson classifications

Variable	Grade II (n=5)	Grade IIIA (n=7)	Grade IIIB (n=5)	Grade IIIC (n=3)	p-value by Kruskal Wallis test
Age (years)	45.60±3.05	38.71±9.11	38.20±10.28	38.67±11.15	0.496
Injury Severity Score	15.60±2.70	15.71±4.07	17.60±4.04	16.33±3.79	0.812
Flap timing (h)	54.40±9.37	49.86±12.08	45.40±14.12	33.67±7.37	0.130
Time to union (weeks)	20.40±2.61	24.29±3.59	24.40±2.97	24.00±5.29	0.244
Puno functional score (/30)	16.40±4.28	15.43±3.31	16.60±4.77	12.67±3.79	0.564

Discussion

This prospective study of 20 patients with Gustilo-Anderson Type II, IIIA, and IIIB tibial fractures managed using the fix and flap approach demonstrated satisfactory anatomical and functional outcomes with an acceptable complication profile. Although the present study did not include a comparison group, the findings suggest that single-stage fixation with early soft tissue reconstruction is a feasible management strategy for appropriately selected patients and are consistent with outcomes reported in previous literature.

The mean time to radiological union in this study was 23.3 weeks, comparable to the 22-week union time reported by Gupta et al. [11] and shorter than the 29.7 weeks reported by Neerumala et al. [12] and the 30.1 weeks reported by Karikalan [13]. Singh et al. reported a longer mean union time of 40.3 weeks, which the authors attributed to the inclusion of Grade IIIC fractures and delays in definitive management [14].

Infection remains a key determinant of functional outcome in open fractures. In this series, no deep infections occurred and only 5% of patients developed superficial infection, notably lower than the 12.1% deep infection rate (with 9% flap failure) reported by Singh et al. [14] and the 7% superficial and 7% deep infection rates reported by Neerumala et al. [12]. Ramasamy reported 16% deep infection and 27% pin-tract infection with a staged fix-and-shift protocol, reflecting the challenges associated with delayed definitive coverage [15]. The comparatively low infection rate observed in this series may be attributable to rigorous debridement, early flap coverage (mean 47.45 hours), and appropriate perioperative antibiotic administration. However, because this study lacked a comparison group, the specific contribution of the fix and flap protocol to the observed infection rate cannot be determined.

By the modified Ketenjian and Shelton criteria, 80% of patients in this study achieved a satisfactory outcome (20% excellent, 30% good, 30% fair), comparable to the 84.5% satisfactory outcome reported by Neerumala et al. [12] and the 91.67% satisfactory outcome (Tucker's score) reported by Ali et al. [16]. Singh et al. reported a lower rate of 57.5% excellent/good outcomes with a substantial 24.2% poor outcome rate, likely reflecting greater injury severity in their cohort [14]. The predominant use of fasciocutaneous flaps (35% of reconstructions overall) in this series is consistent with the observation by Karikalan that fasciocutaneous flaps effectively cover moderate-sized defects with lower donor-site morbidity than muscle flaps [13].

Complication rates in this study (5% nonunion, 5% delayed union, 10% osteomyelitis) were broadly consistent with, or lower than, published series. Gupta et al. reported 5% deep infection and a single case of delayed union [11]. A systematic review by Myatt et al. reported wide variability across studies, with infection being the most frequently reported complication [17]. Ramasamy reported a considerably higher complication and reoperation burden (approximately 50%) with an external fixator-based approach [15]. Only 10% of patients in this series required reoperation, lower than the reoperation rates reported with staged fixation by Cullen et al. and Ramasamy, in whom infection and construct instability were the principal drivers of further surgery [15,18].

At 6 weeks, 60% of patients in this series were fully weight-bearing, comparable to the trend reported by Ayoub et al., who observed 88.5% full weight-bearing by 10 weeks with intramedullary nailing versus only 41.7% with external fixation [19]. These findings are consistent with previous reports suggesting that stable fixation combined with timely soft tissue coverage may facilitate early mobilisation; however, this relationship cannot be established definitively from the present observational study. Good physiotherapy compliance (55%) in this series was associated with better functional scores, consistent with the observation by Patil et al. that early weight-bearing and structured physiotherapy were associated with excellent outcomes in 80% of their cohort, underscoring rehabilitation as an important, often underemphasised, determinant of final functional recovery [20].

There was no mortality and complete (100%) limb salvage in this series, in contrast to the 37 amputations — many attributable to flap failure, infection, or systemic factors — reported in the systematic review by Myatt et al. [17]. This finding is consistent with the concept that timely definitive management within a coordinated orthoplastic framework may contribute to favourable limb salvage outcomes. However, the observational design of the present study does not permit causal inference regarding the effectiveness of this management strategy.

This study is limited by the absence of a formal sample size estimation and a relatively small sample size (n = 20), single-centre design, and relatively short follow-up (6 months), which preclude firm conclusions on long-term union and functional recovery, particularly in Grade IIIC injuries. Convenience sampling may have introduced selection bias, as the enrolled patients may not fully represent the broader population limiting the generalisability of the study results. The absence of a comparison or control group precludes direct assessment of the superiority of the single stage “fix and flap” approach over conventional staged management. Larger, multicentric, and longer-term prospective studies are warranted to confirm these findings.

Conclusion

In this prospective study of 20 patients with open tibial fractures managed by single-stage fix and flap reconstruction, Grade IIIA injuries were the most common presentation, and fasciocutaneous flaps were the most frequently used method of soft tissue cover. The mean time to union across all grades was 23.30 weeks, with a low overall complication rate (45%), a 10% reoperation rate, and complete limb salvage with no mortality. Functional outcome by the modified Ketenjian and Shelton criteria was satisfactory in 80% of patients. Grade II fractures demonstrated the most favourable clinical and functional profile, whereas Grade IIIC fractures were associated with greater complication and reoperation risk and poorer functional scores, indicating that fracture severity remains an important determinant of recovery. Early soft tissue coverage combined with good physiotherapy compliance was associated with favourable functional recovery in this cohort. These findings suggest that single-stage fix and flap management is a feasible treatment strategy for selected patients with severe open tibial fractures; however, comparative studies are required to establish its effectiveness relative to other treatment approaches.

Clinical Implications

The findings of this study suggest that achieving definitive soft tissue coverage within the early post-injury period is feasible in most patients with Gustilo-Anderson Grade II and III open tibial fractures managed in a tertiary care setting. The favourable limb salvage rate and satisfactory functional outcomes observed in this cohort highlight the importance of prioritizing early definitive management and may assist clinicians in counselling patients regarding expected recovery following single-stage reconstruction.

Authors' Contributions

HVM has contributed to the conceptualization, design of the study and manuscript review. TT contributed towards design of the study, literature search and manuscript review. SC has contributed towards data acquisition, statistical analysis, Manuscript writing and editing. SC acted as the corresponding author for this manuscript

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

No funding was received for conducting this study.

Ethical Approval

The study was approved by the Institutional Ethics Committee of Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur. (IECHS/IRCHSNo.638/Dt:09.12.2024)
Written informed consent was obtained from all participants.

References

1. Court-Brown CM, Bugler KE, Clement ND, Duckworth AD, McQueen MM. The epidemiology of open fractures in adults: a 15-year review. Injury. 2012;43(6):891-7.
2. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones. J Bone Joint Surg Am. 1976;58(4):453-8.
3. McGraw JM, Lim EV. Treatment of open tibial-shaft fractures. External fixation and secondary intramedullary nailing. J Bone Joint Surg Am. 1988;70(6):900-11.
4. Giannoudis PV, Papakostidis C, Roberts C. A review of the management of open fractures of the tibia and femur. J Bone Joint Surg Br. 2006;88(3):281-9.
5. Godina M. Early microsurgical reconstruction of complex trauma of the extremities. Plast Reconstr Surg. 1986;78(3):285-92.
6. Gopal S, Majumder S, Batchelor AG, Knight SL, De Boer P, Smith RM. Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. J Bone Joint Surg Br. 2000;82(7):959-66.
7. Naique SB, Pearse M, Nanchahal J. Management of severe open tibial fractures: the need for combined orthopaedic and plastic surgical treatment in specialist centres. J Bone Joint Surg Br. 2006;88(3):351-7.
8. Kotsougiani-Fischer D, Choi D, Ring A, Chia B, Steiert AE, Zhang Z, et al. Primary versus secondary flap coverage in severe open tibial fractures: a retrospective cohort study. Injury. 2020;51(3):706-13.

9. Byrd HS, Spicer TE, Cierny G 3rd. Management of open tibial fractures. Plast Reconstr Surg. 1985;76(5):719-30.
10. Boriani F, Ul Haq A, Baldini T, Urso R, Granchi D, Baldini N, et al. Orthoplastic surgical collaboration is required to optimise the treatment of severe limb injuries: a multi-centre, prospective cohort study. J Plast Reconstr Aesthet Surg. 2017;70(6):715-22.
11. Gupta R, Maheshwari V, Gour S, Nandkarni D, Verma KK. Treatment of grade 3A and 3B compound tibial fractures with external fixation and primary immediate bone grafting. Surg Update Int J Surg Orthop. 2019;5(3):126-31.
12. Neerumala P, Khaleel VM, Kanamarlapudi M. Evaluation of functional and radiological outcome of type III open distal tibial fractures treated with early internal fixation followed by soft tissue reconstruction (fix and flap): a prospective study. Int J Orthop Sci. 2020;6(4):274-80.
13. Karikalan T. Flaps in the management of open tibial fractures. Int J Res Orthop. 2019;5(3):504-8.
14. Singh J, Dhillon MS, Dhatt SS. Single-stage “fix and flap” gives good outcomes in Grade 3B/C open tibial fractures: a prospective study. Malays Orthop J. 2020;14(1):61-73.
15. Ramasamy PR. Management of Gustilo Anderson IIIB open tibial fractures by primary fascio-septo-cutaneous local flap and primary fixation: the ‘fix and shift’ technique. Indian J Orthop. 2017;51(1):55-68.
16. Ali A, Rahman M, Faruquee SR, Islam T, Rahim ZZ, Yusuf A. Treatment of open fracture of shaft of tibia-fibula Gustilo type III-B by SIGN interlocking nail and wound coverage by muscle flap within 72 hours of injury. Int J Res Orthop. 2017;3(5):898-903.
17. Myatt A, Saleeb H, Robertson GAJ, Bourhill JK, Page PRJ, Wood AM. Management of Gustilo-Anderson IIIB open tibial fractures in adults — a systematic review. Br Med Bull. 2021;139(1):48-58.
18. Cullen S, Flaherty D, Fitzpatrick N, Ali A, Elkhidir I, Pillai A. Outcomes following surgical fixation of Gustilo-Anderson IIIB open tibial fractures. Acta Orthop Belg. 2024;90(1):83-9.
19. Ayoub I, Malik AT, Singh T, Basit A, Arfee S. Short term outcome of Gustilo Anderson open type 3A mid shaft tibia fractures using intramedullary interlocking nail and external fixator: a prospective cohort study. Int J Health Sci. 2022;6(S4):8280-6.
20. Patil MY, Gupta SM, Kurupati SKC, Agarwal S, Chandarana V. Definitive management of open tibia fractures using limb reconstruction system. J Clin Diagn Res. 2016;10(7):RC01-4.

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ORIGINAL ARTICLE

Mental Health Literacy and Help-Seeking Attitudes Among Medical Students at a Tertiary Care Teaching Institution in South India

Manikandan R,[1,*] Naveensingh S G[2] and M Vinoth Kumar[3]

[1]*Assistant Professor, Department of Community Medicine, Government Cuddalore Medical College and Hospital, Tamil Nadu*
[2]*Postgraduate, Department of Community Medicine, Government Cuddalore Medical College and Hospital, Tamil Nadu*
[3]*Senior Resident, Department of Community Medicine, Sri Venkateswaraa Medical College Hospital and Research Institute, Sri Venkateswaraa University, Redhills, Chennai-600067*

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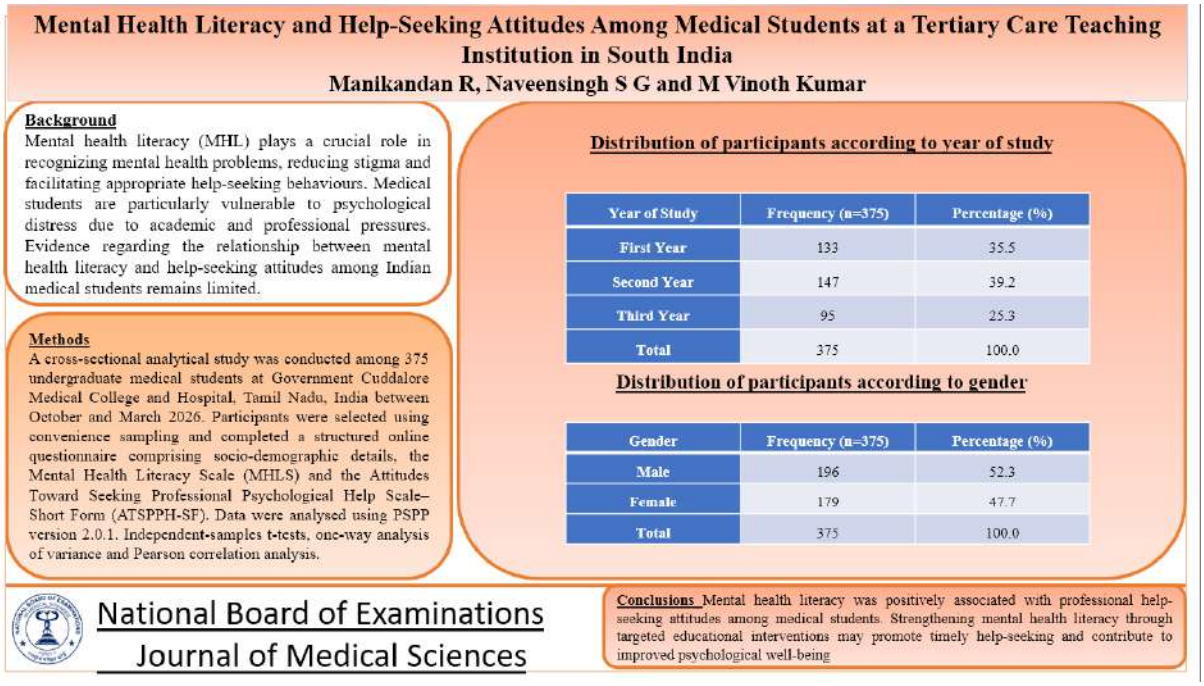
Abstract

Background: Mental health literacy (MHL) plays a crucial role in recognizing mental health problems, reducing stigma and facilitating appropriate help-seeking behaviours. Medical students are particularly vulnerable to psychological distress due to academic and professional pressures. Evidence regarding the relationship between mental health literacy and help-seeking attitudes among Indian medical students remains limited. **Methodology:** A cross-sectional analytical study was conducted among 375 undergraduate medical students at Government Cuddalore Medical College and Hospital, Tamil Nadu, India between October and March 2026. Participants were selected using convenience sampling and completed a structured online questionnaire comprising socio-demographic details, the Mental Health Literacy Scale (MHLS) and the Attitudes Toward Seeking Professional Psychological Help Scale–Short Form (ATSPPH-SF). Data were analysed using PSPP version 2.0.1. Independent-samples t-tests, one-way analysis of variance and Pearson correlation analysis were performed with statistical significance set at $p<0.05$. **Results:** The mean MHLS score was 110.27 ± 14.82 while the mean ATSPPH-SF score was 17.24 ± 5.42. More than half of the participants (53.3%) demonstrated average mental health literacy and 58.4% reported positive help-seeking attitudes. Female students had significantly higher MHLS scores than males (113.56 ± 13.97 vs. 107.08 ± 14.84, $p<0.001$). No significant differences in mental health literacy or help-seeking attitudes were observed according to residence. Help-seeking attitudes differed significantly across academic years ($p=0.045$). A moderate positive correlation was observed between mental health literacy and help-seeking attitudes ($r=0.380$, $p<0.001$). **Conclusions:** Mental health literacy was positively associated with professional help-seeking attitudes among medical students. Strengthening mental health literacy through targeted educational interventions may promote timely help-seeking and contribute to improved psychological well-being among future healthcare professionals.

Keywords: Mental Health Literacy, Help-Seeking Behaviour, Medical Students, Psychological Distress, Mental Disorders

*Corresponding Author: Manikandan R
Email: drmanikandan16@gmail.com

Graphical Abstract



Introduction

Mental health is an essential part of good health and forms a vital part of the fundamental rights of human beings. This includes emotional, psychological and social well-being and has an impact on how people perceive, think, interact with others, manage stressors, act and make important decisions in life [1,2]. Mental disorders form one of the major public health issues in the world contributing significantly to the burden of diseases. The World Health Organization estimates that one in every eight people around the world suffer from a mental disorder with anxiety disorders and depressive disorders being some of the most common illnesses [1,3]. Although there exist effective interventions for these disorders a huge proportion of people suffering from mental disorders lack access to adequate services especially in poorer nations [4,5].

Young adults and college students are an at-risk group when it comes to developing mental disorders owing to academic stressors, societal changes, financial struggles, and future career uncertainties [6,7]. Medical students fall under this category of at-risk individuals because of the stressful and challenging conditions faced during their studies including prolonged periods of studying, immense academic pressures, regular examinations and encounters with illness and human suffering [8,9]. Several research studies have highlighted the increased incidence of mental illnesses among medical students including depression, anxiety, psychological distress, burnout and suicidal ideations [10–13]. In a systematic review Rotenstein et al. found that about one-fourth of the students enrolled in medical courses exhibited signs of depressive symptoms however very few sought professional advice [10]. On the other hand a meta-analysis conducted by Quek et al. revealed the high rate of anxiety problems among medical students around the world [11].

Although there is an increasing prevalence of mental health disorders among young people help-seeking behaviours are still insufficient. Due to such factors as the fear of being stigmatized, lack of information on seeking help, confidentiality issues, discrimination fears, cost considerations and mental health misperception many students who suffer from psychological conditions fail to seek mental health assistance [14–17]. The delay in help-seeking may lead to deteriorated psychological condition, diminished academic achievements, poor quality of life and higher risks of suicidal behaviour [18]. It is thus critical to investigate the reasons for poor help-seeking behaviours in order to create successful intervention strategies.

Mental health literacy has now been recognized as an important predictor for mental health and help seeking. Mental health literacy was initially described by Jorm et al. as "Knowledge and beliefs about mental disorders which aid their recognition, management or prevention" [19]. Mental health literacy encompasses recognition of specific mental disorders, knowledge of risk factors and causes awareness of self-help techniques and professional help for such disorders, attitudes that help in the recognition and help-seeking and ways of acquiring information regarding mental illnesses [20,21]. Mental health literacy is strongly correlated with mental health status and help seeking [22,23].

Studies have shown that mental health literacy is highly influential in the development of attitudes towards seeking help from professionals. People who are well-informed about mental illnesses tend to have higher awareness about their own symptoms, view therapy positively and seek help from professionals when necessary [24,25]. On the other hand low levels of mental health literacy may lead to misunderstandings of what mental illnesses involve, stigmatization, reluctance to undergo therapy and negative views about mental health interventions [26,27]. Therefore, enhancing mental health literacy has emerged as an effective approach to tackling the treatment gap and fostering mental wellness in youth populations [21,28].

A number of studies carried out amongst university students have looked at the link between mental health literacy and help-seeking attitudes. Martina and Deepthi found that there is a positive correlation between mental health literacy and attitude towards seeking professional psychological help amongst college students in South India [29]. Likewise, Hussain and Zaini found that there is a positive correlation between mental health literacy and help-seeking attitudes amongst university students in the Maldives and self-stigma played an adverse role in the intention of seeking help [30]. Baklola et al. found that many Egyptian university students who needed mental health services did not seek any professional help despite suffering from psychological problems [31].

But there have been inconsistencies in previous studies as well. A recent study carried out on Nepali college students revealed no link between mental health literacy and attitudes towards mental illness indicating the impact of sociocultural and demographic characteristics on mental well-being and behaviour [32]. This diversity shows that the connection between mental health literacy and help-seeking behaviour may vary from culture to culture.

Mental health disorders significantly add to the disease burden of

the country, but a large gap exists in treatment. It was revealed in the National Mental Health Survey that up to 80-90% of people suffering from mental health disorders fail to receive appropriate treatment primarily because of inadequate knowledge and stigma associated with it [33]. In the case of medical students who would be future physicians appropriate mental health literacy is especially crucial not only for maintaining their own mental well-being but also for developing positive attitudes towards mentally ill patients and ensuring proper referral in the clinical context [34,35]. However, research on the matter is scarce in the context of Indian medical students, particularly those from Tamil Nadu.

Moreover despite previous research on mental health literacy, stigmatization and mental health help-seeking, very little work has been done on assessing the link between mental health literacy and mental health help-seeking attitudes amongst medical students with the help of validated measures like MHLS and ATSPPH-SF [24,29,30]. It is crucial to understand this link because it will help us design educational interventions that raise mental health awareness, lessen stigmatization and facilitate mental health help-seeking.

Thus, the current research has been carried out to determine the extent of mental health literacy and help-seeking attitude of medical students as well as the correlation between these two factors in relation to certain socio-demographic factors. It is expected that the results will offer important information regarding the mental health literacy of future health care providers.

Materials and Methods

Study Design and Setting

This is an analytical cross-sectional study which was performed on the undergraduate students in medicine studying at the Government Cuddalore Medical College & Hospital (GCMCH), Chidambaram, Tamil Nadu, India. This study was done over a period from October 2025 to March 2026. This study was aimed at finding the association of mental health literacy and attitude towards psychological counselling among medical students with certain socio-demographic factors.

Study Population

The participants were the students of Bachelor of Medicine and Bachelor of Surgery (MBBS) who were enrolled in Government Cuddalore Medical College and Hospital. The students in their first year, second year and third year of MBBS program were selected as the study population. All the students who agreed to take part in the study and gave their consent were chosen for the study. Excluded from the study were interns, non-medical students and those unwilling to participate in the study.

Sample Size and Sampling Technique

The sample size calculation was done through the application of the formula for single population proportion which is $n = Z^2pq/d^2$. A prevalence rate of 58% was assumed considering that the results from another study done among college students yielded the same result. Given a confidence level of 95% ($Z = 1.96$), an acceptable margin error of 5% and a prevalence of 0.58, the minimum sample size needed was determined to be 375 respondents. Convenience sampling technique was utilized in obtaining respondents.

Data Collection Instruments

The data collection method involved the administration of structured and self-report questionnaires administered via Google Forms. The questionnaire comprised three main sections. The first part involved the gathering of demographic information such as age, gender, year of study and place of residence. The second part of the questionnaire involved the assessment of mental health literacy which was done using the Mental Health Literacy Scale (MHLS) which is a tool devised by O'Connor and Casey to measure an individual's knowledge, comprehension and beliefs related to mental health conditions and possible treatments. The last section involved the measurement of attitudes towards seeking professional psychological help through the Attitudes Toward Seeking Professional Psychological Help Scale–Short Form (ATSPPH-SF) designed by Fischer and Farina.

Study Procedure

The rationale behind carrying out this study was communicated to prospective subjects prior to starting data collection. Students willing to take part signed an informed consent form online prior to gaining access to the survey. Survey invitations were sent via the appropriate university communication channels and social media sites frequented by the target group. Data were collected anonymously to guarantee privacy and ensure candid responses from all the subjects. The survey took about 10–15 minutes to complete.

Statistical Analysis

Data was inputted in Microsoft Excel and then analysed using PSPP Statistical Software Version 2.0.1. Categorical data were analysed using frequencies and percentage while continuous data were reported as mean ± Standard Deviation. Normality tests were carried out on continuous data before conducting inferential tests. Comparison of means of mental health literacy and help seeking attitude between two categories (gender and place of residence) was done using independent-sample t-tests. On the other hand comparison of means across years was done using one-way ANOVA. The correlation coefficient was computed using Pearson's test to measure the correlation between mental health literacy and help-seeking attitude. Statistical significance was defined as a p-value less than 0.05.

Ethical Considerations

The present study adhered to the guidelines mentioned in the Declaration of Helsinki for ethical practices. Approval for conducting the study was sought from the institutional board prior to beginning the study. Participation was purely voluntary and written informed consent was sought from all participants prior to gathering data. There was no use of any personal identifiers, and the answers provided were kept confidential. The participants were informed that they had the option of dropping out of the study at any point without facing any repercussions.

Results

From Table 1 below it can be observed that out of 375 students involved in the study there were 147 students (39.2%) from second year these formed the greatest number of students taking part in the study. The number of first-year students was 133 (35.5%) while 95 (25.3%) students were from third year.

Table 1. Distribution of participants according to year of study

Year of Study	Frequency (n=375)	Percentage (%)
First Year	133	35.5
Second Year	147	39.2
Third Year	95	25.3
Total	375	100.0

The gender distribution of the participants of the study can be seen in Table 2 below. From 375 participants 196 (52.3%) were males and 179 (47.7%) females thus showing that there was relative equality between male and female students.

Table 2. Distribution of participants according to gender

Gender	Frequency (n=375)	Percentage (%)
Male	196	52.3
Female	179	47.7
Total	375	100.0

The distribution of gender per year of study is highlighted in Table 3 below. For third-year students, 62 (46.3%) were males and 71 (53.7%) females. For second-year students 69 (46.9%) were males and 78 (53.1%) females. While for first-year students 47 (49.6%) were males and 48 (50.4%) females.

Table 3. Distribution of gender according to year of study

Year of Study	Male n (%)	Female n (%)
Third Year	62 (46.3)	71 (53.7)
Second Year	69 (46.9)	78 (53.1)
First Year	47 (49.6)	48 (50.4)

As evident from Table 4, 223 (59.5%) participants resided in urban areas while 152 (40.5%) participants lived in rural areas. Hence urban residents formed the majority group in the study sample.

Table 4. Distribution of participants according to place of residence

Residence	Frequency (n=375)	Percentage (%)
Rural	152	40.5
Urban	223	59.5
Total	375	100.0

Distribution of place of residence according to year of study is depicted in Table 5. Third-year students comprised of 88 (66.3%) participants residing in urban areas and 45 (33.7%) participants residing in rural areas. On the other hand among first-year students there were 83 (56.4%) urban residents and 64 (43.6%) rural residents. In addition, for second-year students 55 (57.8%) participants resided in urban areas, whereas 40 (42.2%) participants resided in rural areas.

Table 5. Distribution of residence according to year of study

Year of Study	Rural n (%)	Urban n (%)
Third Year	45 (33.7)	88 (66.3)
First Year	64 (43.6)	83 (56.4)
Second Year	40 (42.2)	55 (57.8)

Descriptive statistics for the scores obtained on MHLS and ATSPPH-SF scales are described in Table 6. The scores obtained by participants on MHLS varied between 62 and 160 with an average score of 110.27 ± 14.82. Likewise, participants ATSPPH-SF scale scores varied between 0 and 30 with an average score of 17.24 ± 5.42.

Table 6. Descriptive statistics of MHLS and ATSPPH-SF scores

Variable	Minimum	Maximum	Mean	Standard Deviation
MHLS Score	62	160	110.27	14.82
ATSPPH-SF Score	0	30	17.24	5.42

Table 7 illustrates the distribution of participants with regard to MHLS score categories. The number of participants who showed average mental health literacy constituted the majority with a total of 53.3%. High mental health literacy was exhibited by 84 participants (22.4%) and low mental health literacy was shown by 72 participants (19.2%). Very low mental health literacy level was found among 11 participants (2.93%) while very high MHLS was recorded among 8 (2.13%) participants.

Table 7. Distribution of participants according to Mental Health Literacy Scale scores

MHLS Score Category	Score Range	Frequency (N=375)	Percentage (%)
Very Low	60–80	11	2.93
Low	81–100	72	19.20
Average	101–120	200	53.30
High	121–140	84	22.40
Very High	141–160	8	2.13
Total	—	**375**	**100.00**

The distribution of mental health literacy levels with regard to year of study is illustrated in Table 8. The largest number of participants in each year of study fell into the average MHLS category with 80 participants from the first year 75 participants from the second year and 45 participants from the third year. The high MHLS category consisted of 28 participants in the first year 31 participants in the second year and 25 participants in the third year. Very high MHLS was rare among all years of study.

Table 8. Distribution of Mental Health Literacy Levels According to Year of Study (N = 375)

MHLS Score Category	First Year (n=133)	Second Year (n=147)	Third Year (n=95)	Total (N=375)
Very Low (60–80)	3	6	2	11
Low (81–100)	21	30	21	72
Average (101–120)	80	75	45	200
High (121–140)	28	31	25	84
Very High (141–160)	1	5	2	8
Total	**133**	**147**	**95**	**375**

As indicated in Table 9 a positive attitude towards professional psychological help-seeking was found among 219 (58.4%) participants while a negative attitude towards professional psychological help-seeking was found among 156 (41.6%) participants.

Table 9. Distribution of Participants Based On ATSPPH-SF Score

Help-Seeking Attitude	Frequency (N = 375)	Percentage (%)
Negative Attitude	156	41.6
Positive Attitude	219	58.4
Total	**375**	**100.0**

Table 10 depicts the attitude towards professional psychological help in accordance with the year of study. Thus, positive attitudes towards receiving help from professionals were noted in 77 (57.9%) first-year students 90 (61.2%) second-year students and 52 (54.7%) third-year students. At the same time negative attitudes were found in 56 (42.1%) first-year students 57 (38.8%) second-year students and 43 (45.3%) third-year students.

Table 10. Distribution of Help-Seeking Attitudes (ATSPPH-SF) According to Year of Study (N = 375)

Year of Study	Positive ATSPPH-SF Score n (%)	Negative ATSPPH-SF Score n (%)	Total
First Year (n=133)	77 (57.9)	56 (42.1)	133
Second Year (n=147)	90 (61.2)	57 (38.8)	147
Third Year (n=95)	52 (54.7)	43 (45.3)	95
Total (N=375)	**219 (58.4)**	**156 (41.6)**	**375**

The relationship between mental health literacy and gender can be seen from Table 11. Thus, MHLS values among female students were higher (113.56 ± 13.97) compared with males (107.08 ± 14.84). An independent-samples t-test revealed that the difference between the two groups was statistically significant ($t = -4.33$, $df = 373$, $p < 0.001$).

Table 11. Association between mental health literacy and gender

Gender	n	Mean MHLS Score	SD	t-value	df	p-value
Male	196	107.08	14.84	-4.33	373	<0.001
Female	179	113.56	13.97			

Table 12 depicts the relationship between mental health literacy and location. In particular the mean MHLS score in the sample of rural respondents was 109.01 ± 14.77, while for those living in cities the average value was 110.96 ± 14.84. The difference was not statistically significant ($t = -1.25$, $df = 373$, $p = 0.213$).

Table 12. Association between mental health literacy and residence

Residence	n	Mean MHLS Score	SD	t-value	df	p-value
Rural	152	109.01	14.77	-1.25	373	0.213
Urban	223	110.96	14.84			

According to Table 13 the average MHLS was 110.54 ± 12.42 for first year students 109.31 ± 16.55 for second-year students and 110.94 ± 15.23 for third-year students. There was no statistically significant difference in terms of mental health literacy levels between the three academic years (F = 0.41, p = 0.661) according to one-way analysis of variance.

Table 13. Association between mental health literacy and year of study

Year of Study	n	Mean MHLS Score	SD	F-value	p-value
First Year	133	110.54	12.42		
Second Year	147	109.31	16.55	0.41	0.661
Third Year	95	110.94	15.23		

Help-seeking attitude and gender association is indicated in Table 14. The average ATSPPH-SF score of female students was slightly higher (17.66 ± 5.31) than that of male students (16.85 ± 5.51). There was no statistically significant difference between the groups (t = -1.46, df = 373, p = 0.145).

Table 14. Association between help-seeking attitude and gender

Gender	n	Mean ATSPPH-SF Score	SD	t-value	df	p-value
Male	196	16.85	5.51	-1.46	373	0.145
Female	179	17.66	5.31			

Table 15 highlights the association between help-seeking attitude and residence. Those who resided in rural areas had a mean ATSPPH-SF score of 17.37 ± 4.89 whereas those who stayed in urban areas had an average score of 17.15 ± 5.77. There was no statistically significant difference between the two categories (t = 0.39, df = 373, p = 0.700).

Table 15. Association between help-seeking attitude and residence

Residence	n	Mean ATSPPH-SF Score	SD	t-value	df	p-value
Rural	152	17.37	4.89	0.39	373	0.700
Urban	223	17.15	5.77			

According to Table 16, the average ATSPPH-SF scores ranged from 16.34 ± 5.73 (first-year students) to 17.94 ± 5.38 (second-year students) and 17.38 ± 4.87 (third-year students). It was found that there was a statistically significant difference in the help-seeking attitude scores in three different academic years ($F = 3.12$, $p = 0.045$) and students of the second year scored the highest points on average.

Table 16. Association between help-seeking attitude and year of study

Year of Study	n	Mean ATSPPH-SF Score	SD	F-value	p-value
First Year	133	16.34	5.73		
Second Year	147	17.94	5.38	3.12	0.045
Third Year	95	17.38	4.87		

Table 17 illustrates the relation between mental health literacy and help-seeking attitude. As indicated by Pearson correlation analysis MHLS and ATSPPH-SF scores showed a statistically significant positive correlation ($r = 0.380$, $p < 0.001$). In other words, the greater students level of mental health literacy the more positively they regarded professional psychological assistance.

