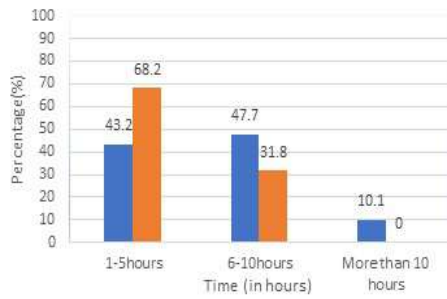
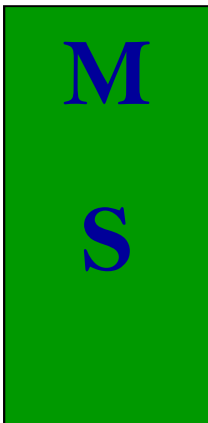
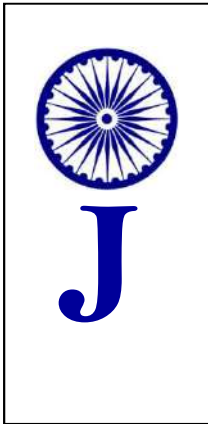


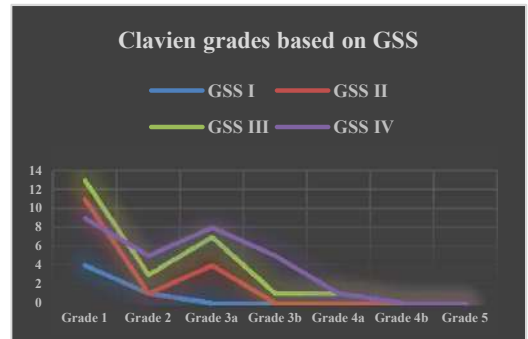


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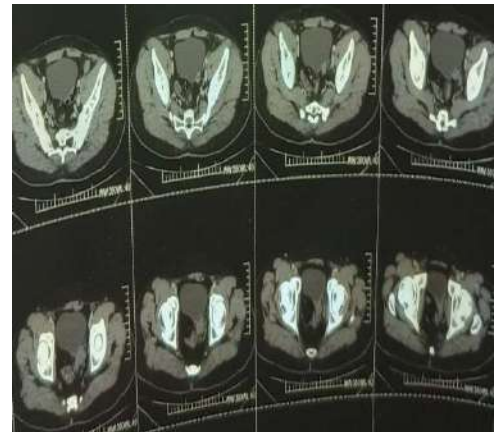
Time spent on Gadgets (N=44)



Distribution of complications based on Clavien grading system among GSS groups



Histopathology images showing endometrial



Serial axial sections of CT scan

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EDITORIAL

Moment of Convergence: Training of medical graduates in bridging the gap between evolving technology in Artificial Intelligence-Machine Learning (AI-ML) & health care education

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Artificial intelligence (AI) gives healthcare professionals ease when it comes to monitoring, understanding and analyzing needs and lifestyle patterns. The application of AI in recent years has effectively improved Cancer screening, Tuberculosis diagnosis, Diabetic retinopathy screening, Chronic Obstructive Pulmonary Disease (COPD) diagnosis and management. It can also aid in the early detection and prevention of diseases by capturing the vitals of patients. Natural language processing (NLP)-based virtual personal assistants can help in appointment scheduling, monitoring, and understanding the needs of patients.

By 2040, there will be a major impact of health on the global economy & almost 1/4th of the economy generated by Artificial Intelligence-Machine Learning (AI-ML) will be through the latter's health applications.

AI for "Precision medicine, sometimes known as 'personalized medicine' is an innovative approach & increasingly gaining momentum. It comprises tailoring disease prevention and treatment that takes into account differences in **people's genes, environments, and lifestyles. Health-related applications on AI-ML are far-reaching, such as:**

- a) Diagnostics, Devices- artificial retina, Imaging, histo-pathology, etc.
- b) AI for hospital administration
 1. Fraud detection and prevention
 2. Supply chain management

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3. Automated documentation and data entry
4. Readmission risk prediction
5. Clinical decision support system
6. Patient engagement and remote monitoring
7. Operational efficiency through automation

The involvement of tech companies in healthcare is consumer-like. This is part of a broader trend that is driving change in healthcare. Digital technology and data are putting more information in patients' hands, increasing their data needs.