Table 17. Correlation between mental health literacy and help-seeking attitude

Variables	n	Pearson Correlation (r)	p-value
MHLS Score vs ATSPPH-SF Score	375	0.380	<0.001

Discussion

In the current study the association between mental health literacy and attitudes towards seeking psychological professional help was examined for undergraduate medical students and the relation between these two constructs was analysed. The results have shown that most of the participants showed average mental health literacy, over 50% were characterized by positive help-seeking attitudes females were found to show significantly higher mental health literacy levels compared to male counterparts and there was a statistically significant positive association between mental health literacy and help-seeking attitudes.

The average MHLS score obtained in the current study was 110.27 ± 14.82 where over half of the participants had average mental health literacy. Based on this result one can deduce that even though medical students have a relatively good grasp of mental health there is still a lot that needs to be done. In this regard it should be mentioned that similar results were recorded among university students from both Australia and the United Kingdom here mental health literacy was described as being moderate as opposed to being ideal even though the individuals belonged to

very educated societies [22,23]. As pointed out by Furnham et al., university students commonly have partial knowledge of mental disorders and treatment [35]. The reason why medical students only had average mental health literacy is because of poor formal learning concerning the subject matter and societal perceptions [21,23].

About one-fourth of participants had high literacy regarding their mental health status while very few showed extremely high literacy scores. This is in accordance with observations made by O'Connor and Casey who noted a significant disparity in mental health literacy among well-educated individuals [24]. Likewise, Wei et al. observed notable differences in the literacy scores of students with regard to their mental health thereby indicating that educational experiences may not always contribute to mental health literacy [25]. The low number of students with very high mental health literacy may be an indication of ineffective mental health education at an undergraduate level [21,25].

Over fifty percent of the respondents in the current study exhibited positive attitudes towards seeking professional psychological treatment. This result is promising in light of the psychological stress that often affects medical students along with barriers to seeking help. Martina and Deepthi found similar results when reporting on the help-seeking attitudes of South Indian college students, which were positive among a majority of the respondents [29]. Likewise Hussain and Zaini described the help-seeking attitudes of students in universities of the Maldives as being generally positive even though stigma still played a role in their willingness to seek help [30]. The relatively positive attitudes displayed in our study might be due to increased mental health awareness and information access through the Internet [21,30].

Although the majority of attitudes were positive many students within this particular study sample still exhibited negative attitudes toward seeking professional assistance. Such results correlate with the existing literature on barriers such as stigma, fear of judgment, confidentiality problems and uncertainty about efficacy of professional services [14-18]. Stigma and embarrassment have been found to be significant barriers preventing young people from seeking professional mental health care services by Gulliver et al. [15]. Similarly, according to Eisenberg et al., social stigma and peer pressure often deter college students from seeking professional psychological help when such opportunities are available [17]. It can be concluded that simply raising awareness may not be enough and additional steps may need to be taken [26,27].

One significant finding of the current research is that mental health literacy among female students is notably higher than among male students. These differences between males and females have been identified in multiple other studies. For example, according to Reavley & Jorm females usually show better recognition of mental illnesses and more positive attitudes towards mental illness treatment than men [22]. In a similar study by Hussain & Zaini higher mental health literacy rates were found among females at universities. This was explained by their increased emotional awareness and readiness to learn about mental health issues [30]. Higher mental health literacy rates among females can be caused by increased willingness to discuss emotions, use health information resources and

participate in mental health awareness campaigns [22,30].

On the other hand no noticeable gender disparity was noted in the area of attitudes towards seeking help in the current study. Such a finding is in contrast with some studies in which more positive attitudes towards seeking help were found among the female participants [16,29]. The reason for such an occurrence might be the gradual normalization of talking about mental health issues by both males and females in the modern setting of medical schools [21,34].

No relationship was found between the residence of the respondents and mental health literacy or attitudes towards seeking help for mental illness in the present study. This result has also been observed in previous studies involving university students where education had a stronger effect on mental health knowledge compared to the geographical location of the students [23,30]. This lack of difference in the rural/urban areas could be attributed to the similarity in the academic background of the students, medical course structure and internet-based access to mental health information [21,35].

Similarly, there were no statistical variations in mental health literacy among the three years. This result contradicts the assumption that there should be progressive improvement in mental health literacy due to advancement in medical training. Several previous studies have indicated conflicting results on the effect of academic year on mental health literacy. Although some studies showed positive correlation between academic exposure and mental health literacy others found almost no differences among various levels of academic exposure [23,24]. The lack of any statistically significant result in the current study could mean that there is inadequate integration of mental health education in the early undergraduate training program [21,24].

Remarkably help-seeking attitudes varied markedly with respect to the level of academic year with second-year students scoring higher than other levels on average. While very few studies have explored year-wise differences in help-seeking attitudes in medical students some earlier studies indicate that academic burden, examination anxiety, and coping with the demands of the medical curriculum could impact help-seeking attitudes [8,9]. Second-year students may have greater knowledge about various forms of help available to them without having too many clinical duties compared to other academic levels.

The main outcome of the current study was a statistically significant positive correlation between mental health literacy and attitude towards seeking psychological help. Individuals who showed high levels of mental health literacy tended to demonstrate more positive attitudes towards seeking professional help. This result corroborates the theory put forward by Jorm and states that mental health literacy promotes recognizing the problem and encourages help-seeking behaviour [19,20]. Other authors found a similar positive association between mental health literacy and help-seeking attitudes for example Martina and Deepthi among South Indian college students and Hussain and Zaini among Maldivian university students [29,30]. These findings contribute to the scientific literature which shows that increased awareness about mental health problems helps overcome stigmatization and seek professional help [21,28].

The results obtained in this study carry a great significance in relation to

medical education. Being the future healthcare practitioners, medical students have a vital responsibility for diagnosis, treatment and referral of patients suffering from mental disorders. Improved mental health literacy can not only positively impact the psychological state of the students but can also enhance their skills for dealing with mental health issues among clinical patients [21,34]. The integration of mental health literacy programs, stigma reduction activities, peer support systems and mental health education into the medical curriculum can be of significant benefit [28,34].

The current findings have important bearing on undergraduate medical education. It is recommended that universities include mental health literacy modules within the competency based curriculum for medical colleges that include the ability to recognize various mental conditions, reduce stigma, manage stress and seek appropriate assistance facilities. Orientation programs at the start of college for incoming students, conducting workshops, using simulation training for mental health cases, providing peer-support programs and taking part in Mental Health First Aid trainings can increase their knowledge and understanding of mental health issues. Universities should also focus on improving their confidential counselling services for students, develop faculty mentor programs, conduct frequent screenings and awareness campaigns, and hold wellness programs throughout the year.

Conclusion

This study brings into limelight the importance of mental health literacy in influencing the attitudes towards seeking professional help for any psychological problem. It emphasizes the need for mental health awareness, mental health stigma reduction and appropriate support system integration into undergraduate medical education in order to create a positive environment of mental health literacy among the medical students. Improvement in such skills through proper education can be beneficial for the students not only in improving their own psychological condition but also in being able to detect and manage mental problems in their future practices. There should be further multi-centre studies in the matter to explore more about the issue.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. World Health Organization. Mental health. Geneva: World Health Organization; 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response
2. World Health Organization. Mental health: strengthening our response. Geneva: World Health Organization; 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response
3. Institute for Health Metrics and Evaluation. Global burden of mental disorders. Seattle, WA: IHME; 2023.

Available from: https://www.healthdata.org
4. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, et al. The Lancet Commission on global mental health and sustainable development. Lancet. 2018;392(10157):1553–1598. doi:10.1016/S0140-6736(18)31612-X.
5. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry. 2016;3(2):171–178. doi:10.1016/S2215-0366(15)00505-2.
6. Arnett JJ. Emerging adulthood: A theory of development from the late teens through the twenties. Am Psychol. 2000;55(5):469–480. doi:10.1037/0003-066X.55.5.469.
7. Auerbach RP, Mortier P, Bruffaerts R, Alonso J, Benjet C, Cuijpers P, et al. WHO World Mental Health Surveys International College Student Project: prevalence and distribution of mental disorders. J Abnorm Psychol. 2018;127(7):623–638. doi:10.1037/abn0000362.
8. Dyrbye LN, Thomas MR, Shanafelt TD. Systematic review of depression, anxiety, and other indicators of psychological distress among U.S. and Canadian medical students. Acad Med. 2006;81(4):354–373. doi:10.1097/00001888-200604000-00009.
9. Ishak W, Nikravesh R, Lederer S, Perry R, Ogunyemi D, Bernstein C. Burnout in medical students: a systematic review. Clin Teach. 2013;10(4):242–245. doi:10.1111/tct.12014.
10. Rotenstein LS, Ramos MA, Torre M, Segal JB, Peluso MJ, Guille C, et al. Prevalence of depression, depressive symptoms, and suicidal ideation among medical students: a systematic review and meta-analysis. JAMA. 2016;316(21):2214–2236. doi:10.1001/jama.2016.17324.
11. Quek TTC, Tam WWS, Tran BX, Zhang M, Zhang Z, Ho CSH, et al. The global prevalence of anxiety among medical students: a meta-analysis. Int J Environ Res Public Health. 2019;16(15):2735. doi:10.3390/ijerph16152735.
12. Puthran R, Zhang MWB, Tam WW, Ho RC. Prevalence of depression amongst medical students: a meta-analysis. Med Educ. 2016;50(4):456–468. doi:10.1111/medu.12962.
13. Hope V, Henderson M. Medical student depression, anxiety and distress outside North America: a systematic review. Med Educ. 2014;48(10):963–979. doi:10.1111/medu.12512.
14. Rickwood D, Deane FP, Wilson CJ, Ciarrochi J. Young people's help-seeking for mental health problems. Aust e-J Adv Ment Health. 2005;4(3):218–251. doi:10.5172/jamh.4.3.218.
15. Gulliver A, Griffiths KM, Christensen H. Perceived barriers and facilitators to mental health help-seeking in young people: a systematic review. BMC Psychiatry. 2010;10:113. doi:10.1186/1471-244X-10-113.
16. Vogel DL, Wade NG, Hackler AH. Perceived public stigma and willingness to seek counseling: the mediating roles of self-stigma and attitudes toward counseling. J Couns

Psychol. 2007;54(1):40–50. doi:10.1037/0022-0167.54.1.40.
17. Eisenberg D, Downs MF, Golberstein E, Zivin K. Stigma and help-seeking for mental health among college students. Med Care Res Rev. 2009;66(5):522–541. doi:10.1177/1077558709335173.
18. Czyz EK, Horwitz AG, Eisenberg D, Kramer A, King CA. Self-reported barriers to professional help-seeking among college students at elevated risk for suicide. J Am Coll Health. 2013;61(7):398–406. doi:10.1080/07448481.2013.820731.
19. Jorm AF, Korten AE, Jacomb PA, Christensen H, Rodgers B, Pollitt P. "Mental health literacy": a survey of the public's ability to recognise mental disorders and their beliefs about the effectiveness of treatment. Med J Aust. 1997;166(4):182–186. doi:10.5694/j.1326-5377.1997.tb140071.x.
20. Jorm AF. Mental health literacy: public knowledge and beliefs about mental disorders. Br J Psychiatry. 2000;177(5):396–401. doi:10.1192/bjp.177.5.396.
21. Kutcher S, Wei Y, Coniglio C. Mental health literacy: past, present, and future. Can J Psychiatry. 2016;61(3):154–158. doi:10.1177/0706743715616609.
22. Reavley NJ, Jorm AF. Young people's recognition of mental disorders and beliefs about treatment and outcome: findings from an Australian national survey. Aust N Z J Psychiatry. 2011;45(10):890–898. doi:10.3109/00048674.2011.614215.
23. Furnham A, Swami V. Mental health literacy: a review of what it is and why it matters. Int Perspect Psychol. 2018;7(4):240–257. doi:10.1037/ipp0000094.
24. O'Connor M, Casey L. The Mental Health Literacy Scale (MHLS): a new scale-based measure of mental health literacy. Psychiatry Res. 2015;229(1-2):511–516. doi:10.1016/j.psychres.2015.05.064.
25. Wei Y, McGrath PJ, Hayden J, Kutcher S. Mental health literacy measures evaluating knowledge, attitudes and help-seeking: a scoping review. BMC Psychiatry. 2015;15:291. doi:10.1186/s12888-015-0681-9.
26. Corrigan PW. How stigma interferes with mental health care. Am Psychol. 2004;59(7):614–625. doi:10.1037/0003-066X.59.7.614.
27. Corrigan PW, Watson AC. Understanding the impact of stigma on people with mental illness. World Psychiatry. 2002;1(1):16–20.
28. Jorm AF. Mental health literacy: empowering the community to take action for better mental health. Am Psychol. 2012;67(3):231–243. doi:10.1037/a0025957.
29. Martina M, Deepthi C. Mental health knowledge, attitude towards seeking help and perceived stigma among college students of Tamil Nadu, Kerala and Karnataka. Indian J Ment Health. 2021;8(2):145–156.
30. Hussain MH, Zaini NAB. Understanding mental health literacy, stigma, and help-seeking attitudes among university students in the Maldives: a mediation analysis. BMC Psychol. 2025;13(1):1165. doi:10.1186/s40359-025-03468-4.
31. Baklola M, Terra M, Elzayat MA, Abdelhady D, El-Gilany AH. Pattern, barriers, and predictors of mental

health care utilization among Egyptian undergraduates: a cross-sectional multicentre study. BMC Psychiatry. 2023;23:539. doi:10.1186/s12888-023-05030-4.

32. Poudel DB, Sharif LS, Acharya S, Mahsoon A, Sharif K, Wright R. Mental health literacy and attitudes towards mental health problems among college students in Nepal. Behav Sci (Basel). 2024;14(12):1189. doi:10.3390/bs14121189.
33. Gururaj G, Varghese M, Benegal V, Rao GN, Pathak K, Singh LK, et al. National Mental Health Survey of India, 2015–16: prevalence, patterns and outcomes. Bengaluru: National Institute of Mental Health and Neurosciences (NIMHANS); 2016.
34. Kutcher S, Wei Y. School mental health literacy: a national curriculum guide shows promising results. Child Adolesc Psychiatr Clin N Am. 2014;23(2):251–263. doi:10.1016/j.chc.2013.12.007.
35. Furnham A, Cook R, Martin N, Batey M. Mental health literacy among university students. J Public Ment Health. 2011;10(4):198–210. doi:10.1108/17465721111188207.

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ORIGINAL ARTICLE

Knowledge, Attitude and Practice Regarding Foremilk–Hindmilk Balance Among Breastfeeding Mothers Attending a Tertiary Care Hospital in Tamil Nadu

Sivanandam Sundaram,[1] Madhumathi Gunasekaran,[2] Prabhu Vikash Ravichandran,[3] Umakanthan Muniappan,[1] Rajendran Karupanan,[1] Jeevithan Shanmugam[4,*] and Ramesh Rathinamoorthy[5]

[1]*Professor in Pediatrics, KMCH Institute of Health Sciences and Research, Coimbatore-641014*

[2]*Assistant Professor in Pediatrics, KMCH Institute of Health Sciences and Research, Coimbatore-641014*

[3]*Associate Professor in Pediatrics, KMCH Institute of Health Sciences and Research, Coimbatore-641014*

[4]*Professor in Community Medicine, KMCH Institute of Health Sciences and Research, Coimbatore-641014*

[5]*Medical Social Worker in Community Medicine, KMCH Institute of Health Sciences and Research, Coimbatore-641014*

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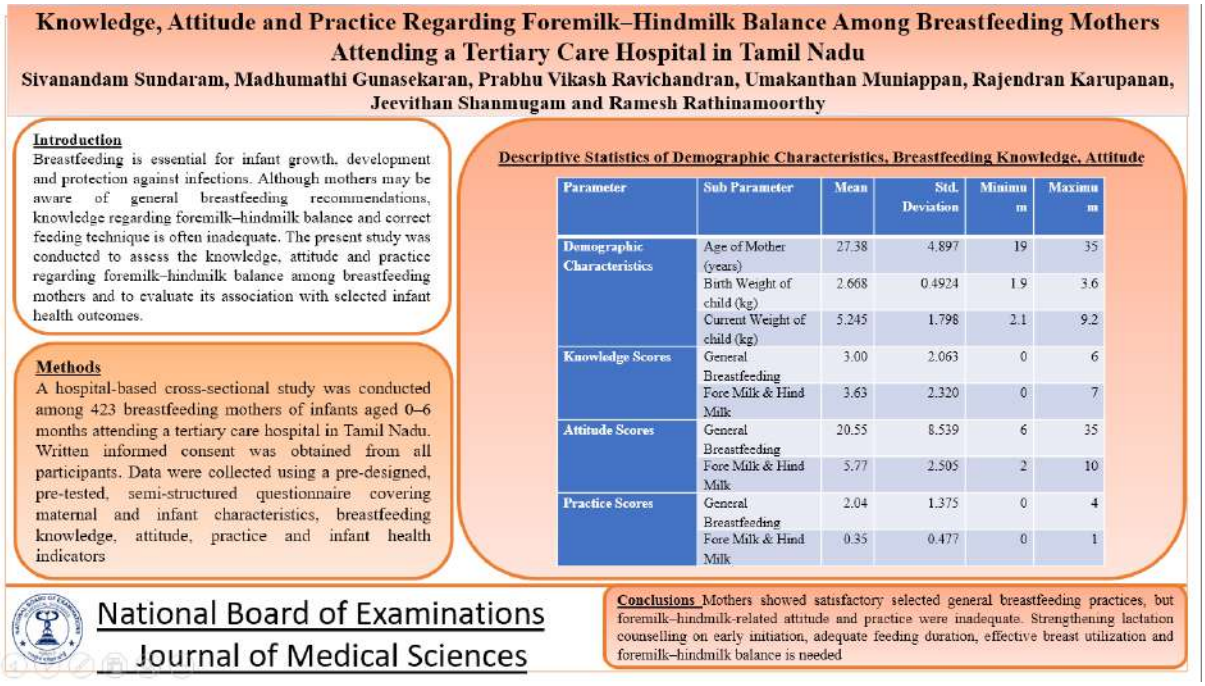
Abstract

Introduction: Breastfeeding is essential for infant growth, development and protection against infections. Although mothers may be aware of general breastfeeding recommendations, knowledge regarding foremilk–hindmilk balance and correct feeding technique is often inadequate. The present study was conducted to assess the knowledge, attitude and practice regarding foremilk–hindmilk balance among breastfeeding mothers and to evaluate its association with selected infant health outcomes. **Materials and Methods:** A hospital-based cross-sectional study was conducted among 423 breastfeeding mothers of infants aged 0–6 months attending a tertiary care hospital in Tamil Nadu. Written informed consent was obtained from all participants. Data were collected using a pre-designed, pre-tested, semi-structured questionnaire covering maternal and infant characteristics, breastfeeding knowledge, attitude, practice and infant health indicators. **Results:** Among 423 breastfeeding mothers, the mean age was 27.38 ± 4.897 years. Good knowledge was observed in 43.7% for general breastfeeding and 53.0% for foremilk–hindmilk balance. Good attitude was present in 50.6% for general breastfeeding and 35.7% for foremilk–hindmilk balance, while good practice was observed in 40.2% and 34.8%, respectively. Maternal education and parity were not significantly associated with domain-wise KAP scores. **Conclusion:** Mothers showed satisfactory selected general breastfeeding practices, but foremilk–hindmilk-related attitude and practice were inadequate. Strengthening lactation counselling on early initiation, adequate feeding duration, effective breast utilization and foremilk–hindmilk balance is needed.

Keywords: Breastfeeding, Foremilk, Hindmilk, Diarrhoea

*Corresponding Author: Jeevithan Shanmugam
Email: dr.jeevithan@gmail.com

Graphical Abstract



Introduction

Breastfeeding is one of the most important public health interventions for improving infant survival, growth and development. The World Health Organization (WHO) and United Nations International Children's Emergency Fund (UNICEF) recommend initiation of breastfeeding within the first hour of birth, exclusive breastfeeding for the first six months of life, and continued breastfeeding up to two years or beyond with appropriate complementary feeding. Optimal breastfeeding practices are estimated to prevent more than 820,000 deaths among children under five years annually, emphasizing their importance in reducing infant and child morbidity and mortality [1].

Breast milk is a dynamic biological fluid that changes in composition during lactation and even during a single feed. Milk available at the beginning of a feed is commonly referred to as foremilk, while milk obtained later in the feed is referred to as hindmilk. These are not two separate types of milk; rather, the fat content of breast milk gradually increases as the breast is drained [2]. A lipidomic analysis of human breast milk demonstrated differences in lipid composition between foremilk and hindmilk, supporting the concept that milk composition changes during a feeding episode [3]. Hence, adequate feeding duration and effective breast emptying are important to ensure that infants receive sufficient milk volume and energy.

Inadequate breastfeeding technique, frequent switching between breasts, short feeding duration, and ineffective latch may interfere with adequate milk transfer. These practices may contribute to concerns regarding foremilk–hindmilk imbalance, which is commonly associated with infant fussiness, gassiness, frequent stools, and poor satiety. However, lactation guidance emphasizes that the focus should not be on

rigid separation of foremilk and hindmilk, but on ensuring effective latch, feeding on demand, adequate feeding duration, and allowing the infant to complete feeding from one breast before switching when appropriate [2].

Breastfeeding also has a protective role against diarrhoeal morbidity in infancy. Exclusive breastfeeding has been consistently associated with reduced risk of gastrointestinal infections. A rapid review and meta-analysis reported that exclusive breastfeeding was associated with a 43% reduction in diarrhoea risk among infants aged 0–6 months [4]. Similarly, reviews of childhood morbidity have shown that exclusive breastfeeding reduces the risk of gastrointestinal, respiratory, and other infectious illnesses in early childhood [5].

In India, breastfeeding promotion remains a major maternal and child health priority. National-level data from NFHS-4 and NFHS-5 have shown that exclusive breastfeeding practices are influenced by maternal, infant and health-system-related factors [6]. Studies from Indian tertiary care settings, including Southern Tamil Nadu, have also reported gaps in breastfeeding knowledge, attitude and practice among mothers of infants below six months [7]. However, limited evidence is available regarding mothers' understanding of foremilk–hindmilk balance and related feeding techniques. Misconceptions regarding foremilk and hindmilk may lead to maternal anxiety, inappropriate switching of breasts, inadequate feeding duration, unnecessary supplementation and suboptimal breastfeeding practice.

Therefore, the present study was undertaken to assess the knowledge, attitude, and practice regarding foremilk–hindmilk balance among breastfeeding mothers of infants aged 0–6 months attending a tertiary care hospital in Tamil Nadu.

Materials and methods

This Prospective cross sectional study was conducted among breastfeeding mothers of infants aged 0–6 months attending the Paediatric Department of a tertiary care hospital in Tamil Nadu. Mothers who were currently breastfeeding and willing to participate were included in the study. Mothers who were not breastfeeding due to maternal illness, neonatal illness, or any other reason were excluded from the study. The final study population consisted of 423 breastfeeding mothers. Written informed consent was obtained from all eligible breastfeeding mothers before enrolment into the study. The purpose of the study was explained to the participants in their local language, and confidentiality of the information collected was assured.

Data were collected using a pre-designed, pre-tested, semi-structured questionnaire. The questionnaire included details regarding maternal and infant characteristics, knowledge about breastfeeding and foremilk–hindmilk balance, attitude towards breastfeeding, breastfeeding practices, and selected infant health characteristics. Knowledge-related questions included timing of breastfeeding initiation, recommendation regarding prelacteal feeds, recommended duration of exclusive breastfeeding, awareness of foremilk and hindmilk, type of milk the baby should receive, methods to ensure receipt of both foremilk and hindmilk, and breast utilization technique during each feed. Attitude-related questions assessed the mothers' opinion regarding timing of breastfeeding initiation and prelacteal feeding. Practice-related questions included

actual timing of breastfeeding initiation, history of prelacteal feeding, exclusive breastfeeding practice, feeding technique, and average duration of each breastfeeding session.

Infant-related data included birth weight, history of diarrhoea or acute gastroenteritis, history of taking the child to a doctor for diarrhoea, history of hospital admission due to diarrhoea, sleep pattern, stool frequency, urination frequency, constant fussiness, abdominal distension or perianal excoriation, and difficulties encountered during breastfeeding. The responses were coded as appropriate or inappropriate for knowledge items, positive or negative for attitude items, and correct or incorrect for practice items. Individual scores were calculated for knowledge, attitude, and practice based on the number of appropriate or correct responses.

The collected data were entered in Microsoft Excel and analysed using SPSS 28 software. Descriptive statistics were used to summarize the data. Categorical variables were expressed as frequency and percentage. Knowledge, attitude, and practice scores were presented as score distributions. Association between selected categorical knowledge, attitude, and practice variables and infant health outcomes, particularly diarrhoea or acute gastroenteritis, was assessed using the Chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

The study included 423 participants, with almost equal representation of primipara 215 (50.8%) and multipara 208 (49.2%) mothers. Most participants had completed school education 163 (38.5%), followed by primary education 117 (27.7%) and graduate and above 107 (25.3%), while only 3 (0.7%) were illiterate. Vaginal delivery was the commonest mode of delivery, reported among 304 mothers (71.9%), whereas 119 (28.1%) had undergone caesarean section. Among multipara mothers, spacing between pregnancies was more than 2 years in 143 (68.8%) and 2 years or less in 65 (31.2%). The infants were fairly distributed across the age group of neonate to 6 months, with neonates forming 68 (16.1%) and 6-month-old infants forming 53 (12.5%). Male children were slightly more common, 229 (54.1%), compared to female children, 194 (45.9%). With regard to birth weight, 226 infants (53.4%) had birth weight between 2.5 and ≤3.5 kg, while 183 (43.3%) had birth weight ≤2.5 kg and 14 (3.3%) had birth weight of >3.5 kg. Diarrhoea was reported in 91 infants (21.5%), while 332 (78.5%) did not have diarrhoea (Table 1).

Table 1. Distribution of study participants based on Socio-Demographic, Obstetric, and Child Baseline Characteristics

Parameter	Sub Classification	Frequency (n)	Percentage (%)
Parity	Primipara	215	50.8
	Multipara	208	49.2
Education	Illiterate	3	0.7
	Just literate	33	7.8
	Primary completed	117	27.7
	School completed	163	38.5
	Graduate and above	107	25.3
Mode of Delivery	Vaginal	304	71.9
	C-section	119	28.1
Spacing Between Pregnancies(n=208)	> 2 years	143	68.8
	≤ 2 years	65	31.2
Age of child	Neonate	68	16.1
	1 month	63	14.9
	2 months	61	14.4
	3 months	64	15.1
	4 months	57	13.5
	5 months	57	13.5
	6 months	53	12.5
Sex of Child	Male	229	54.1
	Female	194	45.9
Birth Weight	≤2.5kg	183	43.3
	2.5 - ≤3.5kg	226	53.4
	>3.5kg	14	3.3
Diarrhoea	Yes	91	21.5
	No	332	78.5

The mean age of mothers was 27.38 ± 4.897 years, with ages ranging from 19 to 35 years. The mean birth weight of the children was 2.668 ± 0.4924 kg, while the mean current weight was 5.245 ± 1.798 kg. Among the knowledge domains, the mean score for general breastfeeding knowledge was 3.00 ± 2.063 out of a possible score range of 0–6, whereas the mean score for foremilk–hindmilk knowledge was 3.63 ± 2.320. The mean attitude score for general breastfeeding was 20.55 ± 8.539, while the mean attitude score for foremilk–hindmilk balance was 5.77 ± 2.505. Practice scores were comparatively lower, with a mean general breastfeeding practice score of 2.04 ± 1.375 and a mean foremilk–hindmilk practice score of 0.35 ± 0.477 (Table 2).

Table 2. Descriptive Statistics of Demographic Characteristics, Breastfeeding Knowledge, Attitude, and Practice Scores (n= 423)

Parameter	Sub Parameter	Mean	Std. Deviation	Minimum	Maximum
Demographic Characteristics	Age of Mother (years)	27.38	4.897	19	35
	Birth Weight of child (kg)	2.668	0.4924	1.9	3.6
	Current Weight of child (kg)	5.245	1.798	2.1	9.2
Knowledge Scores	General Breastfeeding	3.00	2.063	0	6
	Fore Milk & Hind Milk	3.63	2.320	0	7
Attitude Scores	General Breastfeeding	20.55	8.539	6	35
	Fore Milk & Hind Milk	5.77	2.505	2	10
Practice Scores	General Breastfeeding	2.04	1.375	0	4
	Fore Milk & Hind Milk	0.35	0.477	0	1

The domain-wise score distribution showed that good general breastfeeding knowledge was present in 185 participants (43.7%), while 238 (56.3%) had poor general breastfeeding knowledge. In contrast, good foremilk–hindmilk knowledge was observed in 224 participants (53.0%), while 199 (47.0%) had poor knowledge in this domain. General breastfeeding attitude was almost equally distributed, with 214 participants (50.6%) having good attitude and 209 (49.4%) having poor attitude. However, attitude towards foremilk–hindmilk balance was lower, with only 151 participants (35.7%) showing good attitude and 272 (64.3%) having poor attitude. Practice scores were poor in both domains, with good general breastfeeding practice seen in 170 participants (40.2%) and good foremilk–hindmilk practice in only 147 participants (34.8%) (Table 3).

Table 3. Distribution of Study Participants According to Domain-wise Knowledge, Attitude and Practice Scores on General Breastfeeding and Foremilk–Hindmilk Balance

Parameters	Sub Group	Poor		Good	
		F	%	F	%
Knowledge	General Breastfeeding	238	56.3	185	43.7
	Foremilk- Hind milk	199	47.0	224	53.0
Attitude	General Breastfeeding	209	49.4	214	50.6
	Foremilk- Hind milk	272	64.3	151	35.7
Practice	General Breastfeeding	253	59.8	170	40.2
	Foremilk- Hind milk	276	65.2	147	34.8

The association analysis showed that maternal education and parity were not significantly associated with any of the domain-wise knowledge, attitude or practice scores. General breastfeeding knowledge was not significantly associated with education ($\chi^2 = 0.669$, $p = 0.955$) or parity ($\chi^2 = 1.168$, $p = 0.280$). Similarly, foremilk–hindmilk knowledge showed no significant association with education ($\chi^2 = 4.208$, $p = 0.379$) or parity ($\chi^2 = 1.942$, $p = 0.163$). General breastfeeding attitude, foremilk–hindmilk attitude, general breastfeeding practice and foremilk–hindmilk practice were also not significantly associated with either education or parity, as all p values were greater than 0.05 (Table 4).

Table 4. Association of selected domain-wise KAP scores with maternal education and parity

Domain	**Variable**	**Chi-square value**	**p value**	**Inference**
General breastfeeding knowledge	Education	0.669	0.955	Not significant
	Parity	1.168	0.280	Not significant
Foremilk–hindmilk knowledge	Education	4.208	0.379	Not significant
	Parity	1.942	0.163	Not significant
General breastfeeding attitude	Education	3.902	0.419	Not significant
	Parity	0.959	0.327	Not significant
Foremilk–hindmilk attitude	Education	1.271	0.866	Not significant
	Parity	0.252	0.616	Not significant
General breastfeeding practice	Education	2.921	0.571	Not significant
	Parity	1.624	0.203	Not significant
Foremilk–hindmilk practice	Education	0.390	0.983	Not significant
	Parity	0.218	0.683	Not significant

Discussion

The present study assessed selected knowledge, attitude and practice-related domains regarding general breastfeeding and foremilk–hindmilk balance among breastfeeding mothers of infants aged 0–6 months attending a tertiary care hospital in Tamil Nadu. The study showed that responses varied across domains, with better knowledge related to foremilk–hindmilk balance than general breastfeeding, but lower attitude and practice scores in the foremilk–hindmilk domain.

In the present study, the participants represented a mixed group of breastfeeding mothers, with almost equal distribution of primipara and multipara mothers. Most mothers had some level of formal education, and vaginal delivery was the

commonest mode of delivery. The infants were distributed across the age range of neonate to 6 months, and diarrhoea was reported among nearly one-fifth of infants. These baseline characteristics indicate that the study population was suitable for assessing breastfeeding-related responses during the early infancy period, which is the critical period for exclusive breastfeeding and appropriate feeding practices.

The mean knowledge score for general breastfeeding was 3.00 ± 2.063, while the mean knowledge score for foremilk–hindmilk balance was 3.63 ± 2.320. In the domain-wise classification, good general breastfeeding knowledge was observed in 43.7% of participants, whereas good foremilk–hindmilk knowledge was observed in 53.0%. This finding suggests that although awareness regarding foremilk–hindmilk balance was present among nearly half of the mothers, a considerable proportion still had poor knowledge in both domains. Breastfeeding counselling programmes commonly emphasize early initiation, exclusive breastfeeding, avoidance of prelacteal feeds and continuation of breastfeeding, in line with WHO recommendations [1]. However, the concept of foremilk–hindmilk balance may not be routinely explained in a simple and practical manner during antenatal or postnatal counselling sessions.

The finding that foremilk–hindmilk knowledge was only moderate is important because breast milk composition changes during a feed, and effective feeding duration and breast emptying are required for adequate milk transfer. Foremilk and hindmilk are not two separate types of milk; rather, the fat content of breast milk gradually increases as the feed progresses [2,3]. Hence, mothers should be counselled to focus on effective latch, feeding on demand, adequate duration of feeding and allowing the infant to complete feeding adequately rather than prematurely switching breasts. Inadequate understanding of this concept may lead to anxiety, inappropriate feeding practices or unnecessary supplementation.