Evolving technology - Generative and Transformative

Generative Technology

Generative technologies involve the creation of new content, data, or information. These systems are capable of producing outputs that are not explicitly programmed but are instead generated based on patterns and learning from data such as:

- Generative adversarial networks (GANs) - GANs consist of two neural networks, a generator, and a discriminator, that are trained together competitively. For example, DeepArt and This Person Does Not Exist use GANs to generate realistic images of non-existent people or artwork.
- Natural Language Generation (NLG) – NLG is a technology that converts structured data into human-readable text. For example, chatbots, news article generation,

and report writing systems often use NLG to create content.

- Style Transfer Algorithms - These algorithms can take the artistic style of one image and apply it to another, creating visually appealing compositions. For example, PRISMA is an app that uses neural networks to transform photos into artworks by emulating famous painting styles.

Transformative Technology

Transformative technologies bring about significant changes and innovations, often reshaping entire industries or aspects of society such as:

AI-ML involves the development of systems that can learn and make decisions without explicit programming. For example, predictive analytics, image and speech recognition, and autonomous vehicles are transformative applications of AI and ML.

Blockchain Technology - A decentralized and distributed ledger technology that ensures secure and transparent transactions without the need for intermediaries. For example, cryptocurrencies like Bitcoin and Ethereum use blockchain for secure and transparent financial transactions.

5G Technology - The fifth generation of wireless technology that provides faster and more reliable communication, enabling the Internet of Things (IoT) and other advanced applications. For example, enhanced mobile broadband, low-latency communications, and support for massive IoT connectivity are transformative aspects of 5G.

These examples illustrate the dynamic nature of technology, with generative technologies creating new content and transformative technologies reshaping how we interact with the world.

Healthcare education and practice ***Medical education – implementation, evaluation, and feedback***

The implementation of medical education involves the design and execution of educational programs for aspiring healthcare professionals. It encompasses the delivery of content, practical training, and the use of technology to enhance learning experiences, for example, virtual reality (VR) simulations, online learning platforms, etc.

Evaluation in medical education involves assessing the knowledge, skills, and competencies of students to ensure they meet the required standards. Various assessment methods are employed to measure the effectiveness of the educational process. For example, objective structured clinical examination (OSCE), computer-based testing (CBT), etc.

Feedback is an essential component of medical education, providing learners with information on their performance, identifying areas for improvement, and reinforcing positive aspects of their work for example, obtaining feedback from peers, instructors, and self-assessment to provide a holistic view of a learner's performance offers a well-rounded perspective and helps learners understand their strengths and weaknesses.

Health Administration

AI and ML have the potential to significantly enhance efficiency and reduce costs in hospital administration.

Predictive analysis for patient flow:

ML algorithms can analyze historical data to predict patient admissions, discharges, and transfers. This helps in optimizing bed utilization, reducing wait times, and improving overall patient flow (Figure 1).

It's important to note that integrating AI and ML into healthcare requires a deep understanding of both medical principles and technology. Therefore, combining a medical background with specialization in AI and ML can position a professional to contribute significantly to the intersection of medicine and technology.

Clinicians predict that technological literacy will be the most important capability for doctors and nurses in 10 years. However, there is currently a maze on whether could it be integrated. Many clinicians report on being overwhelmed by the sheer amount of data and information they are expected to take on. This has led to concerns that, increasing the role of health technology will take up more of their time rather than saving it. There is also widespread support amongst clinicians to overhaul education and training to ensure they can keep pace with the rapid rate of technological advances. Thus,

- 56% of clinicians globally predict they will base most of their clinical decisions using tools that utilize artificial intelligence.
- 69% report being overwhelmed with the current volume of data.
- 69% predict the widespread use of digital health technologies to become an even more challenging burden in the future.
- 83% believe training needs to be overhauled so they can keep pace with technological advancements [1].