The present study showed that attitude scores were comparatively better for general breastfeeding than for foremilk–hindmilk balance. Good general breastfeeding attitude was observed in 50.6% of participants, whereas good attitude towards foremilk–hindmilk balance was observed in only 35.7%. This indicates that even when mothers have some knowledge regarding foremilk–hindmilk balance, it may not necessarily translate into a favourable attitude towards related feeding practices. Similar gaps between breastfeeding knowledge, attitude and practice have been reported in Indian studies, where mothers may be aware of recommended breastfeeding practices but may not consistently follow them due to practical barriers [8,9]. Such barriers may include maternal fatigue, caesarean delivery, pain, poor latch, perceived insufficient milk, family advice and inadequate postnatal support.

Practice scores were lower than knowledge and attitude scores in both domains. Good general breastfeeding practice was seen in 40.2% of participants, while good foremilk–hindmilk practice was seen in only 34.8%. This suggests that practice remains the weakest component, particularly for foremilk–hindmilk-related feeding behaviour. The low practice score may reflect the difficulty of translating advice into actual feeding behaviour without direct support and demonstration. Breastfeeding is a skill-based practice, and

mothers may require repeated counselling, observation of feeding, correction of latch and reassurance regarding infant behaviour. Therefore, practical lactation counselling may be more effective than knowledge-based health education alone.

The relatively lower foremilk–hindmilk attitude and practice scores in the present study are comparable with the study by Siregar, which reported gaps in mothers' knowledge regarding foremilk and hindmilk among mothers of infants aged 0–6 months [10]. This suggests that foremilk–hindmilk balance remains a relatively less emphasized area in routine breastfeeding education. While general messages regarding breastfeeding are widely promoted, practical aspects such as adequate feeding duration, breast utilization technique and effective milk transfer require more emphasis.

The present study found no significant association between maternal education and any of the domain-wise knowledge, attitude or practice scores. Similarly, parity was not significantly associated with general breastfeeding or foremilk–hindmilk-related knowledge, attitude or practice. This finding suggests that gaps in breastfeeding-related domains were not confined to mothers with lower education or to primipara mothers alone. Even educated mothers and multipara mothers may require structured breastfeeding counselling. Therefore, lactation counselling should be universal and should not be restricted only to specific high-risk groups.

Diarrhoea was reported in 91 infants (21.5%) of infants in the present study. Breastfeeding is known to have a protective role against gastrointestinal infections, and exclusive breastfeeding has been associated with reduced diarrhoeal morbidity among infants [1,4,5]. However, the present analysis focused primarily on domain-wise KAP scores and their association with maternal education and parity. Since diarrhoea is multifactorial, it may be influenced by sanitation, hygiene, environmental exposure, complementary feeding practices, bottle feeding and health-seeking behaviour. These factors should be considered in future studies exploring the relationship between breastfeeding practices and infant diarrhoeal morbidity.

The findings of the present study have important public health implications. The moderate knowledge scores and lower practice scores indicate the need to strengthen breastfeeding counselling beyond routine messages. Counselling should include practical demonstration of latch, advice on feeding on demand, adequate duration of feeding, avoidance of premature switching between breasts and reassurance regarding normal variations in infant stooling, sleep and feeding behaviour. Foremilk–hindmilk balance should be explained in a simple, non-alarming manner so that mothers understand the importance of effective milk transfer without developing unnecessary anxiety.

The study has certain limitations. The study was hospital-based and may not represent all breastfeeding mothers in the community. Some responses were self-reported and may be affected by recall bias or social desirability bias. Since the study was cross-sectional, causal relationships could not be established.

Conclusion

The study showed that breastfeeding mothers had variable knowledge, attitude and practice-related responses regarding general breastfeeding

and foremilk–hindmilk balance. Knowledge regarding foremilk–hindmilk balance was comparatively better than general breastfeeding knowledge, but attitude and practice in this domain were inadequate. Maternal education and parity were not significantly associated with domain-wise scores, indicating that counselling gaps were present across all groups. Universal, practical lactation counselling focusing on adequate feeding duration, effective breast utilization and foremilk–hindmilk balance should be strengthened during antenatal and postnatal care.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. World Health Organization. Infant and young child feeding. Geneva: World Health Organization; 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/infant-and-young-child-feeding
2. La Leche League International. Foremilk and hindmilk. Raleigh (NC): La Leche League International;. Available from: https://llli.org/breastfeeding-info/foremilk-and-hindmilk
3. Takumi H, Kato K, Nakanishi H, Tamura M, Ohto-N T, Nagao S, Hirose J. Comprehensive Analysis of Lipid Composition in Human Foremilk and Hindmilk. J Oleo Sci. 2022 Jul 1;71(7):947-957. doi: 10.5650/jos.ess21449.
4. Ganbold G, Farnaz N, Scutts T, Borg B, Mihrshahi S. The Association Between Exclusive Breastfeeding and Diarrhoea Morbidity in Infants Aged 0-6 Months: A Rapid Review and Meta-Analysis. Matern Child Nutr. 2025 Jul;21(3):e70042. doi: 10.1111/mcn.70042.
5. Hossain S, Mihrshahi S. Exclusive Breastfeeding and Childhood Morbidity: A Narrative Review. Int J Environ Res Public Health. 2022 Nov 10;19(22):14804. doi: 10.3390/ijerph192214804.
6. Reddy NS, Dharmaraj A, Jacob J, Sindhu KN. Exclusive breastfeeding practices and its determinants in Indian infants: findings from the National Family Health Surveys-4 and 5. Int Breastfeed J. 2023;18:69. doi:10.1186/s13006-023-00602-z.
7. Shanmugavel S, Elango S, Baskaran V, Jeyaraman B. Insights into the Knowledge, Attitudes, and Practices of Mothers with Infants under 6 Months at a Tertiary Care Center in Southern Tamil Nadu. Ann Child Health. 2024;1:32-7. doi: 10.25259/ACH_12_2024
8. Sekar I, Meenakshi K. Knowledge, Attitude, and Breastfeeding Practices of Mothers Visiting Tertiary Care Hospital. Ann Child Health. 2024;1:38-42. doi: 10.25259/ACH_9_2024.
9. Shunmugavel S, Elango S, Baskaran V, Jeyaraman B. Insights into the Knowledge, Attitudes, and Practices of Mothers with Infants under 6 Months at a Tertiary Care

Center in Southern Tamil Nadu. Ann Child Health. 2024;1:32-7. doi: 10.25259/ACH_12_2024.

10. Siregar EY. Overview of mother's knowledge about foremilk balance and hindmilk in 0-6 months old babies at the Primary Clinic Sunggal Medan 2021. Jurnal Kesehatan LLDikti Wilayah 1. 2022;2(1):14-8. doi:10.54076/jukes.v2i1.104.

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ORIGINAL ARTICLE

Tendon-Dominant in the Hand, Joint-Dominant in the Foot: The Diagnostic Spectrum of High-Resolution Sonography in 406 Consecutive Small-Joint Referrals

Shriram Natarajan[1,*] and Bhawna Dev[2]

[1]*Assistant Professor, Department of Radiology, JR Medical College and Hospital, Villupuram, Tamil Nadu*

[2]*Professor, Department of Radiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu*

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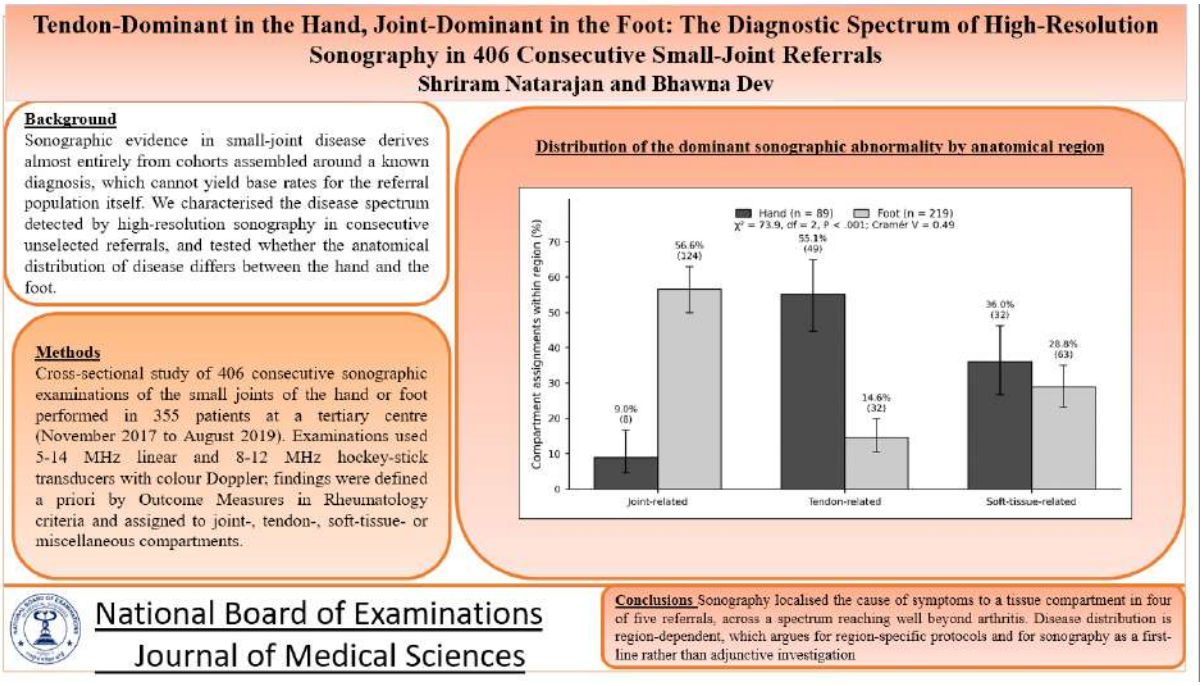
Abstract

Background and Objectives: Sonographic evidence in small-joint disease derives almost entirely from cohorts assembled around a known diagnosis, which cannot yield base rates for the referral population itself. We characterised the disease spectrum detected by high-resolution sonography in consecutive unselected referrals, and tested whether the anatomical distribution of disease differs between the hand and the foot. **Methods:** Cross-sectional study of 406 consecutive sonographic examinations of the small joints of the hand or foot performed in 355 patients at a tertiary centre (November 2017 to August 2019). Examinations used 5-14 MHz linear and 8-12 MHz hockey-stick transducers with colour Doppler; findings were defined a priori by Outcome Measures in Rheumatology criteria and assigned to joint-, tendon-, soft-tissue- or miscellaneous compartments. Proportions carry Wilson 95% confidence intervals (CI); the regional distribution was compared by chi-square with Cramer V. Reporting follows STROBE. **Results:** Patients were aged 1-85 years (mean 45.6, SD 16.0); 191 of 355 (53.8%) were male. Sonography identified an abnormality in 322 of 406 examinations (79.3%, 95% CI 75.1-83.0). The compartment distribution differed sharply by region (chi-square = 73.9, df = 2, $P < .001$; Cramer V = 0.49): tendon-related disease predominated in the hand (49/89; 55.1%, 95% CI 44.7-65.0) and joint-related disease in the foot (124/219; 56.6%, 95% CI 50.0-63.0), a difference of 40.4 percentage points for tendon disease (95% CI 28.8-51.2). Tenosynovitis was the commonest single diagnosis (57/406; 14.0%, 95% CI 11.0-17.8). Infection accounted for 50 examinations, and the spectrum also included tendon tear, plantar fasciitis, ganglion, lipoma and radiolucent foreign body. Of 26 patients with isolated tenosynovitis investigated for inflammatory arthritis, 14 (53.8%) received a final diagnosis of rheumatoid arthritis. **Conclusions:** Sonography localised the cause of symptoms to a tissue compartment in four of five referrals, across a spectrum reaching well beyond arthritis. Disease distribution is region-dependent, which argues for region-specific protocols and for sonography as a first-line rather than adjunctive investigation.

Keywords: arthritis, foot, hand, high-resolution ultrasonography, musculoskeletal ultrasound, point-of-care ultrasound, small joints, tenosynovitis

*Corresponding Author: Shriram Natarajan
Email: drshriramnatarajan@gmail.com

Graphical Abstract



Introduction

Pain and swelling in the small joints of the hand and foot are among the least specific presentations in clinical medicine. The complaint localises poorly, physical examination rarely separates a synovial process from a tendinous or subcutaneous one [1-3], and the investigation ordered first—a plain radiograph—reports on the one tissue that is usually last to change [4,5]. The consequence is a diagnostic sequence in which the initial imaging study is frequently normal and the patient is either reassured prematurely or referred onward for cross-sectional imaging that may be neither affordable nor timely [6].

High-resolution sonography occupies an unusual position in that sequence because it does not respect the anatomical boundary the referral question implies. A probe placed over a painful metacarpophalangeal joint interrogates skin, subcutaneous fat, tendon, sheath, pulley, enthesis, bursa, joint recess, cartilage and cortical surface in a single sweep, and adds a functional dimension—flow on colour Doppler, behaviour under dynamic stress—that no static modality supplies [6]. The physical basis was settled decades ago [7,8], and the descriptive vocabulary has since been standardised through Outcome Measures in Rheumatology (OMERACT) consensus definitions [9] and European scanning protocols [10], so the modality is now reproducible enough to carry clinical weight [11,12].

What has followed that consolidation is a literature organised almost entirely by disease. Sonography has been validated against radiography for erosion detection in rheumatoid arthritis [4], against clinical examination for synovitis [2], against clinical examination again for flexor tenosynovitis [3], as a predictor of progression in undifferentiated arthritis [13], and, in dermatological and surgical practice, for the characterisation of

lipomas, epidermal cysts and ganglia [14]. Plantar fasciitis has its own sonographic literature [15,16], as do hand osteoarthritis [17], connective-tissue disease [18] and crystal deposition [19,20]. Each of these bodies of work begins by selecting patients who already carry the diagnosis under study. That is the correct design for estimating accuracy, but it conditions on the answer, and so produces an evidence base that cannot address the question a referring clinician actually asks. The clinician does not want to know whether sonography detects tenosynovitis in a patient known to have rheumatoid arthritis; the clinician wants to know what a swollen finger of uncertain cause is likely to turn out to be, and whether an ultrasound examination will settle it.

Answering that requires the opposite sampling frame: a consecutive series defined by the referral rather than by the diagnosis, in which the denominator contains the normal studies, the infective and traumatic presentations that never reach a rheumatology clinic, and the incidental mass lesions that arrive under a joint-pain heading. Such cohorts are uncommon, and Indian data are sparser still, despite an adult rheumatoid arthritis prevalence of roughly 0.75% translating into several million people [21] competing for imaging in settings where sonography is often the only musculoskeletal modality immediately available at the point of care.

We therefore analysed 406 consecutive examinations of the small joints of the hand or foot performed at a single tertiary centre, with no restriction by suspected diagnosis. The objectives were to describe the distribution of disease across joint, tendon, soft-tissue and miscellaneous compartments; to test whether that distribution differs between hand and foot in a way that should alter scanning practice; and to identify the presentations in which sonography redirects the diagnostic pathway rather than merely confirming it.

Materials and Methods

Design, setting and reporting

This was a single-centre cross-sectional observational study conducted in the Department of Radiology and Imaging Sciences of a tertiary-care teaching hospital in southern India, with consecutive accrual between November 2017 and August 2019. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee (approval number: CSP-MED/17/NOV/40/147). Written informed consent was obtained from every participant in English or Tamil, and from a parent or legal guardian for participants younger than 18 years. The manuscript is reported in accordance with the STROBE statement for cross-sectional studies [22].

Participants and unit of analysis

All patients referred for sonographic evaluation of pain or swelling involving the small joints of the hand or foot during the study window were eligible, irrespective of age, referring specialty or working diagnosis. Patients who had undergone previous surgery at the region of interest, and those in whom an adequate examination was precluded by a cast, an overlying dressing or inability to cooperate, were not enrolled.

The unit of analysis is the examination rather than the patient, because a substantial minority of patients were examined more than once, either at a second anatomical site or at a second time point. In total, 406 examinations were

performed in 355 patients: 304 patients contributed a single examination and 51 contributed two. Demographic characteristics are therefore reported at patient level and all imaging findings at examination level, and each denominator is stated explicitly wherever a proportion is given. No sample-size calculation was performed; the study was designed to characterise a complete consecutive referral stream rather than to test a pre-specified hypothesis, and the sample comprises all eligible examinations performed during the accrual period.

Sonographic technique

Examinations were performed on a Toshiba Aplio 500 Platinum (Canon Medical Systems, Otawara, Japan) and GE Logiq P5, P9 and E platforms (GE Healthcare, Milwaukee, WI) using a 5-14 MHz linear transducer and, for the digits and superficial structures, an 8-12 MHz L-shaped hockey-stick transducer. A stand-off pad constructed from an acoustic-gel-filled glove was used where the structure of interest lay immediately beneath the skin. For hand examinations the patient sat facing the operator with the limb supported on a pillow, which allows the wrist and digits to be rotated freely through extensor, collateral and flexor windows; foot examinations were performed supine with the symptomatic side nearer the operator.

The clinically dominant limb was scanned. Metacarpophalangeal and interphalangeal joints were examined in the hand and metatarsophalangeal joints in the foot, together with skin, subcutaneous tissue, tendons and sheaths, entheses, bursae, digital expansions and flexor pulleys, following established normal sonographic anatomy [23]. Each joint was interrogated in longitudinal and transverse planes, the longitudinal plane serving as the primary assessment and the transverse plane as confirmation; coronal imaging with the digit flexed to 90° was added at the proximal interphalangeal joints. Dynamic flexion was used routinely, since bunching of the synovium into the proximal recess renders conspicuous a degree of hypertrophy that is easily overlooked in the neutral position. The extensor aspect was examined first, then the collateral aspects, then the flexor aspect. Colour Doppler was applied to every region of interest with pulse-repetition frequency and gain set to the lowest values that did not generate motion artefact. Anisotropy was managed by heel-toe angulation, and any hypoechoic focus that resolved with angulation was disregarded.

All examinations were performed and interpreted by a single radiologist with access to the clinical history and to prior imaging using a standardized protocol to ensure methodological consistency. Interobserver reliability was consequently not assessed; this is addressed under Limitations.

Definitions and compartment assignment

Sonographic pathology was defined a priori using OMERACT criteria [9]. Simple effusion was compressible, transonic intra-articular material without Doppler signal; synovial hypertrophy was non-displaceable, poorly compressible intra-articular tissue, graded 0-3 (absent; <2 mm; 2-4 mm; >4 mm); synovial vascularity on colour Doppler was graded 0-3 (absent; isolated vessels; <50% of the synovial area; >50%); tenosynovitis was anechoic or hypoechoic distension of the tendon sheath relative to the tendon fibres; erosion was an intra-articular cortical discontinuity visible in two orthogonal planes; and enthesitis

was entheseal thickening and hypoechogenicity with Doppler signal.

Each examination was assigned to the tissue compartment in which the dominant abnormality lay: joint-related (synovitis, effusion, erosion, crystal deposition, osteoarthritis, bursitis, inflammatory arthritis); tendon-related (tenosynovitis, tendon tear, calcific tendinosis, trigger digit, tendon-associated ganglion); soft-tissue-related (abscess, cellulitis, myositis, subcutaneous oedema, plantar fasciitis, callosity, ulcer, haematoma); miscellaneous (lipoma, haemangioma, vascular malformation, nerve entrapment or thickening, foreign-body granuloma, epidermal inclusion cyst, implantation dermoid); and no sonographic abnormality. In 10 examinations, abnormalities of comparable clinical weight were present in two compartments—for example flexor tenosynovitis coexisting with a joint effusion, or a subcutaneous collection with an underlying tendon tear—and were assigned to both. Compartment assignments therefore exceed the number of abnormal examinations by that margin, and this is stated in the relevant table footnotes rather than concealed by forcing an arbitrary single assignment.

Ancillary data

Erythrocyte sedimentation rate, C-reactive protein, IgM rheumatoid factor, anti-cyclic citrullinated peptide antibody and serum urate were recorded when available from the hospital information system, and prior radiographs were retrieved from the picture archiving and communication system. These ancillary data were incomplete by design, having been requested on clinical rather than research grounds, and are reported with their own denominators.

Statistical analysis

Analyses were performed in SPSS version 17.0 (SPSS Inc., Chicago, IL). Age is summarised as mean with standard deviation and as median with interquartile range, the distribution having been inspected graphically. Categorical variables are presented as counts with percentages and Wilson score 95% confidence intervals, which are preferred to the normal-approximation interval at the small cell counts encountered among the rarer diagnoses; differences between two proportions are given with Newcombe hybrid-score confidence intervals.

The primary comparison—the distribution of the three principal tissue compartments between hand and foot examinations—was tested by the Pearson chi-square test, with the strength of association expressed as Cramer V and the source of the association localised through standardised residuals; residuals exceeding ±2 identify cells contributing disproportionately to the overall statistic. Two-sided P values below .05 were considered significant. The analysis was performed with available case and no imputation was undertaken. Analyses of individual diagnoses are descriptive and hypothesis-generating; no correction for multiplicity was applied and these estimates are interpreted as such rather than as confirmatory tests.

Results

Cohort

A total of 406 examinations were performed in 355 patients (Figure 1 and Table 1). Patients were aged 1 to 85 years (mean 45.6, standard deviation 16.0;

median 46, interquartile range 36-57), and 191 of 355 (53.8%, 95% CI 48.6-58.9) were male. The distribution was broad but weighted towards middle age, with 235 of 355 patients (66.2%) aged between 31 and 60 years. Referrals concerned the foot considerably more often than the hand, in a ratio of approximately three to one.

Table 1. Characteristics of the study cohort

Characteristic	Value
Patients, n	355
Examinations, n	406
Patients contributing one examination, n (%)	304 (85.6)
Patients contributing two examinations, n (%)	51 (14.4)
Male, n (%)	191 (53.8)
Female, n (%)	162 (45.6)
Sex not recorded as male or female, n (%)	2 (0.6)
Age, mean ± SD, years	45.6 ± 16.0
Age, median (IQR), years	46 (36–57)
Age, range, years	1–85
Age ≤30 years, n (%)	59 (16.6)
Age 31–60 years, n (%)	235 (66.2)
Age >60 years, n (%)	61 (17.2)

SD, standard deviation; IQR, interquartile range.

Demographic characteristics are reported at patient level (n = 355); all imaging findings are reported at examination level (n = 406).

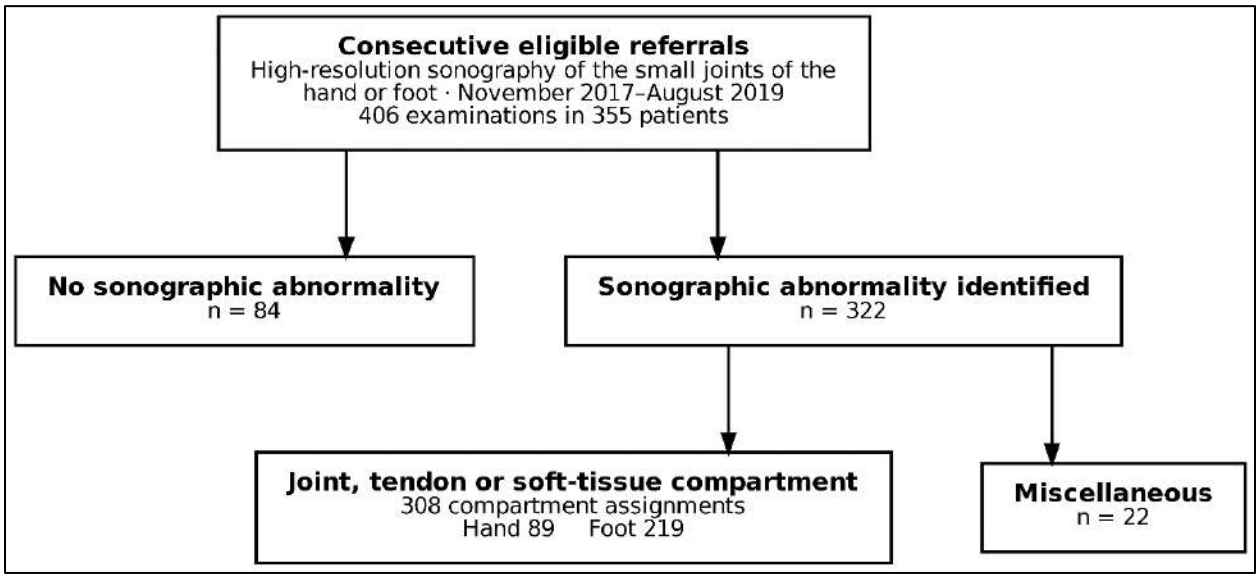


Figure 1. Flow of examinations through the study

Yield of the examination

Sonography demonstrated an abnormality in 322 of 406 examinations (79.3%, 95% CI 75.1-83.0); 84 studies (20.7%, 95% CI 17.0-24.9) were normal. The abnormalities encountered spanned the full width of the periarticular soft-tissue envelope and were, in aggregate, only partly rheumatological (Table 2). Tenosynovitis was the commonest single diagnosis, present in 57 examinations (14.0%, 95% CI 11.0-17.8). Urate-related crystal disease accounted for 71 examinations (17.5%, 95% CI 14.1-21.5) and rheumatoid arthritis for 17 (4.2%, 95% CI 2.6-6.6). Infection was conspicuous: abscess was identified in 28 examinations and cellulitis in 22, together 50 of 406 (12.3%, 95% CI 9.5-15.9)—a substantial fraction of a referral stream ostensibly directed at joint disease, and one in which the distinction between a drainable collection and diffuse phlegmon carried immediate surgical consequence.

Table 2. Sonographic diagnoses across the cohort (N=406)

Diagnosis	n	% (95% CI)*
No sonographic abnormality	84	20.7 (17.0–24.9)
Tendon and sheath		
Tenosynovitis	57	14.0 (11.0–17.8)
Ganglion cyst	13	3.2 (1.9–5.4)
Tendon or pulley tear (all partial)	11	2.7 (1.5–4.8)
Trigger digit	2	0.5 (0.1–1.8)
Calcific tendinosis	2	0.5 (0.1–1.8)
de Quervain tenosynovitis	2	0.5 (0.1–1.8)
Joint		
Urate-related crystal disease	71	17.5 (14.1–21.5)
Rheumatoid arthritis	17	4.2 (2.6–6.6)
Inflammatory arthritis, unclassified	13	3.2 (1.9–5.4)
Erosion without other joint finding	8	2.0 (1.0–3.8)
Bursitis	8	2.0 (1.0–3.8)
Joint effusion, isolated	8	2.0 (1.0–3.8)
Osteoarthritis	4	1.0 (0.4–2.5)
Calcium pyrophosphate deposition disease	2	0.5 (0.1–1.8)
Soft tissue		
Abscess	28	6.9 (4.8–9.8)
Cellulitis	22	5.4 (3.6–8.1)
Subcutaneous oedema	14	3.4 (2.1–5.7)
Plantar fasciitis	12	3.0 (1.7–5.1)
Haematoma	5	1.2 (0.5–2.9)
Callosity or plantar fibroma	5	1.2 (0.5–2.9)
Myositis	4	1.0 (0.4–2.5)
Miscellaneous		
Lipoma	7	1.7 (0.8–3.5)

Diagnosis	n	% (95% CI)*
Haemangioma or vascular malformation	5	1.2 (0.5–2.9)
Carpal tunnel syndrome	4	1.0 (0.4–2.5)
Foreign body or foreign-body granuloma	3	0.7 (0.3–2.1)
Epidermal inclusion cyst	1	0.2 (0.0–1.4)
Implantation dermoid	1	0.2 (0.0–1.4)
Ulnar nerve thickening	1	0.2 (0.0–1.4)
Lymphoedema	1	0.2 (0.0–1.4)

*CI, confidence interval (Wilson score).

Ganglion cyst: 9 of 13 were tendon-associated.

Diagnoses are not mutually exclusive: 10 examinations disclosed abnormalities in more than one compartment (for example tenosynovitis with joint effusion, or a subcutaneous collection with an underlying tendon tear) and are counted under each; percentages therefore sum to slightly more than 100%. Mass lesions were not confirmed histologically and are sonographic diagnoses.

Beyond infection and arthritis the spectrum included tendon tear (11 examinations, all partial and all managed conservatively), plantar fasciitis (12), ganglion cyst at any location (13, of which 9 were tendon-associated), subcutaneous oedema (14), lipoma (7), haematoma (5), callosity or plantar fibroma (5), haemangioma or vascular malformation (5), carpal tunnel syndrome (4), myositis (4), foreign body (3), and single instances of epidermal inclusion cyst, implantation dermoid, ulnar nerve thickening and lymphoedema. Trigger digit was diagnosed twice, in each case by demonstrating altered echotexture of the flexor digitorum profundus with thickening of the A1 pulley (Figure 2), and de Quervain tenosynovitis twice. In one patient a radiolucent foreign-body granuloma of the thenar eminence was identified as a shadowing echogenic focus that had been invisible on radiography. Histopathological confirmation was not obtained for the mass lesions, which are therefore sonographic diagnoses.

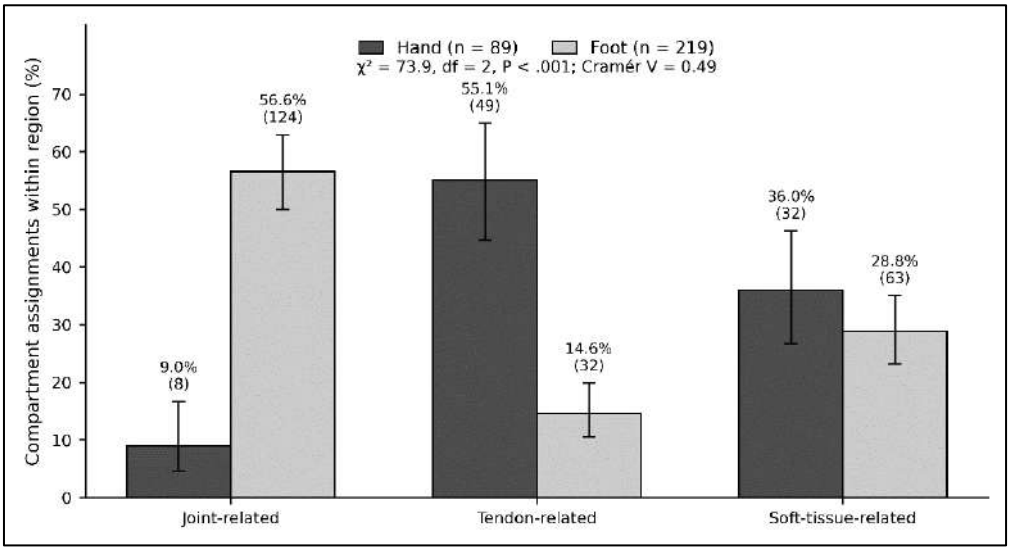


Figure 2. Distribution of the dominant sonographic abnormality by anatomical region.

Regional distribution of disease

The compartment in which disease was found depended strongly on which region was scanned (Table 3, Figure 3). Among the 308 compartment assignments in which the dominant abnormality lay in the joint, tendon or soft tissue, tendon-related disease accounted for 49 of 89 hand assignments (55.1%, 95% CI 44.7-65.0) but only 32 of 219 foot assignments (14.6%, 95% CI 10.5-19.9), a difference of 40.4 percentage points (95% CI 28.8-51.2). The joint compartment showed the mirror image: 124 of 219 in the foot (56.6%, 95% CI 50.0-63.0) against 8 of 89 in the hand (9.0%, 95% CI 4.6-16.7), a difference of −47.6 percentage points (95% CI −55.4 to −37.4). Soft-tissue disease was distributed similarly in both regions (36.0% versus 28.8%; difference 7.2 percentage points, 95% CI −4.0 to 19.0). The overall distribution differed significantly between regions (chi-square = 73.9, df = 2, P < .001), and the association was of moderate-to-large strength (Cramer V = 0.49). Standardised residuals localised the effect precisely to the two reciprocal cells: tendon disease in the hand (+5.3) and joint disease in the hand (−4.9), with the corresponding foot cells at −3.4 and +3.1 and the soft-tissue cells contributing negligibly (+0.9 and −0.6).

Table 3. Distribution of the dominant sonographic abnormality by anatomical region

Compartment	Hand (n = 89), n (%)	Foot (n = 219), n (%)	Difference, pp (95% CI)
Joint-related	8 (9.0)	124 (56.6)	−47.6 (−55.4 to −37.4)
Tendon-related	49 (55.1)	32 (14.6)	+40.4 (+28.8 to +51.2)
Soft-tissue-related	32 (36.0)	63 (28.8)	+7.2 (−4.0 to +19.0)

CI, confidence interval; pp, percentage points.

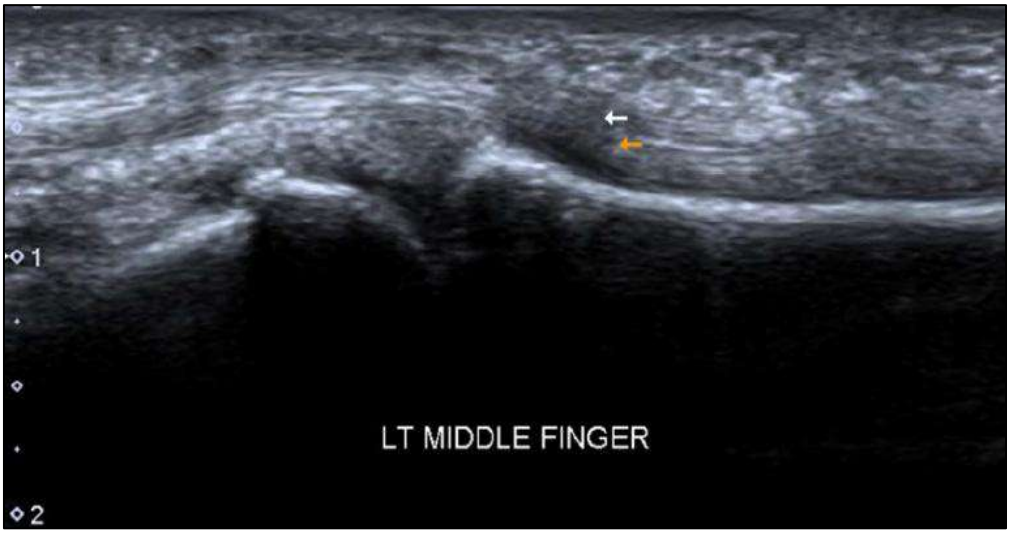


Figure 3. Trigger digit in a 36-year-old woman with painful catching of the left middle finger
*Longitudinal sonogram showing altered echotexture of the flexor digitorum profundus tendon with hypoechoic thickening of the A1 pulley overlying the metacarpal head (arrow).