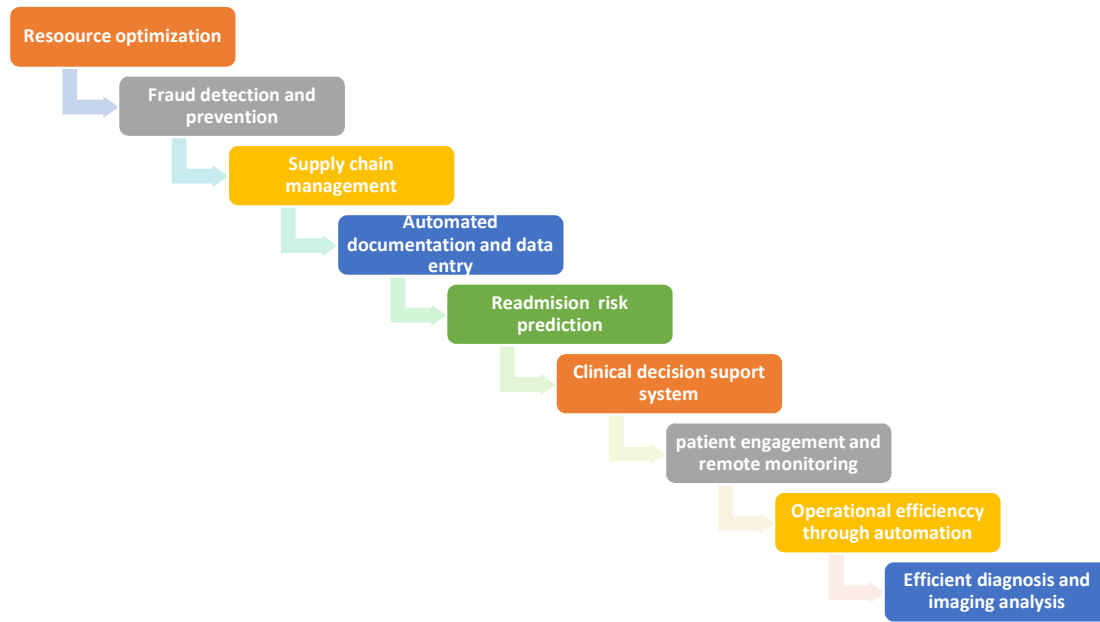


Figure 1. Machine Learning (ML) algorithm

Moment of convergence

There is increasing availability of multi-modal data (genomics, economic, demographic, clinical and phenotypic), coupled with technology innovations in mobile, internet of things (IoT), computing power and data security. It heralds a moment of convergence between healthcare and technology to fundamentally transform models of healthcare delivery through AI-augmented healthcare systems, in particular, Cloud Computing.

AI provides

- Real-time feedback,
- Accurate evaluation, and
- Can be used to monitor teaching quality.

Economic impact

In 2021, AI in the healthcare market was worth around 11 billion US dollars worldwide. It has been forecast that the global healthcare AI market will be worth

almost 188 billion US dollars by 2030, increasing at a compound annual growth rate of 37% from 2022 to 2030 [2]. Satya Nadella's statement aligns with the widespread recognition of AI's transformative impact on various industries, particularly in healthcare. The ability of AI to analyze large datasets, identify patterns, and assist in decision-making processes has made it a valuable tool for improving medical outcomes and optimizing healthcare systems [3].

The statement made by Tim Cook, the CEO of Apple, about healthcare being a business opportunity and its significance in the economy. However, it's not uncommon for tech leaders, including those from companies like Apple, to express interest in the intersection of technology and healthcare. The statement attributed to Google Health aligns with the general sentiment within the technology and healthcare industries regarding the transformative potential of AI. Google

Health, as part of Google's broader efforts in healthcare and life sciences, has been actively exploring ways in which AI and machine learning can contribute to advancements in medicine.

It is important to note, that, statements from companies like Google Health reflect their strategic vision and commitment to leveraging technology for the betterment of healthcare. The actual impact and implementation of AI in medicine may vary, and ongoing research and development are crucial for addressing challenges and ensuring the responsible and effective integration of AI technologies into healthcare practices.

Current limitation

A possible reason why AI has not yet been applied widely to practical teaching may be the disciplinary gap between developers and end-users.

The National Board of Examination in Medical Sciences (NBEMS) is examining ways on the modalities of convergence between AI-ML & training in medicine.