Joint-related diagnoses were correspondingly concentrated in the foot, where crystal-related disease was the largest single group and the first metatarsophalangeal joint the commonest site of positive findings (Table 4). Six patients in the crystal-arthropathy subgroup had a final diagnosis of calcium pyrophosphate deposition disease, of whom only two were identified prospectively on sonography; the remainder were reported as urate disease.

Tenosynovitis as a forerunner of inflammatory arthritis

In 56 examinations tenosynovitis was the only abnormality demonstrated. In total, 26 of these patients were investigated for suspected rheumatoid arthritis on clinical and serological grounds, and 14 (53.8%, 95% CI 35.5-71.2) ultimately received that diagnosis. The subgroup was defined by clinical suspicion rather than prospectively, so this proportion is conditional on having been investigated and is not a positive predictive value for tenosynovitis at large; the outcome of the remaining 30 patients with isolated tenosynovitis was not systematically ascertained. Read with that constraint, the observation is nonetheless material: half of the patients in whom isolated sheath inflammation prompted a rheumatological work-up proved to have rheumatoid arthritis.

Table 4. Joint-related sonographic diagnoses by anatomical region (N=131)

Diagnosis	Hand, n	Foot, n
Urate-related crystal disease	2	69
Rheumatoid arthritis	5	12
Inflammatory arthritis, unclassified	0	12
Joint effusion, isolated	0	8
Bursitis	0	8
Erosion without other joint finding	0	8
Osteoarthritis	0	4
Calcium pyrophosphate deposition disease	0	1
Erosive arthritis	0	1
Metacarpophalangeal subluxation	1	0
Total joint-compartment assignments*	**8**	**123**

*Counts are joint-compartment assignments and correspond to the joint-related row of Table 2. A count of 0 indicates no case in that region.

Discussion

The central finding of this study is not that sonography detects disease—that much is established—but that what it detects depends on where the probe is placed, in a way the referral question does not anticipate. Hands referred for joint pain overwhelmingly harboured tendon disease; feet referred for the same complaint overwhelmingly harboured joint disease. The effect is large rather than marginal (Cramer V = 0.49), and the standardised residuals show that it is not a diffuse difference in case mix but a specific

reciprocal inversion of the tendon and joint compartments. A single scanning protocol applied uniformly to both regions will therefore be systematically misdirected in one of them.

This asymmetry has an anatomical and biomechanical rationale rather than being an artefact of referral. The digital flexor apparatus of the hand is a high-excursion, pulley-constrained system in which the tendon and its sheath, not the joint, absorb the mechanical and inflammatory load; the synovial sheath is also the largest synovium-lined surface in the hand and is correspondingly the tissue most exposed in early inflammatory disease. The forefoot, by contrast, is a weight-bearing, low-excursion structure in which the first metatarsophalangeal joint sustains repeated high compressive load in a relatively cool, acidic and poorly perfused environment that favours urate crystal nucleation. That soft-tissue disease was the one compartment distributed evenly between regions supports this reading: infection and oedema are not governed by joint biomechanics and would not be expected to show regional preference, and they did not.

Our findings both extend and complicate the existing literature. The disease-specific studies that underpin musculoskeletal sonography have consistently shown superiority over radiography and close agreement with magnetic resonance imaging within their chosen diagnosis—for erosion detection and disease-activity correlation in rheumatoid arthritis [4,24], for synovitis [2], for flexor tenosynovitis [3,25] and its extensor counterpart [26], for de Quervain disease [27], for plantar fasciitis [15,16] and for soft-tissue masses [14] and our unselected series is compatible with each of them taken individually. What an unselected series supplies is the base rate. When patients are not pre-sorted by diagnosis, one in five scans is normal, one in seven shows tenosynovitis, and one in eight shows infection rather than arthritis at all. None of these proportions can be recovered from the disease-specific literature, because that literature conditions on the answer. The practical consequence is that the pre-test reasoning brought to a small-joint referral should be re-anchored: the likeliest explanation for a painful digit arriving in a radiology department is not the arthritis named on the request form.

The tenosynovitis observation is where our data intersect most directly with a contested question. Hmamouchi and colleagues argued that clinical examination is specific but insensitive for flexor tenosynovitis and that sonography should be reserved for the clinically negative patient [3]; Sahbudin and colleagues went further, showing that sonographically defined tenosynovitis carries independent predictive weight for the subsequent development of rheumatoid arthritis over and above synovitis and serology [13]. In our cohort, 14 of the 26 patients with isolated tenosynovitis who were investigated for inflammatory arthritis received that diagnosis. We are deliberate about what this can and cannot mean: the denominator is clinically enriched, so 53.8% is not a positive predictive value, and the confidence interval (35.5-71.2) is wide. What survives those caveats is a directional signal concordant with Sahbudin, and a practical corollary—a report of isolated flexor tenosynovitis in a patient with polyarticular symptoms is not a benign endpoint but an indication for serological work-up.

The mirror image of that argument, and the least flattering result in this series, is the calcium pyrophosphate group: of six patients with an eventual diagnosis of pyrophosphate disease, only two were identified prospectively, the remainder being reported as urate disease. The discriminating feature is real and well described—urate crystallises on the cartilage surface, producing a continuous hyperechoic line parallel to and separate from the subchondral bone, whereas pyrophosphate is deposited within the cartilage substance, producing a discontinuous intrasubstance line [19,20] but it is a distinction of a few tenths of a millimetre in the depth at which an echogenic interface sits, and our experience indicates that it is not reliably reproducible by a single operator at ordinary clinical throughput. Loffler and colleagues reached the same conclusion and recommended that the double-contour sign never be interpreted in isolation [19]. This is a limitation of the modality as it is actually used, not merely of this study, and it should temper enthusiasm for sonography as a stand-alone crystal-typing tool.

Three clinical implications follow. Sonography should be positioned as the first-line examination in small-joint referral rather than as an adjunct ordered after a normal radiograph, since the tissues that most often account for the symptom—tendon sheath, subcutaneous plane, fascia—are radiographically invisible, and since a normal sonogram carries far more information than a normal radiograph. The scanning protocol should be region-specific: a hand protocol that does not sweep the full flexor and extensor apparatus in both planes will miss the commonest finding in that region, and a foot protocol weighted towards the tendons will miss the commonest finding in that one. And the modality is inherently a point-of-care technology: the same equipment that establishes the diagnosis performs the guided injection, aspiration or drainage that follows, and can be repeated at every review without cumulative radiation burden or incremental cost (Figure 4). In a health system where magnetic resonance imaging is neither universally accessible nor rapidly obtainable, that consolidation of diagnosis, intervention and follow-up into one inexpensive examination is arguably the strongest argument for its adoption.

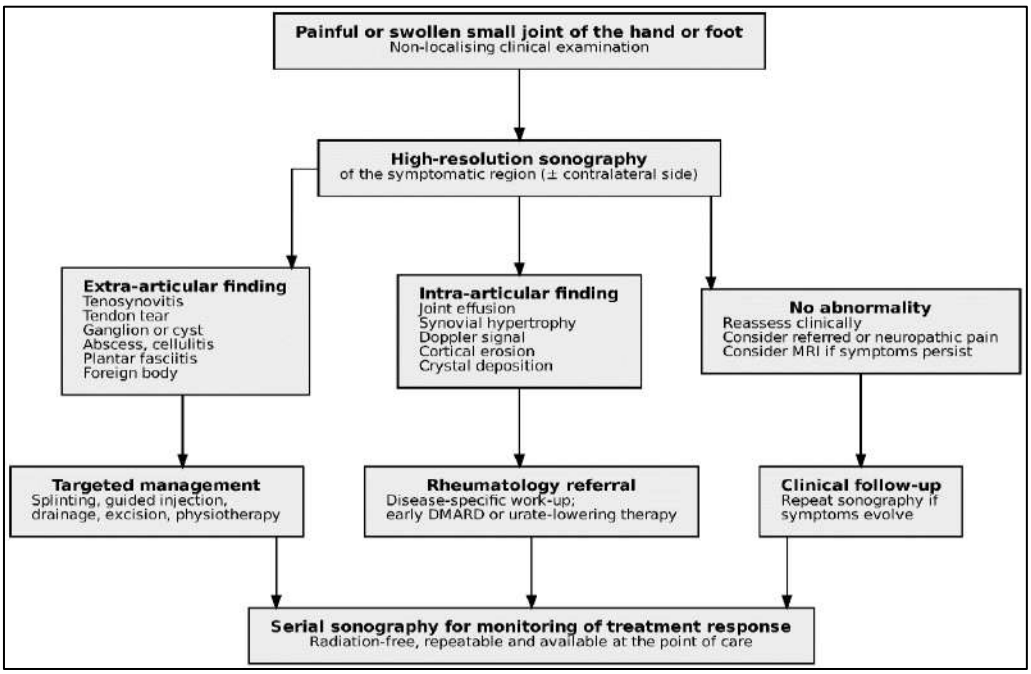


Figure 4. Proposed diagnostic pathway for high-resolution sonography in small-joint referral.

Strengths

The principal strength is the sampling frame. Consecutive, unselected accrual over 22 months with no restriction by suspected diagnosis yields a denominator that reflects real referral practice—precisely the quantity that disease-selected studies cannot supply. All findings were defined a priori against OMERACT criteria [9], so the categories are transportable. Reporting the examination rather than the patient as the unit of analysis, and stating both denominators explicitly, avoids the double-counting that repeat examinations would otherwise introduce. Single-operator interpretation, though a limitation for reliability, removes between-reader variation as a source of heterogeneity in the descriptive estimates.

Limitations

Several constraints bound the inferences. The study is single-centre and hospital-based, so the case mix reflects the referral behaviour of one tertiary institution; the prevalence of infection and mass lesions would almost certainly be lower in primary care. Because one reader performed and interpreted every examination, interobserver agreement could not be estimated and no kappa statistic is available; the reproducibility of these categories in other hands is untested, and the learning curve described by D'Agostino and colleagues [2] suggests it is not trivial. There was no independent reference standard for most diagnoses: mass lesions were not confirmed histologically, and infective and inflammatory diagnoses rested on the composite of clinical course, laboratory data and treatment response rather than on tissue. The number of patients excluded before enrolment on grounds of previous surgery or inadequate access was not logged prospectively, so a formal STROBE exclusion count cannot be given. Laboratory and radiographic data were obtained for clinical rather than research

purposes and are incomplete, with denominators that vary between analyses. Finally, follow-up was neither systematic nor of uniform duration, which precludes any statement about the effect of sonographic diagnosis on hard outcomes; the management consequences described here are inferences from diagnostic information, not measured outcomes.

Future directions

The obvious next study is prospective, multi-reader and outcome-anchored: a consecutive referral cohort scanned independently by two readers, with pre-scan and post-scan management plans recorded, would supply both the reliability estimate this study lacks and a direct measure of the change in management that sonography produces—the quantity that health systems, rather than radiologists, will want to see. A second priority is the crystal-typing problem: if the discrimination between surface and intrasubstance deposition sits at the resolution limit of routine grey-scale imaging, then either standardised acquisition with a defined insonation angle, or a quantitative reference such as dual-energy computed tomography, will be needed to establish where the boundary of reliable sonographic distinction actually lies. Third, the predictive weight of isolated tenosynovitis deserves a dedicated prospective cohort with defined follow-up in which the endpoint is fulfilment of classification criteria rather than a retrospectively assembled clinical diagnosis.

Conclusions

In an unselected referral population, high-resolution sonography localised the cause of small-joint symptoms to a specific tissue compartment in four of every five examinations, across a spectrum reaching well beyond arthritis into infection, tendinopathy, trauma and mass lesions. The distribution of that disease was strongly region-dependent—tendon-dominant in the hand, joint-dominant in the foot—which argues for region-specific scanning protocols rather than a single generic examination, and supports positioning sonography as the first-line imaging investigation for small-joint symptoms, with radiography reserved for the questions it answers well.

Statements and Declarations

Funding

No funding was received for conducting this study.

Conflicts of interest

The authors declare that they do not have conflict of interest.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee (approval number: CSP-MED/17/NOV/40/147).

Informed Consent

Written informed consent was obtained from every participant in English or Tamil, and from a parent or legal guardian for participants younger than 18 years.

References

1. Wakefield RJ, Green MJ, Marzo-Ortega H, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical

disease. Ann Rheum Dis. 2004;63(4):382–385. doi:10.1136/ard.2003.007062

2. D'Agostino MA, Maillefert JF, Said-Nahal R, Breban M, Ravaud P, Dougados M. Detection of small joint synovitis by ultrasonography: the learning curve of rheumatologists. Ann Rheum Dis. 2004;63(10):1284–1287. doi:10.1136/ard.2003.012393
3. Hmamouchi I, Bahiri R, Srifi N, Aktaou S, Abouqal R, Hajjaj-Hassouni N. A comparison of ultrasound and clinical examination in the detection of flexor tenosynovitis in early arthritis. BMC Musculoskelet Disord. 2011;12:91. doi:10.1186/1471-2474-12-91
4. Wakefield RJ, Gibbon WW, Conaghan PG, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum. 2000;43(12):2762–2770. doi:10.1002/1529-0131(200012)43:12
5. Colebatch AN, Edwards CJ, Østergaard M, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72(6):804–814. doi:10.1136/annrheumdis-2012-203158
6. McNally EG. Ultrasound of the small joints of the hands and feet: current status. Skeletal Radiol. 2008;37(2):99–113. doi:10.1007/s00256-007-0356-9
7. Kane D, Grassi W, Sturrock R, Balint PV. A brief history of musculoskeletal ultrasound: "from bats and ships to babies and hips". Rheumatology (Oxford). 2004;43(7):931–933. doi:10.1093/rheumatology/keh004
8. Cooperberg PL, Tsang I, Truelove L, Knickerbocker WJ. Gray scale ultrasound in the evaluation of rheumatoid arthritis of the knee. Radiology. 1978;126(3):759–763. doi:10.1148/126.3.759
9. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32(12):2485–2487. Available from: https://pubmed.ncbi.nlm.nih.gov/16331793/
10. Möller I, Janta I, Backhaus M, et al. The 2017 EULAR standardised procedures for ultrasound imaging in rheumatology. Ann Rheum Dis. 2017;76(12):1974–1979. doi:10.1136/annrheumdis-2017-211585
11. Taljanovic MS, Melville DM, Gimber LH, et al. High-resolution US of rheumatologic diseases. Radiographics. 2015;35(7):2026–2048. doi:10.1148/rg.2015140250
12. Lee SA, Kim BH, Kim SJ, Kim JN, Park SY, Choi K. Current status of ultrasonography of the finger. Ultrasonography. 2016;35(2):110–123. doi:10.14366/usg.15051
13. Sahbudin I, Pickup L, Nightingale P, et al. The role of ultrasound-defined tenosynovitis and synovitis in the prediction of rheumatoid arthritis development. Rheumatology (Oxford). 2018;57(7):1243–1252. doi:10.1093/rheumatology/key025
14. Kuwano Y, Ishizaki K, Watanabe R, Nanko H. Efficacy of diagnostic ultrasonography of lipomas, epidermal cysts, and ganglions. Arch Dermatol. 2009;145(7):761–764. doi:10.1001/archdermatol.2009.61

15. Cardinal E, Chhem RK, Beauregard CG, Aubin B, Pelletier M. Plantar fasciitis: sonographic evaluation. Radiology. 1996;201(1):257–259. doi:10.1148/radiology.201.1.8816554
16. Kane D, Greaney T, Shanahan M, et al. The role of ultrasonography in the diagnosis and management of idiopathic plantar fasciitis. Rheumatology (Oxford). 2001;40(9):1002–1008. doi:10.1093/rheumatology/40.9.1002
17. Haugen IK, Bøyesen P. Imaging modalities in hand osteoarthritis: status and perspectives of conventional radiography, magnetic resonance imaging, and ultrasonography. Arthritis Res Ther. 2011;13(6):248. doi:10.1186/ar3509
18. Iagnocco A, Ceccarelli F, Rizzo C, et al. Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus. Rheumatology (Oxford). 2014;53(3):465–472. doi:10.1093/rheumatology/ket376
19. Löffler C, Sattler H, Peters L, Löffler U, Uppenkamp M, Bergner R. Distinguishing gouty arthritis from calcium pyrophosphate disease and other arthritides. J Rheumatol. 2015;42(3):513–520. doi:10.3899/jrheum.140634
20. Grassi W, Okano T, Filippucci E. Use of ultrasound for diagnosis and monitoring of outcomes in crystal arthropathies. Curr Opin Rheumatol. 2015;27(2):147–155. doi:10.1097/BOR.0000000000000142
21. Malaviya AN, Kapoor SK, Singh RR, Kumar A, Pande I. Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatol Int. 1993;13(4):131–134. doi:10.1007/BF00301258
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–1457. doi:10.1016/S0140-6736(07)61602-X
23. Lee JC, Healy JC. Normal sonographic anatomy of the wrist and hand. Radiographics. 2005;25(6):1577–1590. doi:10.1148/rg.256055028
24. Saigal R, Goyal L, Maharia HR, Sharma M, Agrawal A. Ultrasonographic evaluation of joint involvement in rheumatoid arthritis: comparison with conventional radiography and correlation with disease activity parameters. Indian J Rheumatol. 2017;12(1):6–11. doi:10.4103/0973-3698.199123
25. Saran S, Bansal P, Parashar N. Flexor tenosynovitis in early untreated rheumatoid arthritis: what do ultrasound and MRI show. J Clin Diagn Res. 2018;12(5):TC01–TC04. doi:10.7860/JCDR/2018/34127.11495
26. Evans KD, Farooki S. Sonographic evaluation of extensor tenosynovitis. J Diagn Med Sonogr. 2001;17(5):275–279. doi:10.1177/875647930101700506
27. Kamel M, Moghazy K, Eid H, Mansour R. Ultrasonographic diagnosis of de Quervain's tenosynovitis. Ann Rheum Dis. 2002;61(11):1034–1035. doi:10.1136/ard.61.11.1034

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ORIGINAL ARTICLE

Serial Assessment of Cochlear Changes Using Transient Evoked and Distortion Product Otoacoustic Emissions in Children Receiving Platinum-Based Chemotherapy

Monica Mrudubhashini Michael,[1,*] Kandasamy Kamindan Manjai Sengodan,[2] Gayathri Bhaskaran,[1] Raghavendra KS,[3] Vijay R,[4] Suhel Hasan[5] and Sathya P[6]

[1]*Assistant Professor, Department of ENT, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu – 641014*

[2]*Associate Professor, Department of ENT, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu - 641014*

[3]*Senior Consultant, Department of ENT, Sparsh Hospital, Sarjapur Road, Bangalore, Karnataka - 560035*

[4]*Professor and Head, Department of ENT, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu - 641014*

[5]*Head and Senior Consultant, Department of ENT, Narayana Hrudayalaya Hospital, Bommasandra, Bangalore-560099*

[6]*Audiologist and Speech Language Pathologist, Department of ENT, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu - 641014*

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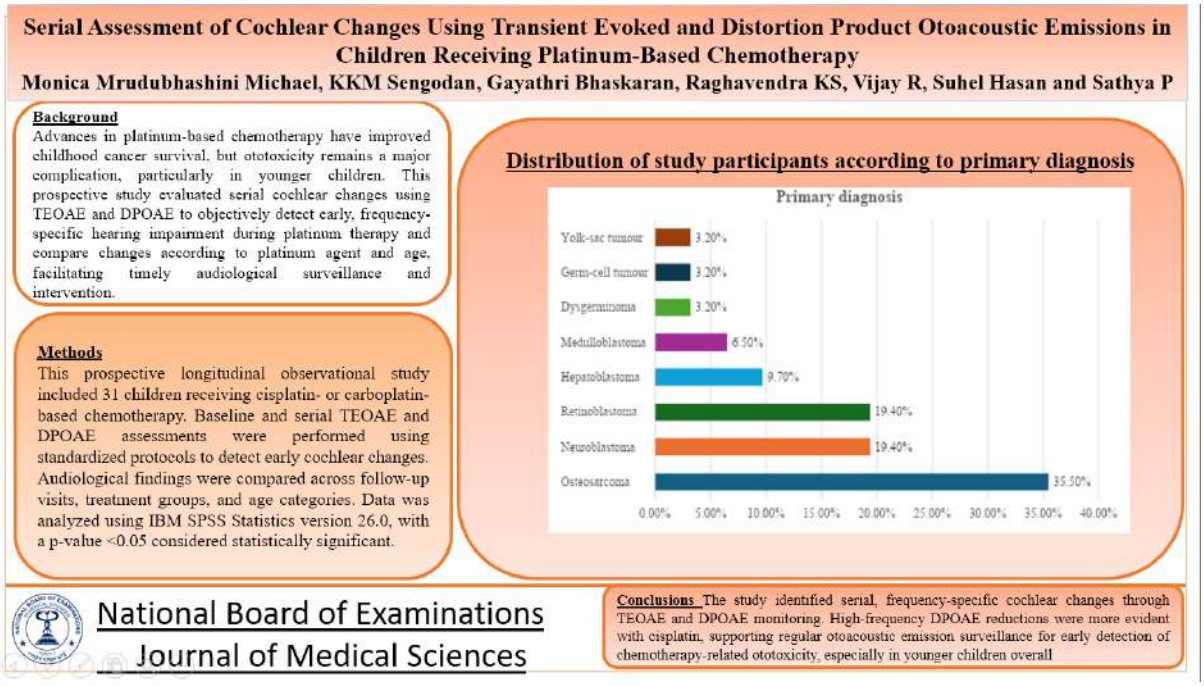
Abstract

Background: Advances in platinum-based chemotherapy have improved childhood cancer survival, but ototoxicity remains a major complication, particularly in younger children. This prospective study evaluated serial cochlear changes using TEOAE and DPOAE to objectively detect early, frequency-specific hearing impairment during platinum therapy and compare changes according to platinum agent and age, facilitating timely audiological surveillance and intervention. **Methods:** This prospective longitudinal observational study included 31 children receiving cisplatin- or carboplatin-based chemotherapy. Baseline and serial TEOAE and DPOAE assessments were performed using standardized protocols to detect early cochlear changes. Audiological findings were compared across follow-up visits, treatment groups, and age categories. Data was analyzed using IBM SPSS Statistics version 26.0, with a p-value <0.05 considered statistically significant. **Results:** Among 31 children (67.7% cisplatin, 32.3% carboplatin), serial otoacoustic emission monitoring demonstrated frequency-specific cochlear changes. DPOAE reductions occurred predominantly above 6 kHz in the cisplatin group, whereas TEOAE showed significant intergroup differences at 4 kHz during the first follow-up (30.0% vs. 0%; p=0.036) and at 1 kHz during the second follow-up (28.6% vs. 8.3%; p=0.049). Younger children showed greater cochlear changes, supporting serial TEOAE and DPOAE as useful tools for early detection of platinum-induced ototoxicity. **Conclusion:** The study identified serial, frequency-specific cochlear changes through TEOAE and DPOAE monitoring. High-frequency DPOAE reductions were more evident with cisplatin, supporting regular otoacoustic emission surveillance for early detection of chemotherapy-related ototoxicity, especially in younger children overall.

Keywords: Pediatric Neoplasms, Cisplatin, Carboplatin, Platinum-Based Chemotherapy, Ototoxicity, Transient Evoked Otoacoustic Emissions (TEOAE), Cochlear Dysfunction

*Corresponding Author: Monica Mrudubhashini Michael
Email: mrudumichael90@gmail.com

Graphical Abstract



Introduction

Advances in multimodal therapy have substantially improved survival rates in childhood cancer, with platinum-based chemotherapeutic agents, particularly cisplatin and carboplatin, forming an integral component of treatment protocols for a wide range of pediatric malignancies, including solid tumors and central nervous system neoplasms [1-3]. Despite their therapeutic efficacy, platinum compounds are frequently associated with ototoxicity, which represents one of the most clinically significant dose-limiting adverse effects of treatment. Platinum-induced ototoxicity typically manifests as bilateral, progressive, irreversible sensorineural hearing loss that initially affects the higher frequencies before extending to lower frequencies with increasing cumulative exposure [2,4]. In children, hearing impairment has far-reaching consequences because it may adversely affect speech and language acquisition, cognitive development, communication, educational achievement, psychosocial well-being, and overall quality of life [1,5]. Several factors influence the risk of ototoxicity, including cumulative platinum dose, younger age at treatment, renal dysfunction, concurrent administration of other ototoxic medications, cranial irradiation, and individual genetic susceptibility [3,6].

The cochlea is particularly susceptible to platinum-induced injury because platinum compounds generate excessive reactive oxygen species, resulting in oxidative stress, mitochondrial dysfunction, inflammation, and apoptotic death of outer hair cells, especially within the basal turn of the cochlea where high-frequency sounds are encoded [2,6]. Conventional pure-tone audiometry remains the standard clinical method for hearing assessment; however, its usefulness in young children is often limited because reliable behavioral responses are required. Objective audiological techniques, particularly otoacoustic emissions (OAEs), provide a practical alternative by directly

evaluating outer hair cell integrity without requiring active patient participation. Transient evoked otoacoustic emissions (TEOAEs) assess cochlear responses predominantly within conventional speech frequencies, whereas distortion product otoacoustic emissions (DPOAEs) enable assessment across a wider frequency spectrum, including higher frequencies that are affected earliest by platinum-induced cochlear injury. Serial evaluation of otoacoustic emission signal-to-noise ratios may therefore facilitate the early detection and longitudinal monitoring of cochlear dysfunction during chemotherapy, even in children who are unable to perform reliable behavioral hearing tests [5,7].

Although otoacoustic emission testing has become an increasingly valuable component of ototoxicity surveillance, evidence describing serial cochlear changes throughout successive cycles of platinum-based chemotherapy in the pediatric population remains relatively limited. Furthermore, there is insufficient information regarding the frequency-specific pattern of cochlear involvement, the earliest occurrence of significant reductions in otoacoustic emission signal-to-noise ratios, and the persistence of these changes during treatment. Comparative data evaluating differences between children receiving cisplatin and carboplatin, as well as variations across different pediatric age groups, are also scarce. Improved characterization of these longitudinal cochlear changes may facilitate earlier identification of auditory dysfunction and contribute to more effective audiological surveillance and timely rehabilitative interventions in children receiving potentially ototoxic chemotherapy [5,7].

Accordingly, the present study was undertaken to evaluate serial cochlear changes using transient evoked otoacoustic emissions and distortion product otoacoustic emissions in children receiving platinum-based chemotherapy. The primary objective was to assess serial changes in TEOAE and DPOAE signal-to-noise ratios following chemotherapy. The secondary objectives were to determine the frequency-wise onset and persistence of significant reductions in signal-to-noise ratios across successive follow-up visits and to compare these changes according to the platinum agent administered and the age group of the study participants.

Methodology

This prospective observational study was conducted over 11 months, from August 2018 to June 2019, in the Department of ENT–Head and Neck Surgery at a tertiary care centre in South India. The sample size was estimated based on a previous study that reported a reduction in otoacoustic emission amplitude from 8.1 dB at baseline to 0.9 dB after treatment, with corresponding standard deviations of 9.2 dB and 12.9 dB. Assuming a 5% level of significance and 90% power, the minimum required sample size was calculated as 27 participants. After accounting for an anticipated 20% attrition, the estimated sample size was 34, which was rounded to 35. During the study period, 31 eligible children (≤18 years) with malignancies receiving platinum-based chemotherapy were enrolled.

Children with newly diagnosed malignancies scheduled to receive cisplatin- or carboplatin-based chemotherapy were included. Patients with pre-existing hearing impairment, chronic middle-ear disease, congenital profound

sensorineural hearing loss, primary tumors involving the auditory system, metastatic involvement of the auditory pathway, or baseline hearing thresholds exceeding 25 dB HL were excluded.

After obtaining written informed consent from parents or legal guardians, demographic and clinical details were recorded using a structured proforma. All participants underwent baseline otological evaluation before initiation of chemotherapy, followed by serial audiological assessments before each subsequent chemotherapy cycle for a maximum of three follow-up visits, depending on treatment completion and patient availability.

Otoacoustic emissions were assessed in a sound-treated room using the Neuro-Audio Neurosoft system. Transient evoked otoacoustic emissions (TEOAE) were recorded using click stimuli, while distortion product otoacoustic emissions (DPOAE) were obtained using paired primary tones with an F2/F1 frequency ratio of 1.22. DPOAE responses were analyzed across frequencies below and above 6 kHz, whereas TEOAE responses were evaluated at 1, 2, 3, 4, and 5 kHz. The signal-to-noise ratio (SNR) was recorded at each frequency during baseline and follow-up assessments, and serial changes in SNR were used to assess cochlear function throughout chemotherapy. Participants received platinum-based chemotherapy according to standard institutional treatment protocols. Serial TEOAE and DPOAE findings were analyzed according to the platinum agent administered (cisplatin or carboplatin), the available follow-up visits, and the age group of the participants to characterize the frequency-wise pattern, onset, and persistence of cochlear changes during treatment.

Continuous variables were summarized as mean ± standard deviation or median with interquartile range, as appropriate, while categorical variables were expressed as frequencies and percentages. Comparisons between cisplatin and carboplatin groups were performed using the Chi-square test or Fisher's exact test for categorical variables. A two-sided p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (IBM SPSS Statistics, version 20.0; IBM Corp., Armonk, NY, USA).

Results

Table 1. Baseline demographic and anthropometric characteristics of the study participants

Characteristic	Category	Value
Age	**Mean ± SD, years**	7.01 ± 6.16
	Median (range), years	3.0 (0.08–18.0)
Age group	**<3 years**	16 (51.6%)
	≥3 years	15 (48.4%)
Gender	**Male**	17 (54.8%)
	Female	14 (45.2%)
Body surface area	**Mean ± SD, m²**	0.80 ± 0.44
	Median (range), years	0.60 (0.50–0.98)

The study included 31 children with a mean age of 7.01 ± 6.16 years and a median age of 3.0 years. Participants were almost evenly distributed between the <3-year and ≥3-year age groups. Males constituted 54.8% of the cohort, while females accounted for 45.2%. The mean body surface area was 0.80 ± 0.44 m², with a median of 0.60 m^2 (Table 1).

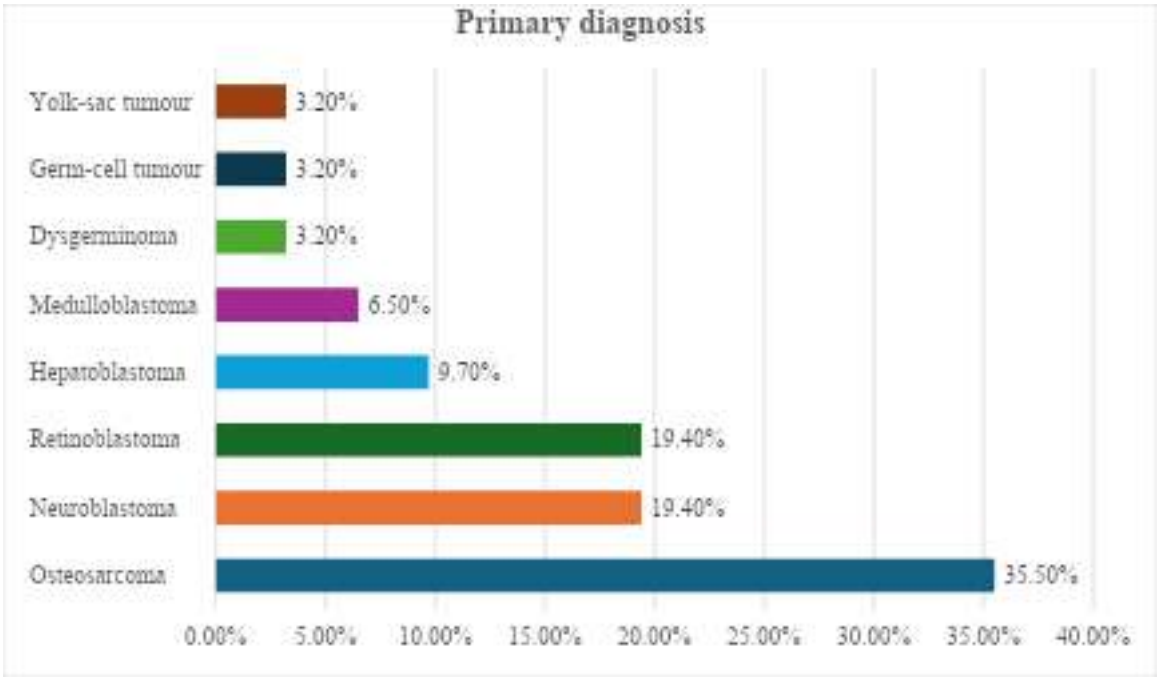


Figure 1. Distribution of study participants according to primary diagnosis

Osteosarcoma was the most common malignancy, affecting 11 children (35.5%). Neuroblastoma and retinoblastoma were each diagnosed in 6 participants (19.4%), followed by hepatoblastoma in 3 (9.7%) and medulloblastoma in 2 (6.5%). Dysgerminoma, germ-cell tumour, and yolk-sac tumour were each observed in one participant (3.2%) (Figure 1).