Conflict of interest

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

References

1. Lucy Goodchild, Adrian Mulligan, Elizabeth Shearing Green, Terri Mueller. Clinician of the Future-Report 2022. Elsevier. 2022. elsevier.com/connect/clinician-of-the-future
2. Arnab Basu. Enabling healthcare with Technology. PwC-BCC&I The Bengal Chamber. 2023 <https://www.pwc.in/assets/pdfs/healthcare/enabling-healthcare-with-technology.pdf>
3. Bajwa J, Munir U, Nori A, Williams B. Artificial intelligence in healthcare: transforming the practice of medicine. Future Health J. 2021; 8(2): e188-e194.



ORIGINAL ARTICLE

Hyperdiploid chromosomes in patients with B cell Acute lymphoblastic leukemia

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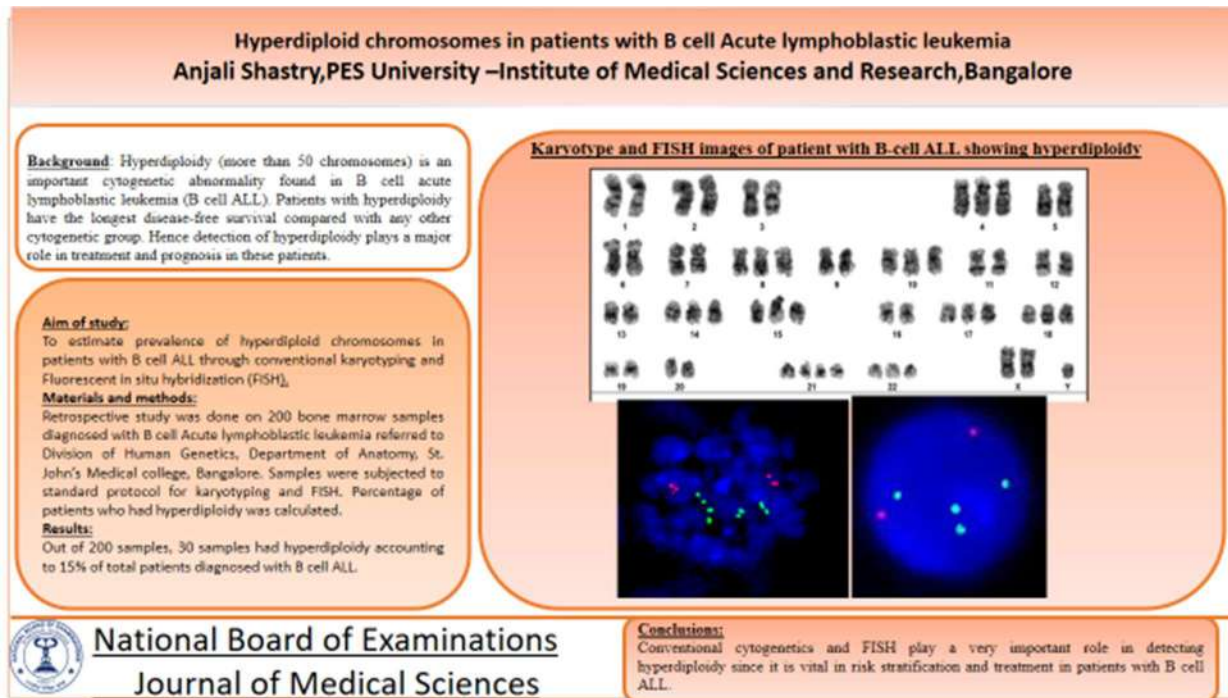
Abstract

Introduction: Hyperdiploidy (more than 50 chromosomes) is an important cytogenetic abnormality found in B cell acute lymphoblastic leukemia (B cell ALL). The presence of hyperdiploidy > 50 is considered to be a good prognostic marker since it has increased sensitivity to standard chemotherapy. Patients with hyperdiploidy have the longest disease-free survival compared with any other cytogenetic group. **Aim of study:** To estimate prevalence of hyperdiploid chromosomes in patients with B cell ALL through conventional karyotyping and Fluorescent in situ hybridization (FISH). **Materials and methods:** Retrospective study was done on 200 bone marrow samples diagnosed with B cell Acute lymphoblastic leukemia referred to Division of Human Genetics, Department of Anatomy, St. John's Medical college, Bangalore. Samples were subjected to standard protocol for karyotyping and FISH. Percentage of patients who had hyperdiploidy was calculated. **Results:** Out of 200 samples, 30 samples had hyperdiploidy accounting to 15% of total patients diagnosed with B cell ALL. **Conclusion:** Conventional cytogenetics and FISH play a very important role in detecting hyperdiploidy since it is vital in risk stratification and treatment in patients with B cell ALL.