Table 2. Distribution of platinum-based chemotherapy and concomitant treatment regimens

Characteristic	Category	Value
Platinum compound administered	**Cisplatin**	21 (67.7%)
	Carboplatin	10 (32.3%)
Mean platinum dose	**Cisplatin, mg/m²**	62.11 ± 10.71
	Carboplatin for retinoblastoma, mg/kg/day	28.45 ± 5.59
	Carboplatin for other malignancies, mg/m²	560.10 ± 75.23
Other chemotherapy regimen administered	**DOX and MTX**	7 (22.6%)
	DOX	7 (22.6%)
	VCR and ETO	6 (19.4%)

	ETO, CPM and DOX	3 (9.7%)
	ETO and BLM	2 (6.5%)
	AMI, VCR and CPM	2 (6.5%)
	ETO	2 (6.5%)
	DOX, VBL and BLM	1 (3.2%)
	ETO and CPM	1 (3.2%)

DOX – Doxorubicin; MTX – Methotrexate; VCR – Vincristine; VBL – Vinblastine; ETO – Etoposide; CPM – Cyclophosphamide; BLM – Bleomycin; AMI – Amifostine.

Cisplatin was administered to 21 participants (67.7%), while 10 (32.3%) received carboplatin. The mean cisplatin dose was 62.11 ± 10.71 mg/m². Carboplatin dosing differed by indication, averaging 28.45 ± 5.59 mg/kg/day for retinoblastoma and 560.10 ± 75.23 mg/m² for other malignancies. Doxorubicin with methotrexate and doxorubicin alone were the most common additional regimens, each used in 7 participants (22.6%), followed by vincristine with etoposide in 6 (19.4%) (Table 2).

Table 3. Follow-up distribution of participants according to platinum compound

Follow-up assessment	**Total participants (N=31)**	**Cisplatin (n=21)**	**Carboplatin (n=10)**
At least one follow-up	26 (83.9%)	16 (76.2%)	10 (100.0%)
At least two follow-ups	19 (61.3%)	12 (57.1%)	7 (70.0%)
Three follow-ups completed	10 (32.3%)	6 (28.6%)	4 (40.0%)
No follow-up available	5 (16.1%)	5 (23.8%)	0 (0.0%)

Among the 31 participants, 26 (83.9%) completed at least one follow-up, 19 (61.3%) completed at least two follow-ups, and 10 (32.3%) completed all three follow-ups. Follow-up completion was consistently higher among carboplatin recipients than cisplatin recipients. All participants receiving carboplatin underwent at least one follow-up, whereas 5 cisplatin-treated participants (23.8%) had no follow-up data available (Table 3).

Table 4. Serial changes in distortion product otoacoustic emission (DPOAE) signal-to-noise ratio (SNR) according to platinum compound

DPOAE frequency range		SNR finding	Cisplatin	Carboplatin	p-value#
At least one follow-up (16 vs 10)	<6 kHz	Significant reduction	1 (6.3%)	0 (0.0%)	0.723
		No significant reduction	12 (75.0%)	8 (80.0%)	
		Invalid response	3 (18.8%)	2 (20.0%)	
	>6 kHz	Significant reduction	2 (12.5%)	0 (0.0%)	0.549
		No significant reduction	6 (37.5%)	6 (60.0%)	
		Invalid response	8 (50.0%)	4 (40.0%)	
At least two follow-ups (12 vs 7)	<6 kHz	Significant reduction	0 (0.0%)	0 (0.0%)	0.563
		No significant reduction	10 (83.3%)	5 (71.4%)	
		Invalid response	2 (16.7%)	2 (28.6%)	
	>6 kHz	Significant reduction	2 (16.7%)	0 (0.0%)	0.423
		No significant reduction	3 (25.0%)	3 (42.9%)	
		Invalid response	7 (58.3%)	4 (57.1%)	
Three follow-ups completed (6 vs 4)	<6 kHz	Significant reduction	0 (0.0%)	0 (0.0%)	0.389
		No significant reduction	5 (83.3%)	4 (100.0%)	
		Invalid response	1 (16.7%)	0 (0.0%)	
	>6 kHz	Significant reduction	1 (16.7%)	0 (0.0%)	0.170
		No significant reduction	1 (16.7%)	3 (75.0%)	
		Invalid response	4 (66.7%)	1 (25.0%)	

Chi-square test

Significant DPOAE SNR reductions were observed predominantly at frequencies above 6 kHz among cisplatin recipients, occurring in 12.5%, 16.7%, and 16.7% of participants across the one-, two-, and three-follow-up cohorts, respectively. No significant reductions were recorded among carboplatin recipients. Invalid responses were more frequent above 6 kHz, particularly in the cisplatin group. However, DPOAE findings did not differ significantly between cisplatin and carboplatin recipients at any follow-up level or frequency range (all $p>0.05$) (Table 4).

Table 5. Serial changes in transient evoked otoacoustic emission (TEOAE) signal-to-noise ratio (SNR) according to platinum compound

DPOAE frequency range		SNR finding	Cisplatin	Carboplatin	p-value[#]
At least one follow-up (16 vs 10)	1 kHz	Significant reduction	4 (25.0%)	1 (10.0%)	0.223
		No significant reduction	9 (56.3%)	4 (40.0%)	
		Invalid response	3 (18.8%)	5 (50.0%)	
	2 kHz	Significant reduction	3 (18.8%)	2 (20.0%)	0.241
		No significant reduction	12 (75.0%)	5 (50.0%)	
		Invalid response	1 (6.3%)	3 (30.0%)	
	3 kHz	Significant reduction	1 (6.3%)	0 (0.0%)	0.711
		No significant reduction	11 (68.8%)	7 (70.0%)	
		Invalid response	4 (25.0%)	3 (30.0%)	
	4 kHz	Significant reduction	0 (0.0%)	3 (30.0%)	0.036*
		No significant reduction	5 (31.3%)	4 (40.0%)	
		Invalid response	11 (68.8%)	3 (30.0%)	
	5 kHz	Significant reduction	0 (0.0%)	0 (0.0%)	0.063
		No significant reduction	0 (0.0%)	1 (10.0%)	
		Invalid response	16 (100.0%)	9 (90.0%)	
At least two follow-ups (12 vs 7)	1 kHz	Significant reduction	1 (8.3%)	2 (28.6%)	0.049*
		No significant reduction	11 (91.7%)	3 (42.8%)	
		Invalid response	0 (0.0%)	2 (28.6%)	
	2 kHz	Significant reduction	3 (25.0%)	3 (42.8%)	0.598
		No significant reduction	8 (66.7%)	3 (42.8%)	
		Invalid response	1 (8.3%)	1 (14.3%)	
	3 kHz	Significant reduction	2 (16.7%)	1 (14.3%)	0.977
		No significant reduction	8 (66.7%)	5 (71.4%)	
		Invalid response	2 (16.7%)	1 (14.3%)	
	4 kHz	Significant reduction	2 (16.7%)	3 (42.8%)	0.087
		No significant reduction	2 (16.7%)	3 (42.8%)	
		Invalid response	8 (66.7%)	1 (14.3%)	

	5 kHz	**Significant reduction**	0 (0.0%)	0 (0.0%)	0.147
		No significant reduction	0 (0.0%)	2 (28.6%)	
		Invalid response	12 (100.0%)	5 (71.4%)	
Three follow-ups completed (6 vs 4)	**1 kHz**	**Significant reduction**	1 (16.7%)	3 (75.0%)	0.091
		No significant reduction	4 (66.7%)	0 (0.0%)	
		Invalid response	1 (16.7%)	1 (25.0%)	
	2 kHz	**Significant reduction**	2 (33.3%)	3 (75.0%)	0.232
		No significant reduction	3 (50.0%)	0 (0.0%)	
		Invalid response	1 (16.7%)	1 (25.0%)	
	3 kHz	**Significant reduction**	2 (33.3%)	2 (50.0%)	0.659
		No significant reduction	3 (50.0%)	2 (50.0%)	
		Invalid response	1 (16.7%)	0 (0.0%)	
	4 kHz	**Significant reduction**	1 (16.7%)	2 (50.0%)	0.108
		No significant reduction	1 (16.7%)	2 (50.0%)	
		Invalid response	4 (66.7%)	0 (0.0%)	
	5 kHz	**Significant reduction**	0 (0.0%)	1 (25.0%)	0.434
		No significant reduction	0 (0.0%)	0 (0.0%)	
		Invalid response	6 (100.0%)	3 (75.0%)	

Chi-square test; * Statistically significant

TEOAE SNR reductions varied across frequencies and follow-up cohorts. At the first follow-up, carboplatin recipients showed significantly more reductions at 4 kHz than cisplatin recipients (30.0% vs 0.0%; p=0.036). Among those completing at least two follow-ups, significant differences were observed at 1 kHz, with reductions in 28.6% of carboplatin recipients versus 8.3% of cisplatin recipients (p=0.049). No significant between-group differences were observed among participants completing all three follow-ups. Invalid responses were frequent at 4 and 5 kHz (Table 5).

Table 6. Association of age group with significant TEOAE and DPOAE signal-to-noise ratio reductions among cisplatin recipients

Follow-up cohort	Age group	TEOAE SR, n/N (%)	p-value#	DPOAE <6 kHz SR, n/N (%)	p-value#	DPOAE >6 kHz SR, n/N (%)	p-value#
One follow-up	<3 years	1/16 (6.3)	0.300	1/16 (6.3)	0.149	2/16 (12.5)	0.106
	>3 years	0/16 (0.0)		0/16 (0.0)		0/16 (0.0)	
Two follow-ups	<3 years	2/12 (16.7)	0.102	1/12 (8.3)	0.121	2/12 (16.7)	0.788
	>3 years	1/12 (8.3)		0/12 (0.0)		0/12 (0.0)	
Three follow-ups	<3 years	1/6 (16.7)	0.269	0/6 (0.0)	0.121	1/6 (16.7)	0.472
	>3 years	0/6 (0.0)		0/6 (0.0)		0/6 (0.0)	

SR – Significant Reduction; # Chi-square test

Across all follow-up cohorts, significant TEOAE and DPOAE SNR reductions were observed predominantly among children aged <3 years. However, no statistically significant association was found between age group and significant reduction in TEOAE, DPOAE below 6 kHz, or DPOAE above 6 kHz at any follow-up level (all p>0.05). The highest proportion of reduction was observed for DPOAE above 6 kHz among children aged <3 years in the one- and two-follow-up cohorts (Table 6).

Table 7. Association of age group with significant TEOAE and DPOAE signal-to-noise ratio reductions among carboplatin recipients

Follow-up cohort	Age group	TEOAE SR, n/N (%)	p-value#	DPOAE <6 kHz SR, n/N (%)	p-value#	DPOAE >6 kHz SR, n/N (%)	p-value#
One follow-up	<3 years	0/10 (0.0)	0.257	0/10 (0.0)	0.301	0/10 (0.0)	1.000
	>3 years	0/10 (0.0)		0/10 (0.0)		0/10 (0.0)	
	<3 years	0/7 (0.0)	0.301	0/7 (0.0)	0.439	0/7 (0.0)	0.273

Two follow-ups	**>3 years**	0/7 (0.0)		0/7 (0.0)		0/7 (0.0)	
Three follow-ups	**<3 years**	1/4 (25.0)	0.513	0/4 (0.0)	0.441	0/4 (0.0)	0.046*
	>3 years	0/4 (0.0)		0/4 (0.0)		0/4 (0.0)	

SR – Significant Reduction; # Chi-square test; * Statistically significant

No significant TEOAE or DPOAE SNR reductions were observed in either age group among participants completing one or two follow-ups. Among those completing three follow-ups, TEOAE reduction occurred in one child aged <3 years, while no DPOAE reductions were recorded. Although the reported comparison for DPOAE above 6 kHz was statistically significant (p=0.046), this finding should be interpreted cautiously because no significant reduction occurred in either age group (Table 7).

Discussion

Early identification of platinum-induced ototoxicity is essential in children because hearing impairment may be irreversible and adversely affect speech, language, learning, and quality of life. Objective monitoring is particularly important in younger children who may not reliably perform conventional audiometry. Therefore, this prospective longitudinal observational study evaluated serial cochlear changes in 31 children receiving cisplatin- or carboplatin-based chemotherapy using Transient Evoked Otoacoustic Emissions (TEOAE) and Distortion Product Otoacoustic Emissions (DPOAE).

Baseline testing was performed before chemotherapy, followed by serial assessments during subsequent treatment visits. Signal-to-noise ratios were recorded at predefined frequencies to identify early and frequency-specific cochlear dysfunction. Demographic, clinical, diagnostic, and treatment-related details were documented using a structured proforma. Children with pre-existing hearing impairment or conditions affecting otoacoustic emission testing were excluded. Findings were compared over time, between cisplatin and carboplatin groups, and across age categories to assess treatment- and age-related differences in ototoxicity.

Clinical feasibility of OAE monitoring

In the present study of 31 children receiving platinum-based chemotherapy, serial TEOAE and DPOAE monitoring was successfully performed without sedation, overcoming the limitations of behavioural pure-tone audiometry in young children. At least one follow-up was completed by 83.9% (26/31), two follow-ups by 61.3% (19/31), and all three by 32.3% (10/31). Hecker et al. (2026) [8] similarly reported reliable behavioural PTA in only 39.2% (60/153), whereas DPOAE testing was completed in 100% (153/153). Brooks et al. (2018) [5], Knight et al. (2007) [9], and Diepstraten et al. (2024) [10] also supported OAEs as objective, rapid, ear-specific, well-tolerated, and suitable for children unable to cooperate with PTA. No

contradictory evidence was identified, supporting OAE monitoring as a practical, reliable, and sedation-free surveillance method.

Cisplatin-related DPOAE reductions

Significant DPOAE signal-to-noise ratio reductions above 6 kHz were observed among cisplatin recipients in 12.5% (2/16) at the first follow-up and 16.7% at both the second (2/12) and third (1/6) follow-ups. Knight et al. (2007) [9] reported bilateral DPOAE amplitude and dynamic-range reductions in 81.3% (26/32) of platinum-treated children. Hecker et al. (2026) [8] demonstrated significant reductions between 10 and 16 kHz ($p=0.01$), most pronounced after the second cycle ($p\leq0.02$). Lopes et al. (2020) [11] described early basal outer hair cell injury with reductions above 4 kHz, while Fetoni et al. (2016) [12] found a significant relationship with cumulative cisplatin dose ($p<0.05$) and hearing loss in 25% (6/24). Diepstraten et al. (2024) [10] reported that each 100 mg/m² increase in cisplatin dose increased the risk of Muenster grade ≥2b hearing loss by OR 1.6 (95% CI 1.4–2.0; $p<0.001$). These findings support high-frequency DPOAE monitoring as a sensitive marker of early cisplatin ototoxicity.

Carboplatin-related DPOAE reductions

No significant DPOAE SNR reductions occurred among carboplatin recipients below or above 6 kHz at any follow-up: 0/10 at the first, 0/7 at the second, and 0/4 at the third assessment, with all p-values >0.05. Hecker et al. (2026) [8] similarly reported a lower risk of sensory hearing loss with carboplatin. Diepstraten et al. (2024) [10] found no significant association with Muenster grade ≥2b hearing loss (OR 0.71, 95% CI 0.38–1.30) or SIOP grade ≥2 hearing loss (OR 1.05, 95% CI 0.57–1.91). Lopes et al. (2020) [11], citing Clemens et al. (2016) [13], reported ototoxicity in 17% of carboplatin-only survivors versus 45% of cisplatin-only survivors. Smits et al. (2006) [14] reported 0% hearing loss and no OAE changes in 25 carboplatin-treated children, while Amorim et al. (2007) [15] observed 100% TEOAE preservation. Fetoni et al. (2016) [12] found no dose–ototoxicity correlation ($p>0.05$), although 19% (9/47) developed hearing loss. Contrastingly, Bhagat et al. (2010) [16] found significant DPOAE reductions at 7996 Hz ($p=0.004$), with 40% (4/10) meeting clinical OAE reduction criteria. Macdonald et al. (1994) [17] reported hearing loss in 50%, while Simon et al. (2002) [18] and Knight et al. (2005) [9] reported hearing impairment in 40% and 38%, respectively, particularly with high-dose carboplatin. Thus, standard-dose carboplatin appears less ototoxic, although high cumulative exposure may affect ultra-high frequencies.

TEOAE reductions

At the first follow-up, carboplatin recipients showed significantly more 4-kHz TEOAE SNR reductions than cisplatin recipients, 30.0% (3/10) versus 0.0% (0/16), respectively ($p=0.036$). The difference persisted without statistical significance at the second follow-up, 42.8% (3/7) versus 16.7% (2/12; $p=0.087$), and third follow-up, 50.0% (2/4) versus 16.7% (1/6; $p=0.108$). Bhagat et al. (2010) [16] reported clinically relevant OAE reductions of more than 6 dB at frequencies ≥4004 Hz in children receiving cumulative carboplatin doses above 1800 mg/m². Brooks et al. (2018) [5] emphasized the clinical importance of monitoring 2 and 4 kHz. However, Hecker et al. (2026) [8]

found no substantial middle-frequency DPOAE changes with carboplatin, while Smits et al. (2006) [14] and Amorim et al. (2007) [15] reported no OAE deterioration and complete TEOAE preservation. The present finding therefore suggests that early subclinical 4-kHz injury may occasionally occur despite carboplatin's generally lower ototoxicity.

At the second follow-up, TEOAE SNR reductions at 1 kHz were significantly more frequent in carboplatin recipients than in cisplatin recipients, 28.6% (2/7) versus 8.3% (1/12), respectively (p=0.049). At the first follow-up, reductions occurred in 25.0% (4/16) of cisplatin and 10.0% (1/10) of carboplatin recipients (p=0.223), while at the third follow-up they occurred in 16.7% (1/6) and 75.0% (3/4), respectively (p=0.091). Brooks et al. (2018) [5] and Lopes et al. (2020) [11] described platinum ototoxicity as predominantly high-frequency, extending to lower speech frequencies only after continued exposure. Fetoni et al. (2016) [12] reported that frequencies between 0.5 and 1 kHz were never affected, while Smits et al. (2006) [14] found no low-frequency deterioration. Therefore, the early 1-kHz reduction observed in the present carboplatin cohort was atypical and differed from the usual basal-to-apical progression of platinum ototoxicity.

Age-related vulnerability

OAE reductions were observed more frequently among cisplatin-treated children aged below 3 years. At the first follow-up, DPOAE reductions above 6 kHz occurred in 12.5% (2/16) of children aged below 3 years compared with 0.0% among those aged 3 years or older (p=0.106). However, no statistically significant age association was demonstrated at any follow-up or frequency range. Diepstraten et al. (2024) [10] found that younger age significantly increased hearing-loss risk under both Muenster criteria (OR 0.9 per year, 95% CI 0.9–1.0; p=0.049) and SIOP criteria (OR 0.9 per year, 95% CI 0.8–1.0; p<0.001). Knight et al. (2007) [9] reported bilateral hearing loss in 76.9% (10/13) of children aged 5 years or younger. Hecker et al. (2026) [8] and Lopes et al. (2020) [11] also identified children below 5 years as particularly susceptible because of immature auditory and antioxidant systems. Conversely, Fetoni et al. (2016) [12] found no significant age association (p>0.05), possibly owing to reduced doses, avoidance of cranial radiotherapy, or preferential carboplatin use in infants. The present trend therefore remains clinically relevant despite limited statistical power.

Progression and persistence across chemotherapy cycles

Cisplatin-related cochlear changes showed a progressive and persistent pattern. DPOAE reductions above 6 kHz increased from 12.5% (2/16) at the first follow-up to 16.7% at the second (2/12) and third (1/6) follow-ups. TEOAE reductions at 2 kHz increased from 18.8% (3/16) to 25.0% (3/12) and 33.3% (2/6), respectively. Fetoni et al. (2016) [12] reported progressive threshold deterioration even after chemotherapy completion in 8.6% of patients. Knight et al. (2007) [9] also demonstrated progressive reductions in OAE amplitudes and hearing thresholds across treatment courses. Diepstraten et al. (2024) [10] identified cumulative cisplatin dose as the strongest predictor, with each 100 mg/m² increase raising the risk of Muenster grade ≥2b hearing loss by OR 1.6 (95% CI 1.4–2.0; p<0.001). Lopes et al. (2020) [11] and Brooks et al. (2018) [5]

similarly described progression from higher to lower frequencies with increasing cumulative exposure. Overall, serial TEOAE and DPOAE monitoring demonstrated the cumulative, progressive, and frequency-spreading nature of platinum-induced cochlear injury.

Limitations

The relatively small sample size and invalid responses might limit the generalisability of this study, requiring more studies to corroborate similar findings in different settings.

Conclusion

The study demonstrated serial, frequency-specific cochlear changes in children receiving platinum-based chemotherapy using TEOAE and DPOAE. DPOAE reductions were predominantly observed above 6 kHz among cisplatin recipients, indicating early high-frequency cochlear involvement, while TEOAE changes varied across treatment groups, frequencies, and follow-up periods. Although younger children receiving cisplatin showed more frequent reductions, age was not significantly associated with otoacoustic emission changes. Differences between cisplatin and carboplatin were limited, and invalid high-frequency responses affected interpretation. These findings support serial otoacoustic emission monitoring for early detection of chemotherapy-related ototoxicity, particularly among younger children and those receiving cisplatin.

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Statements and Declarations

Conflict of interest

The authors declare that they do not have conflict of interest.

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References

1. Brock PR, Knight KR, Freyer DR, Campbell KCM, Steyger PS, Blakley BW, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. J Clin Oncol. 2012;30(19):2408–17.
2. Landier W. Ototoxicity and cancer therapy. Cancer. 2016;122(11):1647–58.
3. Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzi G, Corradini N, et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004;26(10):649–55.
4. Clemens E, van den Heuvel-Eibrink MM, Mulder RL, Kremer LCM, Hudson MM, Skinner R, et al. Recommendations for ototoxicity surveillance in childhood, adolescent and young adult cancer survivors: an International Late Effects of Childhood Cancer Guideline Harmonization Group report. Lancet Oncol. 2019;20(1):e29–e41.
5. Brooks B, Knight K. Ototoxicity monitoring in children treated with platinum chemotherapy. Int J Audiol. 2018;57(Suppl 4):S34–S40.

6. Freyer DR, Brock PR, Chang KW, Dupuis LL, Epelman S, Knight K, et al. Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline. Lancet Child Adolesc Health. 2020;4(2):141–150.
7. Ciorba A, Bianchini C, Pelucchi S, Pastore A. The impact of hearing loss on the quality of life of children. Int J Pediatr Otorhinolaryngol. 2012;76(Suppl 1):S59–S63.
8. Hecker DJ, Remke MK, Linxweiler M, Furtwängler R, Akrasu Y, Schöndorf D, et al. Distortion product otoacoustic emission (DPOAE) reveals hearing loss up to 16 kHz in paediatric chemotherapy patients. Sci Rep. 2026 Apr 18;16(1):12729.
9. Knight KR, Kraemer DF, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. J Clin Oncol. 2007 Apr 1;25(10):1190-1195.
10. Diepstraten FA, Bertram OM, Helleman HW, Boerboom RA, van Grotel M, Zsíros J, et al. A retrospective evaluation of ototoxicity monitoring in a cohort of paediatric patients with solid tumours, treated in the Dutch National Cancer Center. Cancer Rep. 2024 Nov;11(11):e70046.
11. Lopes NB, Silva LA, Samelli AG, Matas CG. Effects of chemotherapy on the auditory system of children with cancer: a systematic literature review. Revista CEFAC. 2020 Mar-Apr;22(2):e13919.
12. Fetoni AR, Ruggiero A, Lucidi D, De Corso E, Sergi B, Conti G, et al. Audiological monitoring in children treated with platinum chemotherapy. Audiol Neurootol. 2016 Jun 11;21(4):203–211.
13. Clemens E, de Vries AC, Pluijm SF, Am Zehnhoff-Dinnesen A, Tissing WJ, Loonen JJ, et al. Determinants of ototoxicity in 451 platinum-treated Dutch survivors of childhood cancer: A DCOG late-effects study. Eur J Cancer. 2016 Nov;69:77–85.
14. Smits C, Swen SJ, Goverts ST, Moll AC, Imhof SK, Schouten-van Meeteren AY. Assessment of hearing in very young children receiving carboplatin for retinoblastoma. Eur J Cancer. 2006 Feb;42(4):492–500.
15. Amorim AM, Azevedo MF, Carvalho CAF, Macedo CRP. Transient evoked otoacoustic emissions in children with retinoblastoma submitted to chemotherapy with carboplatin. Int Arch Otorhinolaryngol. 2007 Oct-Dec;11(4):375–379.
16. Bhagat SP, Bass JK, White ST, Qaddoumi I, Wilson MW, Wu J, et al. Monitoring carboplatin ototoxicity with distortion-product otoacoustic emissions in children with retinoblastoma. Int J Pediatr Otorhinolaryngol. 2010 Oct;74(10):1156–1163.
17. Macdonald MR, Harrison RV, Wake M, Bliss B, Macdonald RE. Ototoxicity of carboplatin: comparing animal and clinical models at the Hospital for Sick Children. J Otolaryngol. 1994 Jun;23(3):151–159.
18. Simon T, Hero B, Dupuis W, Selle B, Berthold F. The incidence of hearing impairment after successful treatment of neuroblastoma. Klin Padiatr. 2002 Jul-Aug;214(4):149–152.

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ORIGINAL ARTICLE

Acceptability and Barriers to Mobile Health Application Use Among Community Healthcare Workers in Rural Tamil Nadu: A Qualitative Study

Sai Santhoshini Thiruvarasan,[1] Madhivanan Arulmozhi[2,*] and Premanandh Kandasamy[3]
[1]*Post Graduate, Department of Community Medicine, Sri Manakula Vinayagar Medical College and Hospital, Puducherry*
[2]*Associate Professor, Department of Community Medicine, Sri Manakula Vinayagar Medical College and Hospital, Puducherry*
[3]*Professor and Head, Department of Community Medicine, Sri Manakular Vinayagar Medical College and Hospital, Puducherry*

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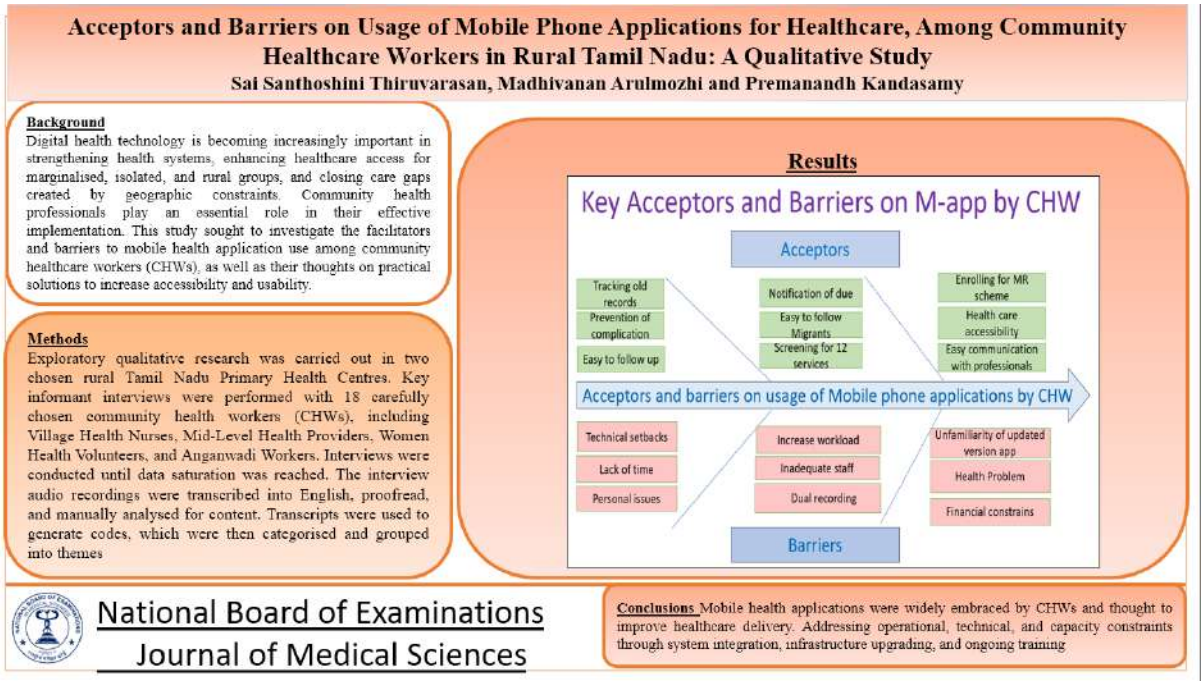
Abstract

Background: Digital health technology is becoming increasingly important in strengthening health systems, enhancing healthcare access for marginalised, isolated, and rural groups, and closing care gaps created by geographic constraints. Community health professionals play an essential role in their effective implementation. This study sought to investigate the facilitators and barriers to mobile health application use among community healthcare workers (CHWs), as well as their thoughts on practical solutions to increase accessibility and usability. **Methodology:** Exploratory qualitative research was carried out in two chosen rural Tamil Nadu Primary Health Centres. Key informant interviews were performed with 18 carefully chosen community health workers (CHWs), including Village Health Nurses, Mid-Level Health Providers, Women Health Volunteers, and Anganwadi Workers. Interviews were conducted until data saturation was reached. The interview audio recordings were transcribed into English, proofread, and manually analysed for content. Transcripts were used to generate codes, which were then categorised and grouped into themes. **Results:** The facilitating factors were user-friendly interface, improved patient tracking, illness monitoring, quick follow-up, referral, and integrated health care services all contributed to the success. The majority of CHWs (n=14) cited technological difficulties, dual recording, and time limits as their main obstacles. Logistical and budgetary difficulties were also identified as impediments to the adoption of mobile health applications. **Conclusion:** Mobile health applications were widely embraced by CHWs and thought to improve healthcare delivery. Addressing operational, technical, and capacity constraints through system integration, infrastructure upgrading, and ongoing training is critical to improving the successful and long-term adoption of mHealth apps in rural primary healthcare settings.

Keywords: Mobile health application, community health worker, Rural, Qualitative, Primary health centre

*Corresponding Author: Madhivanan Arulmozhi
Email: cm.arulmozhim@smvmch.ac.in

Graphical Abstract



Introduction

Digital health has evolved as a transformative way to strengthening health systems by making healthcare more accessible to remote, rural, and marginalised groups [1]. In May 2018, the World Health Assembly formally endorsed the Resolution on Digital Health, recognising these technologies' potential to promote health, prevent disease, and improve access, quality, and cost of care [2]. Mobile devices, especially in low- and middle-income countries, offer unique opportunities for service delivery directly at the point of care. Mobile health (mHealth) technologies have the potential to bridge gaps in care caused by geographic isolation, low demand for services, delayed treatment, poor adherence to clinical protocols, and prohibitive financial costs [3]. Furthermore, World Health Organization (WHO) guidelines on digital health interventions emphasize the necessity of creating supportive environments, ensuring that health workers can seamlessly adapt to and utilize these digital platforms [4].

India has accelerated its digital health transformation through the Ayushman Bharat Digital Mission to enable interoperable electronic health records and digital health services [5]. Furthermore, several programme-specific mobile applications have been developed to support frontline health workers in implementing maternal and child health services, disease surveillance, immunization, nutrition, communicable disease and NCD screening [6,7]. Evidence suggests that incorporating mobile health interventions improved a wide range of outcomes such as improved clinical parameters, treatment outcomes, patient knowledge, health behaviour, satisfaction, and psychosocial wellbeing [8,9].

Community health workers serve as a critical link between health systems and communities, enhancing healthcare access,

service coverage, and progress towards universal health coverage [10]. Studies have shown that the use of mobile phones for health care services enhances frontline health workers' motivation, empowerment, work efficiency, self-efficacy, and credibility within the community. Further, it reduces paperwork and enhances timely reporting, data quality, and data completeness [11]. Despite the greater usefulness of mHealth interventions, their widespread adoption is hindered by barriers such as a lack of smartphones, limited digital literacy, poor internet access, inadequate training, usability concerns, and reluctance among healthcare providers to integrate digital technologies into routine practice [8,12].

Many studies in India have primarily focused only on patient perspectives on digital health are well-documented, qualitative research on the experiences of Community Health Workers (CHWs) implementing mobile health apps in rural Tamil Nadu remains limited. This qualitative study explores CHWs' field experiences to identify the facilitators, barriers, operational gaps, and cultural acceptability of these technologies across the continuum of care. By gathering CHW-proposed solutions, this research provides critical insights to optimize the usability and delivery of grassroots digital health services.

Methodology

The present study was carried out in the field practice area of the Rural Health Training Centre (RHTC) attached to the medical college of Puducherry district. It is a tertiary care teaching hospital with a bed strength of 1180, exclusive of 150 critical care beds, providing comprehensive outpatient and inpatient services across multiple specialties. The study area is located in a village of Tamil Nadu, which is situated approximately 28 kilometres from the teaching institute. It covers four Primary Health Centres (PHCs), of which one PHC serves 34 villages with a population of 63,921 and another PHC within the same block covers 2,686 population.

It was an exploratory qualitative study design and was conducted over a period of three months in the year 2024. Since qualitative research does not require a predefined sample size, a total of 18 key informant interviews (KIIs) were conducted until the point of data saturation, when no new information emerged with additional interviews. After the initial 12 to 14 interviews, the researchers observed that the core themes regarding mHealth facilitators (e.g., easy retrieval of records) and barriers (e.g., dual data entry, network issues) were consistently repeating. To empirically confirm saturation, a stopping criterion of three consecutive interviews was applied. Interviews 16, 17, and 18 were conducted, transcribed, and manually coded against the existing codebook. When these final three transcripts yielded no new descriptive codes, sub-categories, or novel conceptual insights, the theoretical framework was deemed conceptually dense, and data saturation was officially declared achieved. Among the four PHCs located around the selected village, two PHCs were selected using the lottery method to obtain the diverse perspectives.

A purposive sampling technique was employed to recruit study participants from the selected PHCs. The participants included Community Health Workers (CHWs) such as village health nurses (n=6), mid-level health providers (n=4), women health volunteers (n=4), and Anganwadi workers (n=4). These cadres

were purposively selected as they represent the frontline health workforce in rural Tamil Nadu and are directly involved in service delivery, with routine interaction in digital health initiatives and mobile phone–based healthcare applications.

The Principal Investigator trained in qualitative research techniques through academic workshops and posted as a Medical Officer at Rural Health Training Centre during postgraduate training period in Community Medicine, conducted the interview in acquaintance with PHC medical officers as we coordinate IEC activities with the selected PHCs.

Recognizing the inherent hierarchical power dynamic between a medical officer and community healthcare workers, proactive steps were taken to mitigate social desirability bias. Prior to each interview, the investigator explicitly de-emphasized their clinical role, framing the interaction strictly as a collaborative research effort. Participants were reassured that their honest feedback including negative criticisms of the digital platforms would not impact their employment, performance evaluations, or professional relationship with the medical college or PHC. Furthermore, the researcher maintained a reflexive journal throughout the study to document personal preconceptions regarding mHealth utility, ensuring these assumptions did not influence the interview probing or the manual coding process (Table 1).

Table 1. Mobile application used by the community health care workers

S.NO	Health care workers	Mobil Application
1.	Anganwadi workers (4)	Poshan tracker app
2	Village health nurse (6)	PICKEME3.0, HMIS, Thaimai app
3.	Mid-level health provider (4)	AB portal, MTM login, e-sanjeevani, IHIP, Thaimai app
4.	Women health volunteer (4)	MTM portal,

Ethical consideration and permission

The study was initiated after obtaining approval from the institutional ethics committee (Approval No: EC/145/2024 and 14.10.2024). Prior permission was obtained from PHC medical officers. All the information collected from the study participants was kept confidential and their privacy was maintained.

Data collection procedure

After obtaining informed written consent from the study participants, the Principal Investigator, trained in qualitative research methods, conducted the interviews in a language comfortable to the participants at their convenient place and time. The interviews were conducted at the Primary Health Centre (PHC), to minimize potential bias, the interview topic was not disclosed in advance, as prior knowledge of the subject may influence participants'

responses and reduce the authenticity of the data.

A total of 18 key informant interviews (KIIs) were conducted using a pre-designed interview guide. The interview guide was developed based on an extensive literature review to explore the facilitators and barriers to mobile phone application usage among healthcare workers in rural areas. The interview guide consisted of open-ended questions such as: "What are the key motivators for using mobile health applications?", "What challenges do you encounter while using them for healthcare?", and "Can you suggest any solutions to improve usage?" Each interview lasted approximately 30–40 minutes.

With the participants' permission, all the interviews were audio recorded. Following each interview, the Principal Investigator transcribed the recordings verbatim in the local language Tamil on the same day of the interview. The transcripts were then translated into English, maintaining the accuracy of meaning. To ensure reliability, the transcripts were cross-checked against the original recordings, and a random subset was independently reviewed by a faculty supervisor for consistency. Field notes taken during the interviews were incorporated into the transcripts to capture non-verbal cues and contextual details, thereby enhancing the richness of the data.

Following each session, the Principal Investigator conducted a debriefing with the participant, during which they were encouraged to share any additional reflections or insights. These supplementary inputs were duly documented and included in the analysis, ensuring completeness and credibility of the data.

Analysis Plan

The transcripts were meticulously checked for errors, and personal identifiers such as name and address were removed to maintain anonymity. The interview transcripts were read multiple times and analyzed using manual content analysis with an inductive thematic approach. Initially, descriptive codes were generated line-by-line from the raw data to capture key ideas and expressions of participants. Similar codes were then compared, grouped together, and refined to reduce redundancy. These grouped codes were further organized into broader categories that represented patterned responses across participants. Finally, categories were merged into higher-level themes, which reflected the underlying facilitators and barriers influencing the use of mobile phone applications by community health workers.

To enhance reliability, the first two authors independently coded the transcripts, and the codes were cross-verified for inter-rater reliability. The final results were reviewed by the third author to confirm the codes and enhance the credibility of the findings. Any discrepancy arising between the investigators was resolved by mutual consensus. The study findings have been reported using "consolidated criteria for reporting qualitative research" (COREQ) guidelines and Rigour in qualitative research [14].

Coding Framework

An initial coding framework was developed manually by the first two authors. After a detailed, line-by-line reading of the first three information-rich transcripts, meaningful text segments were highlighted and assigned preliminary descriptive labels (codes). A formal

codebook was documented in a spreadsheet, detailing the code name, a brief operational definition, and an exemplar quote to ensure consistent application across all data. For instance, initial descriptive codes such as 'waiting for OTP' and 'inability to edit errors' were established.

Thematic Development

The coding process proceeded iteratively. The researchers utilized a manual thematic charting and color-coding technique to organize the data. As subsequent transcripts were analyzed, new codes were added to the framework. Once all data were coded, the codes were visually mapped and clustered into broader conceptual categories through constant comparison. For example, individual codes relating to operational difficulties and connectivity issues were grouped under the category of 'Technical Setbacks.' Finally, these categories were analytically elevated and synthesized into overarching themes that explained the core phenomena of mHealth facilitators and barriers. To ensure dependability and inter-rater reliability, the manually coded transcripts and the thematic map were cross-verified by the third author, with any conceptual discrepancies resolved through mutual consensus discussions."

Measures undertaken to the trustworthiness of the findings was established utilizing Lincoln and Guba's evaluative criteria [15].

Credibility was enhanced through data triangulation by interviewing a diverse cadre of participants, including VHNs, Staff Nurses, MLHPs, and WHVs, capturing a multi-faceted view of mHealth adoption. Additionally, member checking was implicitly conducted during the post-interview debriefing sessions, where the investigator summarized key takeaways to the participants to verify the accuracy of the interpretations. **Dependability** and **Confirmability** were achieved by maintaining a comprehensive audit trail, which included raw audio files, translated transcripts, field notes, and the manual coding spreadsheets. Furthermore, the inter-coder consensus process between the first three authors minimized individual researcher bias. Finally, **Transferability** was facilitated by providing a thick description of the study setting, participant demographics, and the specific operational contexts of the Thiruvennainallur and Sirumadurai PHCs, allowing readers to determine the applicability of the findings to similar rural landscapes.

Results

The mean age of the participants was 39.0 ± 8.29 years. Of the total 18 community health care workers, the majority 11 (61.1%) were below 40 years of age, while 7 (38.9%) were belongs to age group 40 years and above. About 16 (88.9%) were Hindu, while the remaining two (11.1%) belongs to Christians religion. All the respondents were literate. Table 2 highlights the supportive elements of mobile health platforms as perceived by CHWs, showing features that enhanced their fieldwork and service delivery. Table 3 presents the challenges faced in using these applications, including technical, operational, and contextual barriers. Table 4 outlines the practical solutions suggested by CHWs to overcome these challenges, such as improving efficiency, reducing workload, and enhancing usability of the applications.

Table 2. Supportive elements for CHW in mobile health usage (N=18)

Themes	Categories	Codes
Facilitating factors	Technology-enabled service delivery	• Easy retrieval of patient records through registration or phone number (16) • Able to monitor ANC mothers and chronic conditions (16) • Timely diagnosis and referral to prevent complications (16) • Beneficiary follow-up with due reminders (16) • Tracking follow-up records of migrant patients (15) • App-based colour indicator to flag notified and high-risk cases (8) • Verifies eligibility for enrolment in government health schemes (8) • Immediate notification to the medical officer, as the app is interlinked with both stakeholders (8)
	Operational features	• Easy data entry • Apps are designed in the local language, Tamil • Editable data errors • Lightweight, easy to carry for home visits • User-friendly single interface for screening multiple conditions (NCD, Leprosy, TB, Cancer) • Government training to use mobile health applications
	Patient-centred health outcomes	• Increased health care access to geographically remote beneficiaries (18) • Home-based medicine distribution with concurrent data entry (18) • Instant communication of health information through direct calls & messages (14) • Easy communication with health care personnel for resolving health concerns (14) • Nutrition kit distribution during home visits of TB, leprosy, and cancer patients (8)

Table 2 Key themes identified in the interviews are summarized which Represents the facilitating factors for CHW in mobile health platforms.

Table 3. Challenges faced by HCW in mobile health usage *(N=18)*

Themes	Categories	Codes
Challenges	Resource constraints	• Dual data entry in both digital platforms and registers (13) • Increased workload to Mid-level health provider (MLHP) and women health volunteer (WHV) in field settings (10) • Inadequate manpower among MLHP / WHV (7) • Limited time for other community-centered activities and personal work. (9) • Inadequate remuneration for women health volunteers (8)
	Digital literacy	• Unfamiliarity and lack of knowledge with latest version of apps (6) • Reliance on virtual training (6) • Deficient technical skills (5)
	Technical setbacks	• Poor network connectivity in field areas (13) • Difficulty in obtaining OTP from the beneficiary for login authentication • Takes a long time to complete data entry • Reduced patient cooperation due to increased data entry time. (10)
	Digital health effects	• Eye strain from prolonged screen exposure (15) • Musculoskeletal discomfort, including neck and back pain (10)
	Financial issues	• Inability to afford smartphones (10) • Self-spending for phone Recharge (13) • Limited storage capacity on personal mobile (13)
	Personal related	• Family misunderstandings arising from frequent phone usage (8) • Lack of privacy and scam calls in personal phone numbers (5)

Table 3 in the interview Participants frequently mentioned about the challenges faced by the health care workers on using mobile application for health care.

Table 4 represents about the Solutions given by the CHW for using mobile application for health purpose is identified in the interviews (Figure 1).

Table 4. Solutions given by the CHW (N=18)

Themes	Categories	Codes
Solutions	Digital support	• Ensure stable WIFI (5G) connectivity at every centre (18) • Offer monetary support for mobile data recharges to health care workers (18) • Supply mobile phone or Laptop to health care workers as per the needs (13) *"We are paid less, so most of the time we recharge with our own money for centre work. If recharge benefits are provided, it would be very helpful for us."* (Women health volunteer)
	Capacity building	• Conduct periodic onsite training for the updated app version. (15) • Assign one data entry operator with technical skills at each centre (10) • Recruit additional health care workers (10) • Establish clear protocols for division of work among health care workers (10) *"I don't know about updated version in the app, we need manual training for that periodically, it will be useful for us"* (Mid-level health provider)
	Technology enhancement	• Enable app login without the necessity of OTP (16) • Feasibility to use the app at offline mode (6) • AI based chatbot services to handle user queries (2) *" It will be useful for us if government provides us the wifi connection or 5G network in each PHC network, so that we able to do our work easily "*(Village health nurse)

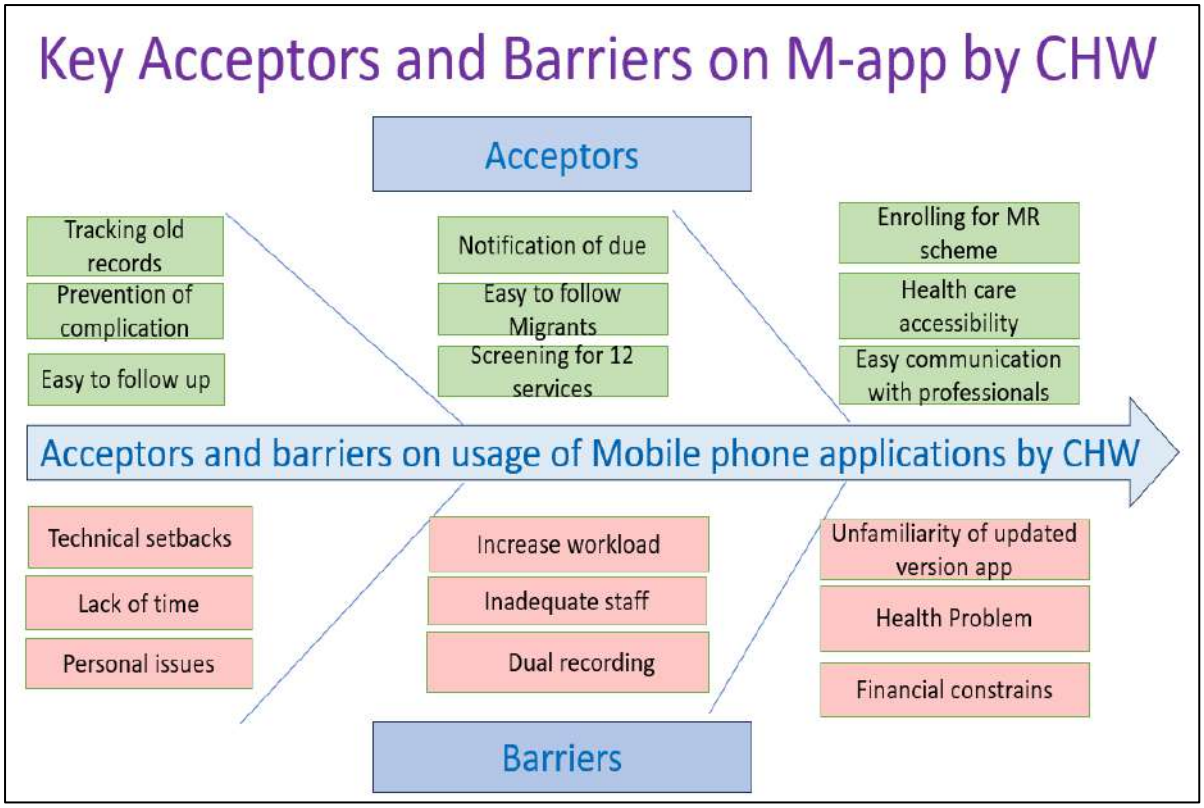


Figure 1. Key Acceptors and Barrieres on M-app by CHW

Facilitating Factors

Verbatim
" One of my patients lost his previous documents. I have recovered the documents by entering his registered number in the application. Another patient, he doesn't have a registration number for him, and we traced the records with his phone number." (Village health nurse 2) *"I have identified an ANC mother with gestational diabetes just because I uploaded her blood sugar levels at each visit and monitored her regularly. Later, she was referred to GH for further management."* (Village health nurse 3) "*We check the eligibility person for the Muthulakshmi Reddy scheme, and we help in due remembrance also."* (Village health nurse 4,5) *"In a particular locality, if there are more fever cases, we screen all the suspected patients, and we will enter into the app to inform the medical officer and Health Inspector of the current area."* (Mid-level health provider 3)
"Earlier, we were writing in big registers in the field; it took more time. In this app, just a few taps and it is done, very easy for us." (Village health nurse 5)

As I struggle to read in English, this app provides in Tamil language, which makes me to understand easily (Mid-level health provider 2) *"Sometimes by mistake, I enter the wrong age or name. In this app I can correct it immediately, but in the register if we make a mistake, we have to use whitener or strike it out, which looks messy."* (Women health volunteer 3) *"Earlier we used to carry many notes and forms* Training to use mobile health application *visits. Now we are just taking mobile and it feels light and easy."*(Women health volunteer 2) *"Through the app I can contact patients directly and also send messages for arranging programs* (Women health volunteer 4)
"*By using the e-Sanjeevani app through video consultation, bedridden persons and in inaccessible areas are getting consulted and treated. "*(Village health nurse 6) *"For every month, during the house visit, I will provide regular tablets to the beneficiary."* (Mid-level health provider 4)

Challenges

Verbatim
"For data entry it takes nearly one hour for each family because of network problem I can't able to enter the data and it compulsory for us to take ten families per day " (Village health nurse 2) *"I used to do data entry while maintaining the register, which made it difficult to manage both tasks at the same time."* (Village health nurse 4)
"I don't know about the mobile app and am not familiar how to operate android mobile phones" (Anganwadi worker 2) *"Our training is done through online sessions. But it is not very effective due to connectivity issues. Offline training would be more useful for learning about the app. "*(Village health nurse 3)
"We have to put 10 house entries per day. Due to network issues, it takes a considerable amount of time to complete one entry for a single patient. So, the other patient starts to scold & complain to us for consuming so much time for one patient. "(Women health volunteer 3) *"I used to enter my daily registration data at mid night because at night, network issues are limited."*(Mid-level health provider 4)

"I have pain in my eyes and blurred vision because of using the mobile app for data entry for a long period. "(Anganwadi worker 2, Mid-level health provider 3)
"I don't have proper devices to handle these apps, and I don't have proper capital to recharge my mobile phone." (Anganwadi worker 1)
"My mother-in-law and my husband used to scold and misunderstand me for using mobile phones late at night. Due to network issues in the morning, I used to enter data at night because at night, there will be limited network problem." (Village health nurse 5)

Discussion

The present qualitative study explored the factors influencing acceptance and barriers to the use of mobile health (mHealth) applications among community healthcare workers in rural Tamil Nadu. The findings indicate that although mHealth tools were generally viewed as useful for enhancing service delivery and continuity of care, multiple operational, technical, and system-level challenges limited their optimal use in routine practice.

In our study, we found that mobile health applications were perceived as user-friendly and interoperable, which enhanced patient tracking, risk identification, and improved health accessibility and health communication, especially in maternal and child health services and in chronic disease conditions. Similar findings were reported in Western states by Gwalani et al. and Maita et al in rural settings, supporting the role of mobile health technologies in strengthening health care delivery [16,17]. Thus, mobile health technologies can contribute to improved patient health outcomes in addition to supporting health management information systems [8]. Expanding mobile health interventions at the patient level can influence patient engagement, promote continuity of care, and lead to sustainable improvement in health outcomes.

Further, the role of training and digital competence emerged as a key facilitator in the adoption of mHealth applications. Participants who had received formal training or had prior experience with digital technologies expressed greater confidence in navigating mobile platforms and addressing minor technical issues. This observation is consistent with evidence from studies conducted in other low- and middle-income countries, where structured training and ongoing technical support were shown to enhance the uptake and sustained use of mHealth interventions [18].

The present study identified increased workload due to parallel paper-based and digital documentation, increased time constraints, and reduced operational efficiency as the prominent challenges in mobile health application use. Comparable findings have been documented in previous studies conducted by Gwalani et al. and Gopalan et al., where duplicate data entry, administrative burden, workforce shortages, and multiple programmatic responsibilities hinder the uptake of mobile digital technologies [16,19]. Findings from these studies suggest that linking mobile applications with existing reporting systems and gradually reducing paper-

based records can help decrease workload and improve efficiency among healthcare workers.

Despite participants being literate, inadequate digital literacy remained a barrier to effective mobile health application use, consistent with findings of Gwalani et al. [16]. A few participants also preferred manual recording because of greater familiarity. Hence, key informants emphasised the need for regular on-site hands-on training of the latest versions and technical support from data entry operators and free chatbot services to improve digital competency and application use.

Technical challenges identified in the present study were poor network connectivity and limited device storage, which hindered the effective mHealth implementation. Similar findings were reported by Prinja et al. in rural and remote areas [21]. Such infrastructural limitations have been widely recognized as critical factors restricting the scalability and long-term sustainability of mHealth interventions in resource-constrained settings across India, despite their potential to improve service delivery [22]. Key informants suggested that offline data entry, strengthening digital infrastructure, minimizing duplicate documentation, and ensuring regular capacity-building of community healthcare workers are essential to improve acceptance and effective use of mHealth applications. In addition, policies that simplify reporting procedures, improve coordination across health programmes, provide adequate training, and strengthen supportive supervision can help ensure sustainability of mHealth initiatives among community healthcare workers in rural areas [23].

Strengths and Limitations

This qualitative study offers a deep understanding of the perceptions, attitudes, and experiences of community healthcare workers regarding mobile health applications. By focusing on rural Tamil Nadu, it captures the socio-cultural, infrastructural, and systemic factors influencing technology adoption, providing valuable insights for policymakers to design locally relevant interventions.

This study findings may have limited generalizability, as they are specific to the rural setting and may not apply to urban areas or other healthcare worker populations, and also, we interviewed different cadre of community health worker across two PHCs which adds diversity and depth to the findings.

Conclusion

Mobile health applications were widely embraced by CHWs and thought to improve healthcare delivery. The integration of mobile health applications into the healthcare system holds the possibility of improving patient management and boosting primary care services. However, solving implementation problems and ensuring that digital innovations are linked with the needs and skills of front-line health workers is critical for their effective use. A user-centered, context-specific approach to designing and implementing mobile health programs is critical for improving health outcomes in rural communities and supporting health information systems.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. Mehl G, Labrique A. Prioritizing integrated mHealth strategies for universal health coverage. Science. 2014;345(6202):1284–1287.
2. Källander K, Tibenderana JK, Akpogheneta OJ, Strachan DL, Hill Z, ten Asbroek AHA, et al. Mobile health (mHealth) approaches and lessons for increased performance and retention of community health workers in low- and middle-income countries: a review. J Med Internet Res. 15:e17.2013.
3. Wallis L, Blessing P, Dalwai M, Shin S, Do. Integrating mHealth at point of care in low- and middle-income settings: the system perspective. Glob Health Action. 2017 Jun;10(sup3):1327686.
4. World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening. 2019; Available from: https://www.who.int/publications/i/item/9789241550505/
5. Mishra US, Yadav S, Joe W. The Ayushman Bharat digital mission of India: an assessment. Health Systems & Reform. 2024 Dec 17;10(2):2392290.
6. Balakrishnan R, Gopichandran V, Chaturvedi S, Chatterjee R, Mahapatra T, Chaudhuri I. Continuum of Care Services for Maternal and Child Health using mobile technology - a health system strengthening strategy in low and middle income countries. BMC Med Inform Decis Mak. 2016 Jul 7;16:84.
7. Venkataramanan R, Subramanian SV, Alajlani M, Arvanitis TN. Effect of mobile health interventions in increasing utilization of Maternal and Child Health care services in developing countries: A scoping review. Digital Health. 2022 Dec;8:20552076221143236.
8. Alkhuzaimi F, Rainey D, Wilson CB, Bloomfield J. The impact of mobile health interventions on service users' health outcomes and the role of health professions: a systematic review of systematic reviews-protocol. Syst Rev. 2024 Jul 27;13(1):199.
9. Mehta PK, Rao AR, Upadhyay N, Mustafa S, Digra V, Wariar AS et al. Use of Mobile Application for Improving Drug Compliance and Clinical Outcomes: A Randomized Controlled Trial. Int J Telemed Appl. 2026 Feb 27;2026:9857793.
10. Gopalakrishnan L, Buback L, Fernald L, Walker D, Diamond-Smith N; in addition to The CAS Evaluation Consortium. Using mHealth to improve health care delivery in India: A qualitative examination of the perspectives of community health workers and beneficiaries. PLoS One. 2020 Jan 15;15(1):e0227451.
11. Agarwal S, Perry HB, Long LA, Labrique AB. Evidence on feasibility and effective use of mHealth strategies by frontline health workers in developing countries: systematic review. Tropical medicine & international health. 2015 Aug;20(8):1003–14.

12. Renukappa S, Mudiyi P, Suresh S, Abdalla W, Subbarao C. Evaluation of challenges for adoption of smart healthcare strategies. Smart health. 2022 Dec 1;26:100330.
13. Creswell JW. Research design: qualitative, quantitative, and mixed methods approaches. 4th ed. Thousand Oaks (CA): SAGE Publications; 2014.
14. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349–357.
15. Lincoln YS, Guba EG. Naturalistic inquiry. Beverly Hills, CA: Sage Publications; 1985.
16. Gwalani R, Chaudhary S, Yadav A. Primary Healthcare Workers' Perspective on Using the Digital Management Information System for Non-communicable Diseases: A Qualitative Study from Western State in India. NMO Journal. 2026 Jan 1;20(1):6–10.
17. Maita KC, Maniaci MJ, Haider CR, Avila FR, Torres-Guzman RA, Borna S et al. The Impact of Digital Health Solutions on Bridging the Health Care Gap in Rural Areas: A Scoping Review. Perm J. 2024;28:130–143.
18. Agarwal S, Perry HB, Long LA, Labrique AB. Evidence on feasibility and effective use of mHealth strategies by frontline health workers in developing countries: systematic review. Trop Med Int Health. 2015 Aug;20(8):1003–14.
19. Gopalan SS, Mohanty S, Das A. Assessing community health workers' performance motivation: a mixed-methods approach on India's Accredited Social Health Activists (ASHA) programme. BMJ Open. 2012;2:e001557.
20. Charanthimath U, Katageri G, Kinshella MW, Mallapur A, Goudar S, Ramadurg U et al. Community Health Worker Evaluation of Implementing an mHealth Application to Support Maternal Health Care in Rural India. Front Glob Womens Health. 2021 Sep 1;2:645–690.
21. Prinja S, Nimesh R, Gupta A, Bahuguna P, Thakur JS, Gupta M et al. Impact assessment and cost-effectiveness of m-health application used by community health workers for maternal, newborn and child health care services in rural Uttar Pradesh, India: a study protocol. Glob Health Action. 2016;9:31473.
22. Shah P, Madhiwala N, Shah S, Desai G, Dave K, Dholakia N et al. High uptake of an innovative mobile phone application among community health workers in rural India: An implementation study. Natl Med J India. 2019;32(5):262–269.
23. Koivunen M, Saranto K. Nursing professionals' experiences of the facilitators and barriers to the use of telehealth applications: a systematic review of qualitative studies. Scand J Caring Sci. 2018 Mar;32(1):24–44.

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ORIGINAL ARTICLE

Correlation Between Vitamin D Levels and Schizophrenia and Its Symptom Profile: A Hospital Based Case-Control Study

Sudha P[1,*] and Arivalagan C[1]
[1]*Assistant Professor, Department of Psychiatry, Government Dharmapuri Medical College, Dharmapuri, Tamilnadu*

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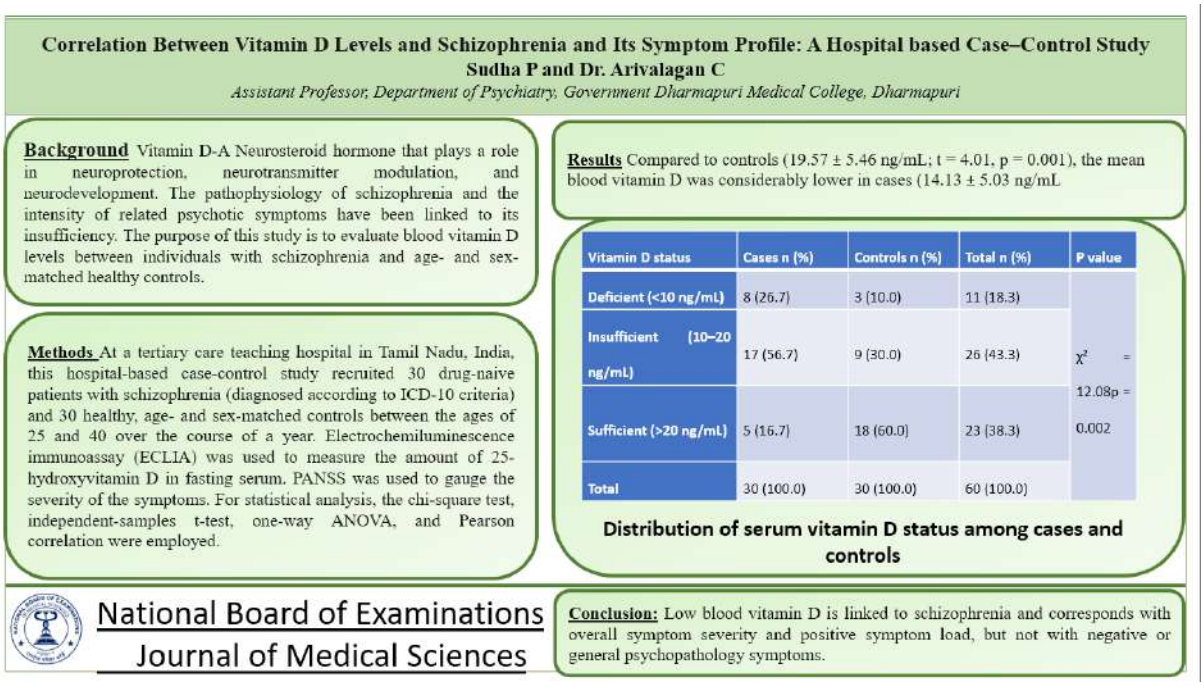
Abstract

Background: Vitamin D is a Neurosteroid hormone that plays a role in neuroprotection, neurotransmitter modulation, and neurodevelopment. The pathophysiology of schizophrenia and the intensity of related psychotic symptoms have been linked to its insufficiency. **Objectives:** The purpose of this study is to evaluate blood vitamin D levels between individuals with schizophrenia and age- and sex-matched healthy controls. Additionally, the Positive and Negative Syndrome Scale (PANSS) will be used to correlate vitamin D status with symptom profile. **Materials and Methods:** At a tertiary care teaching hospital in Tamil Nadu, India, this hospital based case-control study recruited 30 drug-naive patients with schizophrenia (diagnosed according to ICD-10 criteria) and 30 healthy, age- and sex-matched controls between the ages of 25 and 40 over the course of a year. Electrochemiluminescence immunoassay (ECLIA) was used to measure the amount of 25-hydroxyvitamin D in fasting serum. PANSS was used to gauge the severity of the symptoms. For statistical analysis, the chi-square test, independent-samples t-test, one-way ANOVA, and Pearson correlation were employed. **Results:** Compared to controls (19.57 ± 5.46 ng/mL; $t = 4.01$, $p = 0.001$), the mean blood vitamin D was considerably lower in cases (14.13 ± 5.03 ng/mL). Compared to 40.0% of controls, 83.3% of patients had inadequate or deficient vitamin D status ($\chi^2 = 12.08$, $p = 0.002$). Positive PANSS scores ($r = -0.465$, $p = 0.010$) and total PANSS scores ($r = -0.506$, $p = 0.001$) were significantly and negatively linked with vitamin D levels, but not negative PANSS ($r = -0.329$, $p = 0.076$) or general psychopathology scores ($r = -0.006$, $p = 0.976$). **Conclusion:** In this cohort, low blood vitamin D is linked to schizophrenia and corresponds with overall symptom severity and positive symptom load, but not with negative or general psychopathology symptoms. Patients with schizophrenia may benefit from routine metabolic evaluations that include vitamin D assessments, and treating deficiencies may help manage symptoms.

Keywords: Vitamin D, Schizophrenia, PANSS, Vitamin D deficiency, Case-control study, Psychosis

*Corresponding Author: Sudha P
Email: sudharithwik@gmail.com

Graphical Abstract



Introduction

With a lifetime prevalence of roughly 1% worldwide and roughly 3 per 1000 people in India, schizophrenia is a severe, chronic psychiatric condition marked by disordered thought, perception, emotion, and conduct. It continues to be one of the major causes of disability worldwide [1]. Its aetiology is complex, with environmental exposures, neurodevelopmental insults, and genetic susceptibility all influencing the onset and progression of the illness.

Unlike other vitamins, vitamin D acts as a secosteroid hormone rather than a straightforward dietary supplement. Its receptors are widely expressed in the human brain in areas linked to schizophrenia, including the hippocampus, hypothalamus, substantia nigra, and prefrontal cortex [2]. It affects neurotrophic factor expression, dopaminergic neurotransmission, neurodevelopment, and neuroprotection from excitotoxic and oxidative damage. A number of neurobiological and behavioural traits associated with schizophrenia, such as altered dopaminergic ontogeny and poor social and cognitive behaviour, are replicated in animal models of embryonic vitamin D insufficiency [3].

Systematic reviews and meta-analyses have confirmed a significantly higher prevalence of vitamin D deficiency among patients with schizophrenia compared with healthy controls [4,5], and population-based studies have connected low neonatal vitamin D concentrations to an increased risk of schizophrenia in later life [3]. Even though the exact causal mechanism is still unknown, a recent narrative review commemorating two decades of research in this field concluded that the theory relating early-life vitamin D deficiency to schizophrenia risk remains biologically reasonable and continues to justify exploration [1]. Vitamin D supplementation has also been investigated

in early interventional research as a complement to conventional antipsychotic therapy [6].

Beyond illness risk, a number of research have looked at the relationship between vitamin D status and the profile and intensity of psychotic symptoms, which are often assessed using the Positive and Negative Syndrome Scale (PANSS) [7,8]. The results of various studies have been mixed, with some reporting significant negative correlations between vitamin D and positive, negative, or total PANSS scores and others finding no such correlation. This discrepancy may be due to variations in the length of the illness, exposure to antipsychotics, ethnicity, latitude, and assay methodology [5].

Aims and Objectives

The current study was conducted with the primary goal of comparing serum vitamin D levels between patients with schizophrenia and healthy controls, and the secondary goal of evaluating the correlation between vitamin D status and PANSS-rated symptom profile, due to the high prevalence of vitamin D deficiency in the general Indian population despite abundant ambient sunlight and the lack of Indian data specifically correlating vitamin D status with symptom profile in drug-naive schizophrenia.

Materials and Methods

Study design and setting

This was a hospital based case–control study conducted in the Department of Psychiatry of a government tertiary care teaching hospital in Salem, Tamil Nadu, India, over a one-year period (2017–2018), following approval by the Institutional Ethics and Research Committee.

Study population

Inclusion criteria

Individuals diagnosed with schizophrenia as per ICD-10 criteria, aged 25–40 years of either sex, willing to participate and to undergo blood investigation.

Exclusion criteria

Age <25 or >40 years; alcohol or substance dependence; organic brain disorder; metabolic disease affecting serum vitamin D concentration; prior vitamin D supplementation; inadequate sunlight exposure; and prior antipsychotic exposure (only drug-naive cases were enrolled).

Sample size and Sampling

A formal priori sample size calculation was not performed. The study included all eligible consecutive drug-naive patients with schizophrenia who fulfilled the inclusion and exclusion criteria and were recruited during the one-year study period, along with an equal number of age- and sex-matched healthy controls by convenience sampling. Thus, the final sample comprised 30 cases and 30 controls.

Tools

A semi-structured sociodemographic questionnaire (age, sex, education, marital status, height, weight, occupation, smoking status, skin colour, and daily sunlight exposure), an informed consent form, and the Positive and Negative Syndrome Scale (PANSS) were used.

PANSS assessment

The PANSS is a validated 30-item, 7-point rating instrument administered via a structured clinical interview of approximately 45 minutes, comprising a

positive scale (7 items), a negative scale (7 items), and a general psychopathology scale (16 items) [7]. Its reliability and validity in detecting change in schizophrenia symptom domains, including negative symptoms, have been established [8].

Blood collection and vitamin D estimation

In order to separate serum, 3–4 mL of fasting peripheral venous blood was obtained with informed consent, allowed to clot in tubes containing gel, then centrifuged at 4000 rpm for 10 minutes; samples that were hemolyzed or icteric were not included. The electrochemiluminescence immunoassay (ECLIA) method, which was selected for its analytical sensitivity, specificity, low reagent use, and quick turnaround, was used to measure serum 25-hydroxyvitamin D. In accordance with widely accepted clinical cut-offs for the Indian population, vitamin D level was classified as sufficient (>20 ng/mL), insufficient (10–20 ng/mL), or deficient (<10 ng/mL).

Statistical analysis

The chi-square test was used to compare categorical variables. The independent-samples t-test was used to compare the mean serum vitamin D levels between patients and controls. PANSS subscale scores were compared across vitamin D categories using one-way ANOVA, and the relationship between serum vitamin D level and PANSS domain scores was evaluated using Pearson's correlation coefficient. Statistical significance was defined as a p-value of less than 0.05.

Results

A total of 60 subjects were enrolled — 30 patients with schizophrenia (cases) and 30 age- and sex-matched healthy controls.

Sociodemographic profile

The majority of participants were aged between 25 and 35 years, with identical sex distribution in both groups (66.7% males and 33.3% females). Compared with controls, patients with schizophrenia more frequently had school-level education, were unemployed or engaged in manual occupations, and predominantly belonged to the lower-middle socioeconomic class. A family history of psychiatric illness was reported in 40.0% of cases, whereas none of the controls had a positive family history (Table 1).

Table 1. Sociodemographic characteristics of cases and controls (N = 60)

Variable	Category	Cases n (%)	Controls n (%)	Total n (%)
Age (years)	25–30	13 (43.3)	11 (36.7)	24 (40.0)
	31–35	9 (30.0)	11 (36.7)	20 (33.3)
	36–40	8 (26.7)	8 (26.7)	16 (26.7)
Sex	Male	20 (66.7)	20 (66.7)	40 (66.7)
	Female	10 (33.3)	10 (33.3)	20 (33.3)
Education	Illiterate	3 (10.0)	3 (10.0)	6 (10.0)
	School level	23 (76.7)	16 (53.3)	39 (65.0)
	Undergraduate	4 (13.3)	11 (36.7)	15 (25.0)
Occupation	Unemployed	9 (30.0)	6 (20.0)	15 (25.0)
	Manual labourer	11 (36.7)	7 (23.3)	18 (30.0)
	Other (business/skilled /mason/painter/supervisor/tailor)	10 (33.3)	17 (56.7)	27 (45.0)
Marital status	Married	18 (60.0)	20 (66.7)	38 (63.3)
	Unmarried	9 (30.0)	8 (26.7)	17 (28.3)
	Separated	3 (10.0)	2 (6.7)	5 (8.3)
Socioeconomic status (Modified Kuppuswamy)	Lower middle	24 (80.0)	19 (63.3)	43 (71.7)
	Upper lower	4 (13.3)	5 (16.7)	9 (15.0)
	Upper middle	2 (6.7)	6 (20.0)	8 (13.3)
Family history of psychiatric illness	Present	12 (40.0)	0 (0.0)	12 (20.0)
	Absent	18 (60.0)	30 (100.0)	48 (80.0)

Note: Controls were recruited to have no family history of psychiatric illness

Serum vitamin D status

Vitamin D deficiency or insufficiency was observed in 83.3% (25/30) of patients with schizophrenia compared with 40.0% (12/30) of healthy controls. Conversely, sufficient vitamin D levels were present in only 16.7% of cases compared with 60.0% of controls. The distribution of vitamin D status differed significantly between the two groups (χ^2 = 12.08, p = 0.002) (Table 2).

Table 2. Distribution of serum vitamin D status among cases and controls

Vitamin D status	**Cases n (%)**	**Controls n (%)**	**Total n (%)**	P value
Deficient (<10 ng/mL)	8 (26.7)	3 (10.0)	11 (18.3)	χ^2 = 12.08 **p = 0.002***
Insufficient (10–20 ng/mL)	17 (56.7)	9 (30.0)	26 (43.3)	
Sufficient (>20 ng/mL)	5 (16.7)	18 (60.0)	23 (38.3)	
Total	**30 (100.0)**	**30 (100.0)**	**60 (100.0)**	

**Chi-square test; p < 0.05 -statistically significant.*

Mean serum vitamin D concentration was significantly lower among patients with schizophrenia than among controls (14.13 ± 5.03 vs. 19.57 ± 5.46 ng/mL; t = 4.01, p = 0.001) (Table 3).

Table 3. Mean serum vitamin D levels in cases and controls

Group	**N**	**Mean ± SD (ng/mL)**	**t**	**p**
Cases	30	14.13 ± 5.03	4.01	0.001**
Controls	30	19.57 ± 5.46		

**Independent t test; p < 0.05 -statistically significant.*

Vitamin D and PANSS symptom domains

Among patients with schizophrenia, positive symptom severity differed significantly across vitamin D categories (F = 5.262, p = 0.012). Participants with sufficient vitamin D levels demonstrated lower positive PANSS scores (15.60 ± 4.34) than those with deficient (22.63 ± 3.38) or insufficient (22.00 ± 4.44) vitamin D status. In contrast, negative symptom scores (F = 0.731, p = 0.491) and general psychopathology scores (F = 0.560, p = 0.578) did not vary significantly according to vitamin D status (Table 4).

Table 4. Serum vitamin D category and PANSS subscale scores in cases (N = 30)

Vitamin D category	**N**	**Positive PANSS Mean ± SD**	**Negative PANSS Mean ± SD**	**General PANSS Mean ± SD**
Deficient	8	22.63 ± 3.38	19.38 ± 7.44	32.13 ± 3.98
Insufficient	17	22.00 ± 4.44	17.12 ± 5.17	30.00 ± 4.60
Sufficient	5	15.60 ± 4.34	15.80 ± 2.05	31.00 ± 6.21
Total	**30**	**21.10 ± 4.75**	**17.50 ± 5.66***	**30.73 ± 4.65**
ANOVA F		5.262	0.731	0.56
p		0.012*	0.491	0.578

*One-way ANOVA across vitamin D categories; *p < 0.05.*

Pearson correlation analysis demonstrated a significant inverse correlation between serum vitamin D concentration and positive PANSS scores ($r = -0.465$, $p = 0.010$). No statistically significant correlations were observed between vitamin D levels and negative PANSS scores ($r = -0.329$, $p = 0.076$) or general psychopathology scores ($r = -0.006$, $p = 0.976$) (Table 6).

Table 6. Pearson correlation between serum vitamin D level and PANSS domain scores

PANSS domain	**Pearson r**	**p**	**N**
Positive PANSS	−0.465	0.010*	30
Negative PANSS	−0.329	0.076	30
General psychopathology PANSS	−0.006	0.976	30

**p < 0.05-Statistically significant*

Discussion

In this cross-sectional case-control investigation, vitamin D status was inversely linked with both positive and total PANSS symptom scores, and drug-naive patients with schizophrenia had significantly lower serum vitamin D levels than age- and sex-matched healthy controls. These results are in line with a large body of research that connects schizophrenia with vitamin D deficiency.

Schizophrenia and vitamin D deficiency

The Study by Patel and Minajagi's, indicated a significant prevalence of vitamin D deficiency (49%) and insufficiency (42%) among psychiatric inpatients, is consistent with the finding of

lower mean blood vitamin D in cases compared to controls [9]. Our findings are also in line with the more recent meta-analysis by Zhu et al., which verified a significantly higher prevalence of vitamin D deficiency in patients with schizophrenia across observational studies published through 2020 [5], and the meta-analysis by Valipour et al., which found a strong correlation between vitamin D deficiency and schizophrenia [4]. Although the relative proportions of deficient versus insufficient status vary with cut-off values, latitude, and sun-exposure patterns across populations, in our cohort, 56.7% of cases fell into the insufficient category and 26.7% into the deficient category, together accounting for 83.3% of cases. This distribution is generally consistent with the high combined deficiency/insufficiency rates reported across recent case-control studies [9,10].

PANSS symptom domains and vitamin D

Yüksel et al. found a similar link between total vitamin D level and psychotic psychopathology [11], which is consistent with our study's strong negative correlation between vitamin D and positive PANSS score. Although a more recent Iranian case-control study confirmed lower vitamin D levels in schizophrenia overall, it also found no significant correlation between vitamin D and PANSS domain scores. Instead, it found a correlation between vitamin D and extrapyramidal side-effect severity [12]. This is in contrast to the report by Bulut et al., which found lower vitamin D associated with greater negative symptom severity [10]. Similar to Haddad et al. [13], we did not find a significant link between vitamin D and the general psychopathology score; however, Prasanty et al. reported a substantial negative correlation between vitamin D and the general psychopathology PANSS score [14]. The necessity for bigger, standardised multi-center research is highlighted by these discrepancies in the literature, which most likely reflect variations in sample size, illness chronicity, antipsychotic exposure, and rating instrument utilised [15,16].

Methodological factors

Similar to the enzyme-linked immunosorbent test used in similar studies classifying schizophrenia patients by illness severity, the ECLIA method for vitamin D quantification in this investigation offers high analytical sensitivity and specificity [17].

Correlates of Socio demographics

Our study found that over 40% of cases had a family history of mental illness, which is consistent with the acknowledged role that parental socioeconomic status and family history play in the risk of schizophrenia as reported in large population-based studies [18].

Recent evidence

The vitamin D-schizophrenia theory is still supported and improved by more current research. Both low and high newborn vitamin D concentrations were linked to an elevated risk of schizophrenia, according to large Danish population-based case-control research [3]. This suggests a U-shaped rather than a strictly linear association. The importance of vitamin D status in acute presentations of psychosis was reinforced by a cross-sectional study from a tertiary center in Iran that assessed vitamin D, parathyroid hormone, and C-reactive protein in acute psychotic episodes [19]. In terms of intervention, a double-blind randomised controlled trial

discovered that supplementing with both probiotics and vitamin D enhanced cognitive performance; nevertheless, the supplementation-induced decrease in PANSS score was not statistically significant [20]. Low neonatal vitamin D is positively correlated with later schizophrenia risk, and adult vitamin D deficiency is correlated with reduced grey matter volume, poorer bone health, and higher prevalence of metabolic syndrome in this population, according to a 2025 systematic review that synthesised evidence across maternal, neonatal, and adult life stages [16]. These findings further support the inclusion of vitamin D monitoring in routine psychiatric care.

Strengths and Limitations

Strengths

A significant confounding factor observed in many previous investigations was eliminated because all individuals were antipsychotic-naive. Standardised ICD-10 criteria were used to make the diagnosis, the validated PANSS instrument was used to measure the severity of symptoms, other potential causes of vitamin D deficiency were ruled out, and vitamin D was estimated using a particular, sensitive biochemical approach (ECLIA).

Limitations

Because this was a single-center study with a small sample size not formally estimated (n = 30 per group), statistical power and generalisability are limited, especially for subgroup analysis. Seasonal differences in dietary consumption, outdoor physical activity, and vitamin D production were not extensively recorded. Because of the case-control approach, randomisation was not appropriate. Although participants with inadequate sunlight exposure and metabolic disorders affecting vitamin D metabolism were excluded, residual confounding from factors such as body mass index, dietary vitamin D intake, physical activity, smoking status, socioeconomic differences, and variations in actual sunlight exposure could not be completely eliminated, as these variables were not quantitatively adjusted for in the analysis. Therefore, the observed associations should be interpreted with appropriate caution.

Conclusion

Antipsychotic-naive schizophrenia patients had significantly lower serum vitamin D levels than healthy controls, and there was an inverse relationship between vitamin D status and both positive and total PANSS symptom scores, but not negative or overall psychopathology scores. These results lend credence to the idea that schizophrenia and, more especially, positive-symptom load are linked to vitamin D insufficiency. The fact that none of the vitamin D-deficient individuals—cases or controls—showed obvious clinical signs of deficiency highlights the value of biochemical screening as opposed to depending solely on clinical suspicion. From the standpoint of public health, detecting and treating vitamin D deficiency is an easy, safe, and affordable intervention that may be helpful in lowering the morbidity linked to schizophrenia; however, this needs to be confirmed by sufficiently powered randomised controlled trials.

Recommendations for future research

To confirm the association between vitamin D insufficiency and the symptom profile of schizophrenia across a range of populations and latitudes, larger, multi-center investigations are required.

Additionally, interventional research is needed to determine whether vitamin D administration affects the course of symptoms and whether there is a causal association between vitamin D and schizophrenia.

Statements and declarations

Ethics approval

This study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrolment.

Conflict of interest

The authors declare no conflict of interest.

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References

1. Cui X, Gooch H, Petty A, McGrath JJ, Eyles D. Vitamin D and schizophrenia: 20 years on. Mol Psychiatry. 2021;26(7):2708–20.
2. Kesby JP, Cui X, Burne THJ, Eyles DW. Altered dopamine ontogeny in the developmentally vitamin D deficient rat and its relevance to schizophrenia. Front Cell Neurosci. 2013;7:111.
3. Albiñana C, Boelt SG, Cohen AS, Zhu Z, Musliner KL, Vilhjálmsson BJ, et al. Developmental exposure to vitamin D deficiency and subsequent risk of schizophrenia. Schizophr Res. 2022;247:26–32.
4. Valipour G, Saneei P, Esmaillzadeh A. Serum vitamin D levels in relation to schizophrenia: a systematic review and meta-analysis of observational studies. J Clin Endocrinol Metab. 2014;99(10):3863–72.
5. Zhu JL, Luo WW, Cheng X, Li Y, Zhang QZ, Peng WX. Vitamin D deficiency and schizophrenia in adults: a systematic review and meta-analysis of observational studies. Psychiatry Res. 2020;288:112959.
6. Ghaderi A, Banafshe HR, Mirhosseini N, Moradi M, Karimi MA, Mehrzad F, et al. Clinical and metabolic response to vitamin D plus probiotic in schizophrenia patients. BMC Psychiatry. 2019;19(1):77.
7. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res. 1988;23(1):99–110.
8. Edgar CJ, Blaettler T, Bugarski-Kirola D, Le Scouiller S, Garibaldi GM, Marder SR. Reliability, validity and ability to detect change of the PANSS negative symptom factor score in outpatients with schizophrenia on select antipsychotics and with prominent negative or disorganized thought symptoms. Psychiatry Res. 2014;218(1–2):219–24.
9. Patel D, Minajagi M. Prevalence of vitamin D deficiency in adult patients admitted to a psychiatric hospital. BJPsych Bull. 2018;42(3):123–6.
10. Bulut SD, Bulut S, Atalan DG, Berkol T, Gürçay E, Türker T, et al. The relationship between symptom severity and low vitamin D levels in patients with schizophrenia. PLoS One. 2016;11(10):e0165284.
11. Yüksel RN, Altunsoy N, Tikir B, Cingi Külük M, Unal K, Goka S, et al. Correlation between total vitamin

D levels and psychotic psychopathology in patients with schizophrenia: therapeutic implications for add-on vitamin D augmentation. Ther Adv Psychopharmacol. 2014;4(6):268–75.

12. Shahini N, Mousavi Zade Jazayeri SM, Jahanshahi R, Charkazi A. Relationship of serum homocysteine and vitamin D with positive, negative, and extrapyramidal symptoms in schizophrenia: a case–control study in Iran. BMC Psychiatry. 2022;22(1):681.
13. Haddad C, Zoghbi M, Hallit S, Bou Assi T, Hashim M, Nabout R. Vitamin D levels in Lebanese patients with schizophrenia: a case-control study. Ann Nutr Disord Ther. 2017;4(1):1041.
14. Prasanty N, Amin MM, Effendy E, Simbolon MJ. Low vitamin D serum level increases symptom severity in schizophrenic patients measured by Positive and Negative Symptoms Scale (PANSS) in Batak Tribe Sumatera Utara, Medan-Indonesia. Bali Med J. 2018;7(1):249–54.
15. Chiang M, Natarajan R, Fan X. Vitamin D in schizophrenia: a clinical review. Evid Based Ment Health. 2016;19(1):6–9.
16. Mosiołek J, Mosiołek B, Szulc A. Vitamin D as a modifiable risk factor in schizophrenia: a systematic review. Biomolecules. 2025;15(8):1094.
17. Akinlade KS, Olaniyan OA, Lasebikan VO, Rahamon SK. Vitamin D levels in different severity groups of schizophrenia. Front Psychiatry. 2017;8:105.
18. Agerbo E, Sullivan PF, Vilhjálmsson BJ, Pedersen CB, Mors O, Børglum AD, et al. Polygenic risk score, parental socioeconomic status, family history of psychiatric disorders, and the risk for schizophrenia: a Danish population-based study and meta-analysis. JAMA Psychiatry. 2015;72(7):635–41.
19. Arya S, Kamyab A, Sanatkar SA, Pourmehdiardebili M, Ebrahimi A, Kamyab P, et al. Evaluating the association of vitamin D3, parathyroid hormone, and C-reactive protein serum levels in patients with an acute psychotic episode: a cross-sectional study in a tertiary centre in Iran. BMC Psychiatry. 2023;23(1):724.
20. Mohammadi A, Sadighi G, Nazeri Astaneh A, Tajabadi-Ebrahimi M, Dejam T. Co-administration of probiotic and vitamin D significantly improves cognitive function in schizophrenic patients: a double-blinded randomized controlled trial. Neuropsychopharmacol Rep. 2024;44(2):556–65.

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REVIEW ARTICLE

Diethylene Glycol Contamination in Pediatric Cough Syrups: Clinical and Public Health Perspectives

Divyashanthi CM,[1,*] Sathiya Vinotha A T[2] and Dineshkumar N[3]
[1]*Associate Professor, Department of Pharmacology, JIPMER, Karaikal, Puducherry*
[2]*Professor, Department of Pharmacology, KMCH Institute of Health Sciences & Research, Coimbatore, Tamilnadu, India*
[3]*Associate Professor, Department of Paediatrics, JIPMER, Karaikal, Puducherry*

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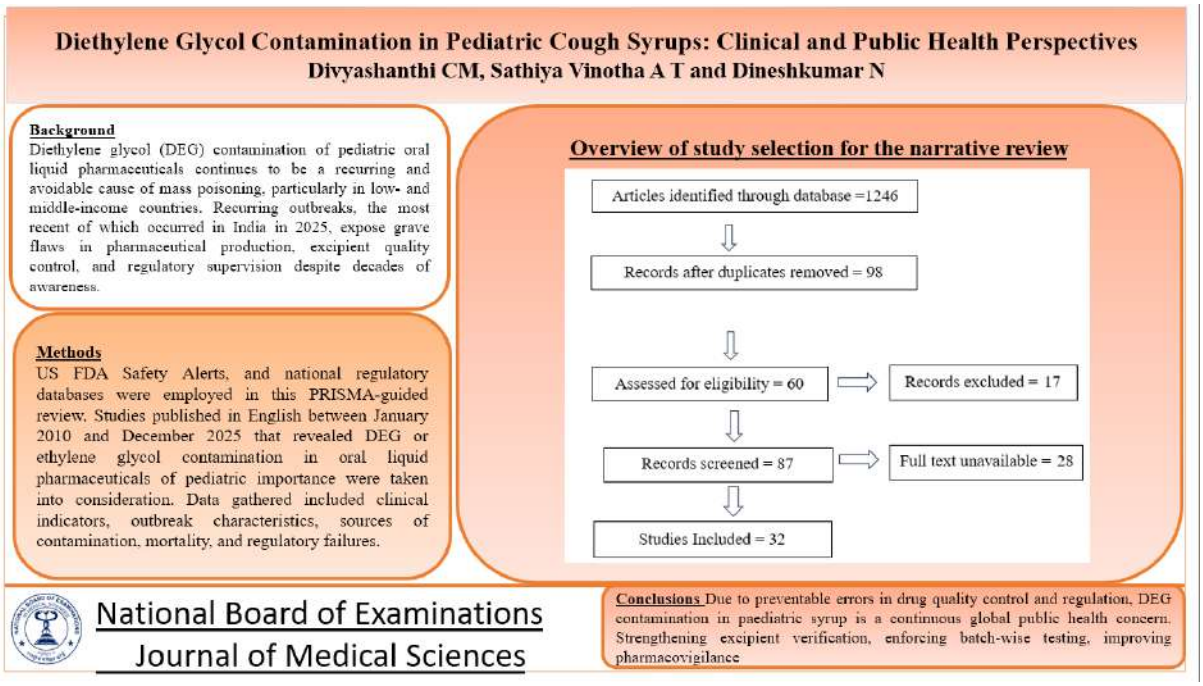
Abstract

Background: Diethylene glycol (DEG) contamination of pediatric oral liquid pharmaceuticals continues to be a recurring and avoidable cause of mass poisoning, particularly in low- and middle-income countries. Recurring outbreaks, the most recent of which occurred in India in 2025, expose grave flaws in pharmaceutical production, excipient quality control, and regulatory supervision despite decades of awareness. Due to their physiological vulnerability and the widespread usage of cough syrups, children are disproportionately affected. **Methods:** PubMed/MEDLINE, Embase, Scopus, Google Scholar, WHO Medical Product Alerts, US FDA Safety Alerts, and national regulatory databases were employed in this PRISMA-guided review. Studies published in English between January 2010 and December 2025 that revealed DEG or ethylene glycol contamination in oral liquid pharmaceuticals of pediatric importance were taken into consideration. Data gathered included clinical indicators, outbreak characteristics, sources of contamination, mortality, and regulatory failures. The dependability of the source was assessed based on the level of documentation and laboratory confirmation. **Results:** Thirty -two of the 1,246 records found satisfied the requirements for inclusion. There were four significant epidemics that were regularly reredoses 300 paediatric deaths occurred in The Gambia (2022), Uzbekistan (2022), Indonesia (2022), and India (2025). Contamination was mostly caused by subpar or adulterated excipients such propylene glycol and glycerine. The clinical presentation was similar, proceeding from gastrointestinal symptoms to metabolic acidosis, severe renal injury, and multi-organ failure, with fatality rates ranging from 30% to 70%. Systemic issues included inadequate excipient testing, falsified certificates of analysis, insufficient regulatory enforcement, poor supply-chain traceability, and delayed recall procedures. **Conclusion:** Due to preventable errors in drug quality control and regulation, DEG contamination in paediatric syrup is a continuous global public health concern. Strengthening excipient verification, enforcing batch-wise testing, improving pharmacovigilance, and implementing robust reforms are essential to preventing further paediatric morbidity and mortality.

Keywords: Diethylene glycol, cough syrup adulteration, Paediatric nephrotoxicity, drug quality control, CDSCO reforms

*Corresponding Author: Divyashanthi CM
Email: dishanthii@gmail.com

Graphical Abstract



Introduction

Some of the deadliest pediatric poisoning outbreaks in the history of world health have been caused by diethylene glycol (DEG) poisoning from tainted oral liquid medications [1,2]. DEG pollution persists despite decades of knowledge, particularly in low- and middle-income countries (LMICs) [3,4]. Due to their smaller stature, delayed diagnosis, and frequent use of cough syrups for minor ailments, children are disproportionately impacted [5].

In September and October of 2025, scores of young children in Madhya Pradesh's Chhindwara area died from a common prescription for cough treatment. After consuming Coldrif cough medication, which included diethylene glycol (DEG) at concentrations up to 500 times the allowable limits, at least 21 children under the age of five died from severe renal damage [6].

This episode demonstrates a persistent failure in drug safety, much with the 2022 Gambia tragedy in which 70 infants perished from Indian-exported syrups contaminated with DEG and ethylene glycol [7]. Since 2022, the World Health Organization (WHO) has issued numerous alerts worldwide, connecting these contaminations to over 300 juvenile fatalities in seven different countries [8,9].

These situations need for prompt observation and response because oral syrups are the most popular pediatric prescription in India because of their palatability and ease of administration. DEG, an inexpensive industrial solvent that mimics the sweetness of glycerin, is used with excipients such as propylene glycol to reduce costs [10,11]. Lethality is increased in children because to their smaller body weight and immature renal clearance; symptoms progress from vomiting to anuria and death in 24 to 48 hours [12]. This article explores the topic from the perspectives of pharmacology and pediatrics through a compilation of reports and literature (searched via PubMed, WHO databases,

and news archives for "DEG cough syrup deaths 2020–2025"). We describe the epidemiology, procedures, quality concerns, policy flaws, and measures to stop such tragedies.

International attention was sparked by the 2025 India incident, where a number of pediatric syrups were declared unsafe due to laboratory results of increased DEG concentrations. In accordance with PRISMA guidelines, this review summarizes the worldwide data, causality, and regulatory shortcomings that contribute to these recurring outbreaks. The important data on deaths from DEG-Contaminated Cough Syrup from 2020 to 2025 is shown in Table 1 [13-17].

Table 1. Key Statistics on DEG-Contaminated Cough Syrup Deaths (2020–2025)

Incident/Year	Location	Product(s)	Child Deaths	Key Findings
Jammu, India (2019–2020)	Jammu &Kashmir	Multiple syrups	≥12	DEG in excipients; underreported acute kidney injury [13]
Gambia (2022)	Gambia	Promethazine Oral Solution, Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup, Magrip N Cold Syrup (Maiden Pharma, India)	66–70	WHO-confirmed DEG/EG; bribery allegations in testing; export scandal [14,15]
Uzbekistan (2022)	Uzbekistan	Doc-1 Max (Marion Biotech, India)	65	Bribery ($33,000) to skip tests; license suspension [16]
India (2025)	Madhya Pradesh/Rajasthan	Coldrif (Sresan Pharma), Respifresh (Rednex Pharma), ReLife (Shape Pharma)	19–24	DEG 500x limit in Coldrif; 364 manufacturing violations; arrests and bans [17].
Total (WHO est., 2020–2025)	Multiple countries	Various Indian syrups	>300	Primarily <5 years; >140 export-linked since 2022.

Methods

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility criteria

Studies were suitable for inclusion if they described diethylene glycol (DEG) or ethylene glycol (EG) contamination in oral liquid pharmaceutical products and offered information relevant to children, including clinical aspects or outcomes. Toxicology or regulatory assessments that looked at the causes, pathways, or system-level failures connected to DEG contamination were also included, as were reports from the US FDA, the European Medicines Agency, the WHO, and national regulatory authorities. Only publications in English from January 2020 to December 2025 were evaluated. Studies describing methanol poisoning unrelated to pharmaceuticals, industrial-use DEG without connection to medicinal products, or purely animal or laboratory studies with no public health relevance were excluded.

Search strategy

A comprehensive search was conducted across PubMed/MEDLINE, Embase, Scopus, Google Scholar, and official regulatory alert systems including the WHO Medical Product Alerts, US FDA Safety Alerts and national regulatory sites from India, Indonesia, Uzbekistan and The Gambia. The keywords used in the search strategy related to DEG contamination, oral liquid medicines, paediatric poisonings were “diethylene glycol” OR “ethylene glycol” AND “cough syrup” OR “oral liquid” OR “paediatric syrup” AND “contamination” OR “adulteration” OR “toxicity” OR “poisoning” AND “children” OR “paediatric”.

A full -text review of possibly suitable studies was conducted after a preliminary screening of titles and abstracts. Any disputes were settled by consensus. Data on the country and year of the epidemic, the type of contaminated product, measured DEG levels, identified sources of contamination, clinical presentations, death figures, regulatory shortcomings, and documented outcomes were collected for each included study.

The risk of bias was evaluated based on the type of source: media accounts were only used when they were backed by credible documentation, but WHO alerts and regulatory reports were regarded as extremely reliable because of laboratory confirmation. Research was included if it: oral liquid medicinal medications have been found to include ethylene glycol (EG) or diethylene glycol (DEG).

Reports from reputable regulatory organizations, such as the US FDA, European Medicines Agency, WHO, or national drug regulatory authorities, contains information pertinent to children, such as clinical manifestations or outcomes, toxicological, epidemiological, or regulatory analyses addressing the causes, pathways, or systemic failures related to DEG contamination. Studies that reported methanol poisoning unrelated to pharmaceutical products, talked about industrial or environmental DEG exposure unrelated to pharmaceutical products, or involved animals, laboratories, or experiments with no direct bearing on public health were all disqualified.

Data Extraction

The following data were extracted from the each included study: Country and year outbreak, Type of contaminated pharmaceutical product, measured levels of diethylene glycol, Source and mechanism of contamination, Clinical manifestations and complications, Mortality data, identified regulatory or manufacturing deficiencies, Reported outcomes and public health responses.

Risk of Bias Assessment

The reliability of the source was assessed by nature of the report. Laboratory confirmation and formal documentation made WHO alerts and regulatory authority reports extremely trustworthy. Media reports were included when they are supported by reliable scientific or regulatory sources.

Results

Out of the 1,246 records, after removal of duplicates 98 were remained.60 full text papers were screened and 32 satisfied the eligibility requirements (Figure 1). These included reports from regulatory investigations, WHO medical alerts, peer – reviewed toxicological and clinical research, analysis of epidemiological outbreaks, and chemical quality evaluations of excipients.

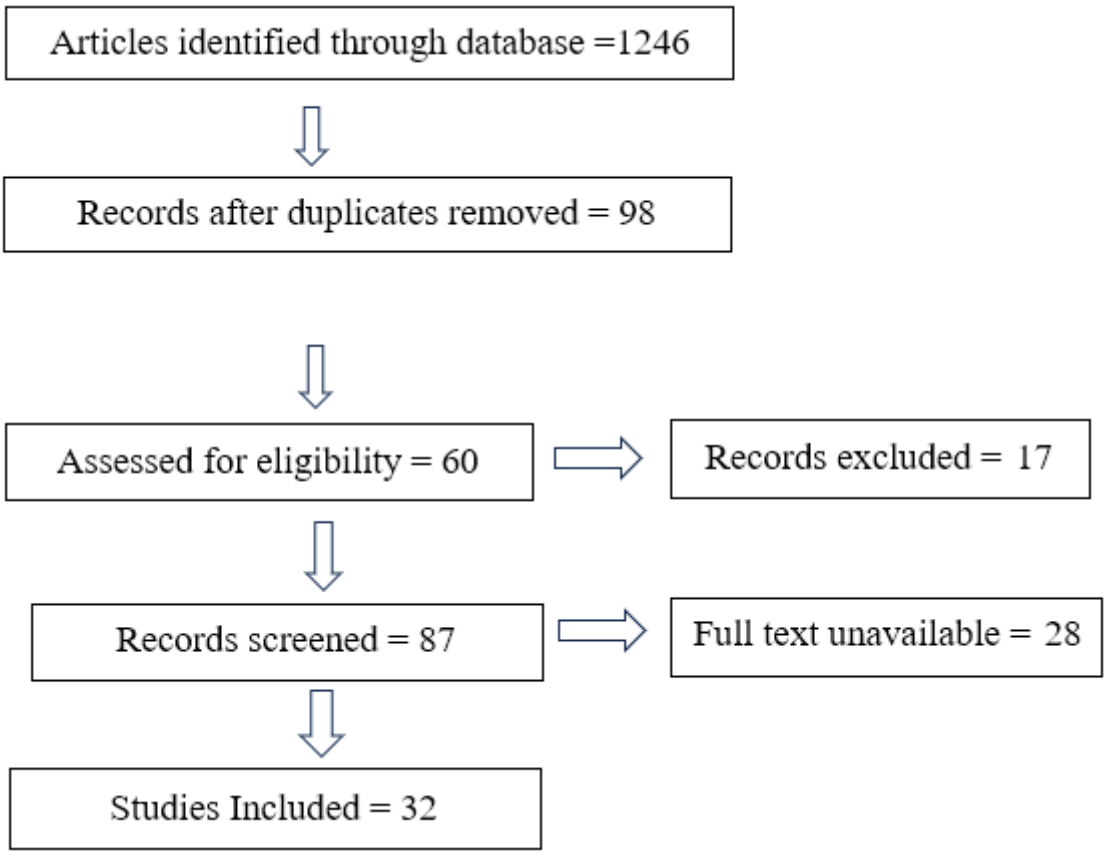


Figure 1. Overview of study selection for the narrative review

Four significant paediatric outbreaks were frequently reported in all of the analyzed sources: India (2025), Indonesia (2022), Uzbekistan (2022) and The Gambia (2022). These incidents collectively accounted for hundreds of deaths, with particularly high mortality in Indonesia and Gambia. The common feature in all outbreaks was contamination of pediatric syrups, typically cough and cold preparations, with DEG or EG. The use of industrial-grade raw ingredients or the replacement of pharmaceutical-grade excipients with less expensive alternatives were the underlying reasons, which varied slightly but were always connected to tainted glycerin or solvent-grade excipients.

Clinical presentations across outbreaks were uniform. Affected children typically presented with nonspecific symptoms such as vomiting and abdominal pain, which rapidly progressed to high-anion-gap metabolic acidosis, Kussmaul respiration and oliguria or anuria. In many cases, clinical deterioration was rapid, leading to acute kidney injury, central nervous system depression, seizures and multi-organ dysfunction. The death rates in several outbreaks, which ranged from 30% to 70%, show the potency of DEG as a renal and metabolic toxin and the challenges of early diagnosis in young populations [18,19].

By examining contamination pathways, recurrent systemic vulnerabilities were discovered. Many manufacturers failed to conduct independent testing of excipients and instead relied on inaccurate or insufficient Certificates of Analysis. Supply chains frequently lacked traceability, and many businesses violated standard Good Manufacturing Practice regulations. Inadequate staffing, few inspections, and a sluggish response to early warning signs are common signs of weak regulatory management in affected countries. Because post-marketing surveillance and recall systems were either nonexistent or poorly implemented, contaminated batches were often permitted to remain in circulation for prolonged periods of time [20,21].

Discussion

This thorough analysis shows that DEG contamination of pediatric oral liquid medications is a persistent worldwide issue linked to avoidable errors in manufacturing and regulation. Poor quality assurance practices, insufficient supply chain verification, tainted excipients, and delayed regulatory responses were common upstream causes of all the outbreaks under examination. Due to serious structural faults in pharmaceutical quality control systems worldwide, widespread poisoning continues despite long-standing WHO standards. The 2025 Indian epidemic is remarkably similar to previous crises in Indonesia, The Gambia, and Uzbekistan, suggesting that production practices and regulatory frameworks have not adequately taken into account the lessons learnt from previous calamities [22].

For a number of reasons, children are more vulnerable to DEG poisoning. Compared to adults, they have a far higher hazardous dose per kilogram due to their lower body weight. The widespread usage of pediatric syrups for common ailments raises the danger of exposure during contamination incidents. Furthermore, early signs of DEG toxicity, such lethargy and vomiting, are frequently confused with common children's diseases, delaying

detection until renal damage is more severe. Reversibility is restricted and mortality rises dramatically once metabolic acidosis or anuria develops, particularly in environments with limited access to dialysis or pediatric critical care [23].

From an epidemiological perspective, these incidents primarily affect children under five in low-resource environments where access to over-the-counter syrup and informal markets are common. 70% of 2025 instances in India are found in rural areas like Chhindwara, where self-medication for respiratory conditions is the main cause. According to WHO data, there have been over 300 deaths worldwide since 2022, with 140 of the deaths being attributed to imports from India. Post-monsoon spikes are correlated with cough season and supply chain vulnerabilities, according to trends [24].

Alcohol dehydrogenase breaks down DEG ($C_4H_{10}O_3$) pharmacologically into toxic intermediates: glycolic acid causes metabolic acidosis, while oxalic acid produces renal calcium oxalate crystals that induce acute tubular necrosis. Glomerular filtration rates in children (5–10 mL/min/1.73 m^2 at birth, maturing to adult levels by 2 years) delay clearance, reducing the lethal dose to 1-2 mL/kg as opposed to 5–10 mL/kg in adults. Case studies from the Gambia show that, despite receiving hemodialysis, children experienced gastrointestinal pain and oliguria 12–24 hours after ingestion, which resulted in unconsciousness and 30–50% mortality. At this point, pharmacovigilance is necessary: pediatricians should query formulations when evaluating a patient's history, while pharmacologists advise routine excipient testing. If nothing is done, annual underreporting could hide thousands of cases [25,26].

Quality Control Issues: From Adulteration to Market Entry

Cost – driven alternatives are the main source of adulteration: DEG enters the market from unregulated vendors and costs around a tenth of pharmaceutical -grade propylene glycol. In the 2025 Coldrif case, the Sresan Pharma Facility broke 364 regulations. Inadequate water purification, poor pest control, and unclean storage were among these infractions, which promoted microbial degradation and ultimately exacerbated the original infection. Toxins may rise due to degradation (such as hydrolysis in humid storage), but production is the main problem because untested batches did not follow good manufacturing procedures (GMP).

As demonstrated by the purported sample switching by Haryana officials in the Gambia bribery case, supply networks increase risks as informal distributors avoid oversight. Pharmacologically, adulterants alter bioavailability; DEG's solubility boosts activity but results in distinct nephrotoxicity. Every year, 80% of Indian youngsters steal over-the-counter formulas, and the allure of syrup in homes with low literacy rates conceals risks. Export biases make matters worse because only foreign syrups will require further testing after 2022, endangering domestic markets. One of the best examples of global ripple effects is the Gambia case, where the WHO blacklisted fifteen Indian businesses [27,28].

Policy Deficiencies and Gaps: Where India Lags

CDSCO monitoring is required by India's Drugs and Cosmetics Act (1940, updated 2023), however enforcement is lacking. Corner-cutting is encouraged by the decriminalization of "not-of-standard-quality" offenses after the Gambia incident. Regulators are understaffed—one inspector for every 1,000 units—and inspections have lapsed for up to two years, as in Sresan pharmaceuticals. Domestically, there are no standard DEG-specific testing; QR traceability (2023 for 300 medicines) focuses on counterfeits rather than inferior excipients. State-specific FDAs differ: Inspectors were suspended in Tamil Nadu, but national coordination is lacking.

Over 1,000 “not-of-standard” samples are not prosecuted annually due to inadequacies in pharmacovigilance and export-domestic inequalities. WHO calls them "deep concerns," and risk-based audits are advised. Despite 2025 warnings against under-twos, pediatricians observe that there are no child-specific prohibitions, and pharmacologists lament the lack of excipient guidelines [29].

International harmonization of excipient-testing standards is desperately needed, as evidenced by the numerous global failures this study finds. While there are accepted analytical techniques for identifying DEG, their application varies by nation. Enforcing batch-wise testing of excipients, bolstering laboratory infrastructure, and enhancing digital traceability in pharmaceutical supply chains are crucial actions. By implementing more dependable recall protocols, frequent surprise inspections, and real-time monitoring, regulatory bodies must move from reactive to proactive oversight. Clinical awareness must also be increased. In clusters of children with acute renal damage, early diagnosis of DEG poisoning could greatly improve outcomes [30].

Recommendations and Future Prevention

Every year, CDSCO conducts risk-based audits that cover at least 20% of pediatric manufacturing facilities, particularly rural suppliers, using AI-enabled supply-chain tracking to identify early anomalies; Expanded traceability is supported by universal QR codes on all syrups and user-friendly apps for real-time verification; pediatric safety initiatives, like the IAP/IPA-led "Syrup-Safe" program, should educate parents about safer alternatives, like inhalers, and tighten restrictions on the sale of over-the-counter syrup to children under five. Two ways to tighten sanctions are to re-criminalize adulteration with 5–10 year prison sentences and to use WHO systems to internationally blacklist repeat offenders.

Harmonizing Indian rules with USFDA and EU quality standards and bolstering the WHO Member State Mechanism for coordinated investigations are two ways to improve international protections. Joint pharmacology-pediatrics training courses on adulterant identification and structured reporting via PvPI should be part of academic integration. Long-term policy modeling suggests that these multilayered reforms might reduce contamination-related events by up to 50% in five years. The need to extend the 2025 emergency restrictions throughout India in the near future is highlighted by physician alerts and urgent statewide recalls.

Enhancing production techniques is essential. Requiring batch testing for DEG

and EG in all excipients, along with digital supply-chain traceability and third-party audits, would significantly reduce contamination risks. Regulators ought to enforce post-marketing surveillance, conduct regular surprise inspections, and take an active role in global alert-sharing networks. To identify tainted items early, public health institutions must increase the capacity of toxicology labs and communicate promptly during recalls. When newborns experience unexplained acute renal injury, especially in clusters of identical instances, clinicians should be educated to recognize DEG poisoning [31,32].

Conclusion

DEG contamination of pediatric cough syrups presents a significant concern to public health even though it is completely avoidable. Over a 15-year span, this PRISMA-guided systematic analysis reveals recurring patterns of excipient adulteration, manufacturing carelessness, and insufficient regulatory enforcement. To stop more pediatric deaths, it is essential to strengthen excipient verification, enforce thorough batch-level testing, and guarantee integrated regulatory control. The safety of children, who suffer the most from these catastrophes, depends on a pharmaceutical system that prioritizes quality, accountability, and transparency. Thus, global reforms need to be put into effect immediately.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. Schier JG, Barr DB, Li Z, Wolkin AF, Baker SE, Lewis LS, McGeehin MA. Diethylene glycol in health products sold over-the-counter and imported from Asian countries. Journal of medical toxicology. 2011 Mar;7(1) 33-8. DOI: 10.1007/s13181-010-0111-9
2. Schep LJ, Slaughter RJ, Temple WA, Beasley DM. Diethylene glycol poisoning. Clinical toxicology. 2009 Jul 1;47(6):525-35. DOI: 10.1080/15563650903086444
3. Amaducci AM, Campleman SL, Li S, Karshenas DL, Spyres MB, Farrugia LA, Kang AM, Culbreth RE, Wax PM, Brent J, Aldy K. The toxicology investigators consortium 2022 annual report. Journal of medical toxicology. 2023 Oct;19(4):313-40.doi: 10.1007/s13181-023-00962-2.
4. Zengin M, Karaca O. A bibliometric analysis of academic publications about intoxication in the period from 1975 to 2020: A global and medical view. Osmangazi Tıp Dergisi. 2022.DOI:10.20515/otd.993562
5. Valeur KS, Hertel SA, Lundstrøm KE, Holst H. The cumulative daily tolerance levels of potentially toxic excipients ethanol and propylene glycol are commonly exceeded in neonates and infants. Basic & clinical pharmacology & toxicology. 2018 May;122(5):523-30.https://dergipark.org.tr/tr/pub/otd/issue/68213/993562

6. Express web desk.Cough syrup deaths: Here are 5 key revelations in the Coldrif case.The Indian Express.15 October 2025. https://indianexpress.com/article/india/cough-syrup-deaths-here-are-top-5-revelations-in-coldrif-case-10305962/
7. Bastani P. Acute kidney injury among children likely associated with diethylene glycol–contaminated medications—The Gambia, June–September 2022. MMWR. Morbidity and Mortality Weekly Report. 2023;72. DOI: 10.15585/mmwr.mm7209a1
8. Dewan S, Muragundi PM, Ramesh VL, Ligade VS, Sreedhar D, Shetty AD. Substandard and falsified pediatric medicines in low–middle-income countries: A narrative review on impacts and strategies. Journal of Applied Pharmaceutical Science. 2025 Nov 5;15(12):013-24.DOI: 10.7324/JAPS.2025.246088
9. Wilder R, Halabi S, Gostin LO. Global and national actions to prevent trade in substandard and adulterated medicines. PLOS Global Public Health. 2025 Feb 20;5(2):e0004024.DOI: 10.1371/journal.pgph.0004024
10. Saito J, Agrawal A, Patravale V, Pandya A, Orubu S, Zhao M, Andrews GP, Petit-Turcotte C, Landry H, Croker A, Nakamura H. The current states, challenges, ongoing efforts, and future perspectives of pharmaceutical excipients in pediatric patients in each country and region. Children. 2022 Mar 23;9(4):453. DOI: 10.3390/children9040453
11. Wu Y, Levons J, Narang AS, Raghavan K, Rao VM. Reactive impurities in excipients: profiling, identification and mitigation of drug–excipient incompatibility. Aaps Pharmscitech.2011 Dec; 12(4): 1248-63. doi: 10.1208/s12249-011-9677-z
12. World Health Organization. WHO urges action to protect children from contaminated medicines [Internet]. 2023 https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines
13. Perazella MA. Hiding in Plain Sight: Catastrophic Diethylene Glycol Poisoning in Children. Kidney360. 2023 Nov 1;4(11):1534-5. DOI: 10.34067/KID. 0000000000000269
14. Thiagarajan K. WHO investigates cough syrups after deaths of 66 children in Gambia.DOI: 10.1136/bmj.o2472
15. Bittaye M, Byakika-Tusiime J, Adisso L, Pavlin BI, Muteba M, Jammeh AH, Udenweze IL, Jallow AW, Fofana N, Kalisa M, Lareef S. Causes and risk factors for an acute kidney injury outbreak among children in The Gambia, June–September 2022: A case-cohort study. PLoS One. 2025 Jun 12;20(6):e0324931. doi: 10.1371/journal.pone.0324931
16. Murtalibova N, Sethi SK, Raina R, Mamatkulov B, Mustakimov A. Sudden spurt in pediatric patients with AKI in Uzbekistan: a call for international drug quality control and pharmaceutical legislation. Kidney360. 2023 Nov 1;4(11):1608-

9. doi: 10.34067/KID.0000000000000255
17. McQuillan C. Cough syrup contamination in India. The Lancet Respiratory Medicine. 2025 Nov 25.DOI: 10.1016/S2213-2600(25)00431-X
18. World Health Organization. Substandard (contaminated) pediatric medicines identified in WHO region of Africa. Geneva, Switzerland: World Health Organization; 2022. Accessed November 11, 2022. https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-(contaminated)-paediatric-medicines
19. Nayyar GM, Breman JG, Mackey TK, Clark JP, Hajjou M, Littrell M, Herrington JE. Falsified and substandard drugs: stopping the pandemic. The American journal of tropical medicine and hygiene. 2019 Mar 11;100(5):1058. DOI: 10.4269/ajtmh.18-0981
20. Sardella M, Belcher G, Lungu C, Ignoni T, Camisa M, Stenver DI, Porcelli P, D'Antuono M, Castiglione NG, Adams A, Furlan G. Monitoring the manufacturing and quality of medicines: a fundamental task of pharmacovigilance. Therapeutic Advances in Drug Safety. 2021 Aug;12:20420986211038436.doi: 10.1177/20420986211038436
21. Fryze I, Naughton BD. Substandard and falsified medicine recalls in the legitimate supply chain: a systematic review of evidence. BMJ open. 2025 Oct 1;15(10):e103672.https://bmjopen.bmj.com/content/15/10/e103672
22. de Almeida Araújo S, Faria BC, Vasconcelos JC, da Cruz AF, de Souza VS, Wanderley DC, Simões-e-Silva AC. Renal toxicity caused by diethylene glycol: an overview. International urology and nephrology. 2023 Nov;55(11):2867-75. doi: 10.1007/s11255-023-03604-2.
23. Akuse RM, Eke FU, Ademola AD, Fajolu IB, Gbelee HO, Ihejiahi U, Bugaje MA, Anochie IC, Asinobi AO, Okafor HU, Adeleke SI. Diagnosing renal failure due to diethylene glycol in children in a resource-constrained setting. Pediatric Nephrology. 2012 Jun;27(6):1021-8.doi: 10.1007/s00467-011-2082-8.
24. Alkahtani S, Sammons H, Choonara I. Epidemics of acute renal failure in children (diethylene glycol toxicity). Archives of disease in childhood. 2010 Dec 1;95(12):1062-4.doi: 10.1136/adc.2010.183392.
25. Wittschieber D, Heuberger K, Schulz R, Köhler H, Varchmin-Schultheiß K. Fatal poisoning with diethylene glycol in an unusual setting. Forensic Science, Medicine and Pathology. 2019 Dec;15(4):649-52.doi: 10.1007/s12024-019-00123-4
26. Alfred S, Coleman P, Harris D, Wigmore T, Stachowski E, Graudins A. Delayed neurologic sequelae resulting from epidemic diethylene glycol poisoning. Clinical toxicology. 2005 Jan 1;43(3):155-9.https://pubmed.ncbi.nlm.nih.gov/15902788/
27. Soleman SR, Adnan ML, Sudiarto HA, Mahathma SB, Tazkia AA, Firdaus HA, Khotijah AA,

Pramaningtyas MD, Choironi EA. Effects of diethylene glycol contamination of pharmaceutical products on unexplained acute kidney injury in children: a systematic review. Clinical and Experimental Pediatrics. 2024 Jan 4;67(8):395. doi: 10.3345/cep.2023.01039.

28. Akram A, Khanna A, Shukla VK, Sharma N. Recent Advancements in Pharmaceutical Packaging and Regulatory Aspects. Journal of Packaging Technology and Research. 2025 Mar;9(1):1-7.DOI:10.1007/s41783-024-00179-w
29. Paliwal D. Reforming India's Pharmaceutical Regulation: Addressing Structural Gaps and Ensuring Drug Safety. DOI:10.21275/SR251024134018
30. Sharma DC. Cough syrup deaths expose lax drug regulation in India. The Lancet. 2022 Oct 22;400(10361):1395. doi: 10.1016/S0140-6736(22)02026-8.
31. Kumar P, Rastogi S, Saini PK, Sahoo S, Raghuvanshi RS, Jadaun GP. Minimizing the risk of ethylene glycol and diethylene glycol poisoning in medications: A regulatory and pharmacopoeial response. Regulatory Toxicology and Pharmacology. 2025 Jan 1;155:105741.DOI:10.1016/j.yrtph.2024.105741
32. Altamimy MA, Alshehri YM, Aldawsari FS, Altalyan NH, AlShmmari SK, Alzaid SF, Al-Qahtani NA, Alsagoor TM, Al Shahrani MS. A Selective Gas Chromatography–Tandem Mass Spectrometry Method for Quantitation of Ethylene and Diethylene Glycol in Paediatric Syrups. Heliyon. 2024 Apr 15;10(7). DOI: 10.1016/j.heliyon.2024.e27559

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CASE REPORT

Sleepless Yet Asleep: A Case Report on Paradoxical Insomnia

Arthi K.K.,[1,*] M. Sasidharan[2] and S.R. Nirmal[3]

[1]*Final Year Post Graduate, Department of Psychiatry, Dhanalakshmi Srinivasan Medical College & Hospital, Perambalur Tamilnadu*
[2]*Second Year Post Graduate, Department of Psychiatry, Dhanalakshmi Srinivasan Medical College & Hospital, Perambalur Tamilnadu*
[3]*Professor, Department of Psychiatry, Dhanalakshmi Srinivasan Medical College & Hospital, Perambalur Tamilnadu*

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Abstract

Background: Paradoxical insomnia, also termed sleep state misperception, is a subtype of chronic insomnia in which a patient's subjective report of severely disturbed or absent sleep is markedly discordant with objective evidence of normal sleep duration and architecture on polysomnography. Patients typically overestimate sleep-onset latency and underestimate total sleep time, often without the daytime impairment expected of comparable objective sleep loss. **Case Report:** We report the case of a 51-year-old married woman with a 15-month history of perceived total sleep loss, constant wakefulness, and early morning awakening, without objective daytime sleepiness. Serial Pittsburgh Sleep Quality Index (PSQI) scores remained abnormal despite sequential trials of dothiepin, mirtazapine, clonazepam, quetiapine, zolpidem, and melatonin. Sleep diaries maintained during inpatient evaluation documented adequate sleep, and nocturnal polysomnography and the Hamilton Depression Rating Scale (HDRS) were within normal limits, confirming a diagnosis of paradoxical insomnia. **Intervention and Outcome:** The patient was managed with psychoeducation and cognitive behavioural therapy (CBT) targeting misperception of sleep, incorporating sleep diaries and sleep hygiene techniques, with sustained clinical improvement. **Conclusion:** This case emphasizes the need for objective sleep assessment in patients with treatment-refractory insomnia and shows that CBT is an effective, medication-sparing strategy for paradoxical insomnia.

Keywords: Paradoxical insomnia, sleep state misperception, polysomnography, cognitive behavioural therapy, Pittsburgh Sleep Quality Index

*Corresponding Author: Arthi K.K.
Email: dr.arthy16@gmail.com

Introduction

Insomnia is among the most common presenting complaints in psychiatric and primary care practice, but not all patients who report an inability to sleep have demonstrable sleep pathology on objective testing. Current diagnostic classifications, including the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), and the International Classification of Sleep Disorders, Third Edition (ICSD-3), define chronic insomnia disorder primarily on the basis of subjective dissatisfaction with sleep quantity or quality rather than any single objective physiological threshold [1,2].

Paradoxical insomnia represents a distinct dissociation between a patient's perception of sleep and its physiological correlates: the individual believes they are awake, or sleeping poorly, while electrophysiological recordings show a pattern consistent with normal, restorative sleep. The construct was first described under the label “sleep state misperception” and remains a recognised, if underdiagnosed, insomnia subtype in contemporary sleep nosology, historically debated as to whether it represents a distinct clinical entity or a variant of psychophysiological insomnia [3]. Proposed neurophysiological correlates include subtle alterations in cortical arousal and sleep microstructure that are not captured by conventional polysomnographic staging [4], and the magnitude of subjective-objective sleep discrepancy in this subtype exceeds that typically observed in other insomnia disorders [5].

Diagnosing paradoxical insomnia is clinically important because these patients frequently undergo repeated, escalating, and often ineffective pharmacological trials before the disorder is correctly identified, exposing them to unnecessary medication burden and side effects. We present a case in which correct recognition of paradoxical insomnia, following extensive and unsuccessful pharmacotherapy, allowed a shift to a targeted psychotherapeutic approach with good outcome.

Case Report

Patient Demographics and Clinical Details

A 51 year old married housewife currently living with her husband and grandchildren, presented with a 15 month history of perceived inability to fall asleep, a sense of being constantly awake and early morning awakening. She reported no daytime sleepiness and described sleep difficulty despite having adequate opportunity for sleep. At her index visit to our outpatient department in December 2023. she gave a 3 month history of these symptoms and was evaluated for insomnia.

Clinical Course

The Pittsburgh Sleep Quality Index (PSQI) score at this visit corresponded to more than 5 hours of subjectively perceived wakefulness at night. She was started on dothiepin, followed later by mirtazapine, with doses titrated to 100 mg and 30 mg respectively. Her symptoms persisted despite these adequate therapeutic doses, and the medications were discontinued after 3 months owing to poor response.

Diagnostic Assessment

Because her symptoms persisted, she underwent a master health check-up, following which clonazepam 0.5 mg was added. Repeat PSQI assessment again corresponded to more than 5 hours of

perceived nocturnal wakefulness even after initiation of the benzodiazepine. She showed only transient improvement lasting about a week before symptoms recurred. She was subsequently admitted for further evaluation and was started on a combination of quetiapine, zolpidem, and melatonin, and was asked to maintain a structured sleep diary. Diary-based monitoring during admission documented objectively adequate sleep, yet she continued to report subjective sleeplessness.

Therapeutic Intervention

She was psycho-educated about the nature of her illness and about the discordance between her perception of sleep and her actual sleep pattern, and was subsequently managed with cognitive behavioural therapy (CBT). On reassessment, PSQI continued to indicate more than 5 hours of perceived nocturnal wakefulness with two reported nighttime awakenings, although the patient's sleep was, on objective review, restorative. Other rating scales, including the Hamilton Depression Rating Scale (HDRS), were within normal limits. Overnight polysomnography demonstrated normal sleep architecture, with a total sleep time of approximately 410 minutes, sleep efficiency of 89%, sleep-onset latency of 18 minutes, rapid eye movement (REM) latency of 92 minutes, wake after sleep onset (WASO) of 24 minutes, and a normal distribution of sleep stages (N1: 6%, N2: 50%, N3: 22%, REM: 22%). No clinically significant respiratory events, periodic limb movements, or other sleep-related abnormalities were identified. These findings were within normal adult reference ranges. This combination of normal objective sleep parameters with persistent subjective sleep complaints, unresponsive to sequential pharmacotherapy, was consistent with a diagnosis of paradoxical insomnia.

Follow-up and Outcome

The patient was managed with a multimodal, non-pharmacological strategy comprising sleep diaries, sleep hygiene education, and CBT directed at her misperception about sleep, and followed up for a period of 6 months. She remained clinically well on this regimen, and her subjective perception of sleep improved progressively over the course of psychotherapy sessions with improved PSQI score from baseline.

Discussion

Paradoxical insomnia occupies an unusual position among insomnia subtypes: patients experience genuine, often severe, distress about their sleep, while standard objective measures show sleep that is largely preserved in duration and architecture, as described in standard psychiatric reference texts [6]. Physiological and polysomnographic evaluation plays a central role in distinguishing this subtype from other insomnia presentations and in identifying medical or psychiatric comorbidities that might otherwise be overlooked [7].

The direction of misperception is also clinically relevant. Insomnia patients with "negative" sleep state misperception, that is, those who underestimate their sleep relative to objective recordings, as in the present case, tend to report higher Pittsburgh Sleep Quality Index (PSQI) scores, longer perceived sleep-onset latency, and more frequent awakenings than those with "positive" misperception, a pattern that correlates with reduced slow-

wave (N3) sleep on polysomnography [8]. The PSQI, used serially in this patient to track her subjective sleep complaints, is a validated instrument originally developed for psychiatric practice and research [9], while her mood status was concurrently screened using the Hamilton Depression Rating Scale (HDRS), a long-established, widely used clinician-administered instrument [10]. Structured sleep diaries, as used during this patient's inpatient evaluation, provide a practical adjunct to objective monitoring, and diary-based sleep estimates have been shown to correlate reasonably well with wearable and research-grade actigraphic measures in patients with insomnia disorder [11].

Management of paradoxical insomnia diverges from that of typical insomnia in that pharmacotherapy directed at increasing sleep duration is unlikely to be effective, since objective sleep duration is often already adequate. In the present case, the patient underwent sequential trials of dothiepin and mirtazapine; the latter is known to alter sleep architecture and increase slow-wave sleep in depressed patients, although its effect on primary sleep misperception specifically is not established [12]. Subsequent addition of an atypical antipsychotic (quetiapine) was similarly unlikely to have produced durable benefit, as systematic review evidence does not support a significant advantage of atypical antipsychotics over placebo for primary insomnia [13]. Likewise, non-benzodiazepine hypnotics such as zolpidem produce only modest reductions in objective and subjective sleep latency compared with placebo [14], and short-term melatonin has not been shown to be consistently effective for primary sleep disorders other than circadian phase disorders [15]. Current evidence-based guidelines reflect this limited pharmacological evidence base, generally offering only weak recommendations in favour of individual hypnotic agents for chronic insomnia [16].

Cognitive behavioural therapy for insomnia (CBT-I) is recommended as first-line treatment for chronic insomnia disorder of any subtype, and polysomnography is specifically indicated when substantial sleep state misperception is suspected, as illustrated in the present case [17]. CBT-I has demonstrated durable effectiveness even when delivered in routine general-practice settings rather than specialised sleep clinics [18], and comparative data indicate that CBT-based interventions produce broader improvements in daytime and psychological functioning than medication-only strategies [19]. Long-term follow-up data further show that the benefits of CBT-I, including in cases with a strong misperception component, persist for years after treatment completion, distinguishing it from the largely short-term benefit profile of pharmacotherapy [20].

In the present case, the patient underwent multiple sequential trials of tricyclic antidepressants, mirtazapine, a benzodiazepine, and finally a combination of an atypical antipsychotic, a non-benzodiazepine hypnotic, and melatonin, none of which produced sustained symptomatic benefit. It was only after structured sleep-diary documentation of objectively adequate sleep, a normal HDRS, and normal polysomnography that the diagnosis of paradoxical insomnia was established, allowing a shift away from pharmacotherapy toward psychoeducation and CBT targeting her misperception of sleep. This sequence illustrates a common and avoidable pattern in clinical practice, in

which repeated medication trials precede rather than follow objective sleep assessment.

If left unrecognised and untreated, patients with paradoxical insomnia may become increasingly distressed and anxious about their perceived sleeplessness, and this heightened concern can, over time, contribute to genuine, objectively measurable sleep disturbance. This case therefore reinforces the importance of maintaining clinical suspicion for paradoxical insomnia in patients whose insomnia is refractory to escalating pharmacological trials, and of using sleep diaries, standardised rating scales, and polysomnography to confirm the diagnosis before committing to further medication changes.

Conclusion

Paradoxical insomnia should be considered in any patient with persistent, treatment-refractory insomnia, particularly when subjective complaints are disproportionate to objective findings and daytime functioning is relatively preserved. Objective assessment with sleep diaries, standardised scales, and polysomnography is essential to establish the diagnosis and to avoid unnecessary escalation of pharmacotherapy. Cognitive behavioural therapy directed at correcting sleep misperception, rather than further medication trials, is the appropriate management strategy and can achieve sustained clinical improvement, as demonstrated in this case.

Patient Perspective

Following psychoeducation and cognitive behavioural therapy, the patient reported reassurance after understanding that she had been sleeping despite perceiving wakefulness. This understanding reduced anxiety surrounding sleep and improved confidence in non-pharmacological management.

Limitations

Objective sleep assessment was based on a single overnight polysomnography, and serial polysomnographic or actigraphic evaluations were not performed to assess longitudinal changes. The follow-up period was limited to six months, precluding assessment of the long-term durability of therapeutic benefit.

Statements and Declarations

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying clinical details.

Conflict of Interest:

The authors declare no conflict of interest.

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association Publishing; 2022.
2. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387–1394. DOI:

https://doi.org/10.1378/chest.14-0970
3. Edinger JD, Krystal AD. Subtyping primary insomnia: is sleep state misperception a distinct clinical entity? Sleep Med Rev. 2003;7(3):203–214. DOI: https://doi.org/10.1053/smrv.2002.0253
4. Bastien CH, Ceklic T, St-Hilaire P, Desmarais F, Pérusse AD, Lefrançois J, et al. Insomnia and sleep misperception. Pathol Biol (Paris). 2014;62(5):241–251. DOI: https://doi.org/10.1016/j.patbio.2014.07.003
5. Rezaie L, Fobian AD, McCall WV, Khazaie H. Paradoxical insomnia and subjective-objective sleep discrepancy: a review. Sleep Med Rev. 2018;40:196–202. DOI: https://doi.org/10.1016/j.smrv.2018.01.002
6. Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 11th ed. Philadelphia: Wolters Kluwer; 2024.
7. Bonnet MH, Burton GG, Arand DL. Physiological and medical findings in insomnia: implications for diagnosis and care. Sleep Med Rev. 2013;18(2):111–122. DOI: https://doi.org/10.1016/j.smrv.2013.02.003
8. Yoon G, Lee MH, Oh SM, Choi JW, Yoon SY, Lee YJ. Negative and positive sleep state misperception in patients with insomnia: factors associated with sleep perception. J Clin Sleep Med. 2022;18(7):1789–1795. DOI: https://doi.org/10.5664/jcsm.9974
9. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213. DOI: https://doi.org/10.1016/0165-1781(89)90047-4
10. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56–62. DOI: https://doi.org/10.1136/jnnp.23.1.56
11. Hamill K, Jumabhoy R, Kahawage P, de Zambotti M, Walters EM, Drummond SPA. Validity, potential clinical utility and comparison of a consumer activity tracker and a research-grade activity tracker in insomnia disorder II: outside the laboratory. J Sleep Res. 2019;29(1):e12944. DOI: https://doi.org/10.1111/jsr.12944
12. Schmid DA, Wichniak A, Uhr M, Ising M, Brunner H, Held K, et al. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. Neuropsychopharmacology. 2006;31(4):832–844. DOI: https://doi.org/10.1038/sj.npp.1300923
13. Thompson W, Quay TAW, Rojas-Fernandez C, Farrell B, Bjerre LM. Atypical antipsychotics for insomnia: a systematic review. Sleep Med. 2016;22:13–17. DOI: https://doi.org/10.1016/j.sleep.2016.04.003
14. Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. Effectiveness of non-benzodiazepine hypnotics in

treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. BMJ. 2012;345:e8343. DOI: https://doi.org/10.1136/bmj.e8343

15. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders: a meta-analysis. J Gen Intern Med. 2005;20(12):1151–1158. DOI: https://doi.org/10.1111/j.1525-1497.2005.0243.x
16. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13(2):307–349. DOI: https://doi.org/10.5664/jcsm.6470
17. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26(6):675–700. DOI: https://doi.org/10.1111/jsr.12594
18. Espie CA, Inglis SJ, Harvey L. Predicting clinically significant response to cognitive behavior therapy for chronic insomnia in general medical practice: analysis of outcome data at 12 months posttreatment. J Consult Clin Psychol. 2001;69(1):58–66. DOI: https://doi.org/10.1037/0022-006X.69.1.58
19. Morin CM, Beaulieu-Bonneau S, Bélanger L, Ivers H, Sánchez Ortuño M, Vallières A, et al. Cognitive-behavior therapy singly and combined with medication for persistent insomnia: impact on psychological and daytime functioning. Behav Res Ther. 2016;87:109–116. DOI: https://doi.org/10.1016/j.brat.2016.09.002
20. Castronovo V, Galbiati A, Sforza M, Poletti M, Giarolli L, Kuo T, et al. Long-term clinical effect of group cognitive behavioral therapy for insomnia: a case series study. Sleep Med. 2018;47:54–59. DOI: https://doi.org/10.1016/j.sleep.2018.03.017