Keywords: Karyotyping, hyperdiploidy, FISH, B cell ALL, chromosomes

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Graphical Abstract



Introduction

Hyperdiploidy is defined by the presence of 51-65 chromosomes, has been classified as a distinct subtype of B-Acute lymphoblastic leukemia (ALL) in the World Health Organization classification of tumors of hematopoietic and lymphoid tissues [1]. Most of B cell ALL with current chemotherapy will go for remission but relapse rate is higher in adults when compared to pediatric age group. Relapse usually occur within two years of chemotherapy. Hyperdiploidy is a common numerical chromosomal abnormality in ALL whereas structural chromosomal abnormalities like translocations [t(9;22),t(12;21),t(1;19)] and deletions are common in these patients. Hyperdiploidy involves addition of chromosomes whereas polyploidy refers to addition of new set of chromosomes. Commonly involved chromosomes in hyperdiploidy are 4, 6, 10,

14, 17, 18, 20, 21, and X [2]. Reason for hyperdiploidy is still debatable. The extra chromosomes may result from specific mutation or it can be vice versa stating that increase in chromosomes can cause proliferation of blasts due to increase or change in dosage of genes. According to literature, clinical outcome in patients with hyperdiploid karyotype is favorable due to increased sensitivity of these lymphoid cells to standard chemotherapy [3]. Hence hyperdiploidy is considered as good prognostic marker in patients with B cell ALL. When compared with other cytogenetic abnormalities, patients with hyperdiploidy have disease free survival for long period of time probably due to increased accumulation of polyglutamates which makes it more sensitive to chemotherapy. In present study, importance was laid on detection of hyperdiploidy through conventional

karyotyping and Fluorescent in situ hybridization (FISH).

Materials and methods

After obtaining ethical clearance, informed consent was taken from patient or his/her relatives before the test. Age group of patients ranged from one year to sixty years. There were 124 pediatric patients ranged from 1 year to 15years in which 78 were males and 46 were females. Age of adult patients ranged from 18 to 60 years. Out of 76 adult patients, 48 were males and 28 were females. After confirmation of B cell ALL through flow cytometry study, 200 samples were randomly selected from samples referred to Division of Human Genetics, Department of Anatomy, St. John’s Medical college, Bangalore. Study period was from October 2019 to March 2020. Statistical method used was calculation of percentage of patients showing positive result.

Culture was done on bone marrow samples without Phytohemagglutinin to prevent growth of normal cells and stimulate growth of cancer cells. Samples were incubated for one night and one day followed by harvesting. Cells were fixed on slide and

Giemsa banding was done for karyotyping. FISH procedure was done using Metasystem probes [4]. Once slides were ready, images were captured using florescent microscope. Probes used were t(9;22), t(12;21),11q23 breakapart.

Results

Out of 200 samples 30 showed hyperdiploidy. Out of 30 patients who had hyperdiploidy, 25 were pediatric ALL and remaining 5 were adult B cell ALL concluding that hyperdiploidy is more common in pediatric patients when compared to adult ALL. Also, commonly seen abnormalities were trisomy 6, trisomy 10, tetrasomy and trisomy of 21 and 22, gain/loss of X and Y chromosomes. Structural abnormalities seen in these patients along with hyperdiploidy were t(9;22) and t(1;19). In cases where conventional karyotyping could not be cultured, FISH showed increase in number of signals revealing hyperdiploid status of chromosomes. Out these 30 patients with positive results 20 were males and 10 were females which implies hyperdiploidy was more prevalent in males than females (Table 1).

Table 1: Showing number of patients showing only hyperdiploidy and other Chromosomal variants along with hyperdiploidy

Chromosomal variants	Number of patients
Only hyperdiploidy	23
Hyperdiploidy along with Translocation	6
Hyperdiploidy along with deletion	1

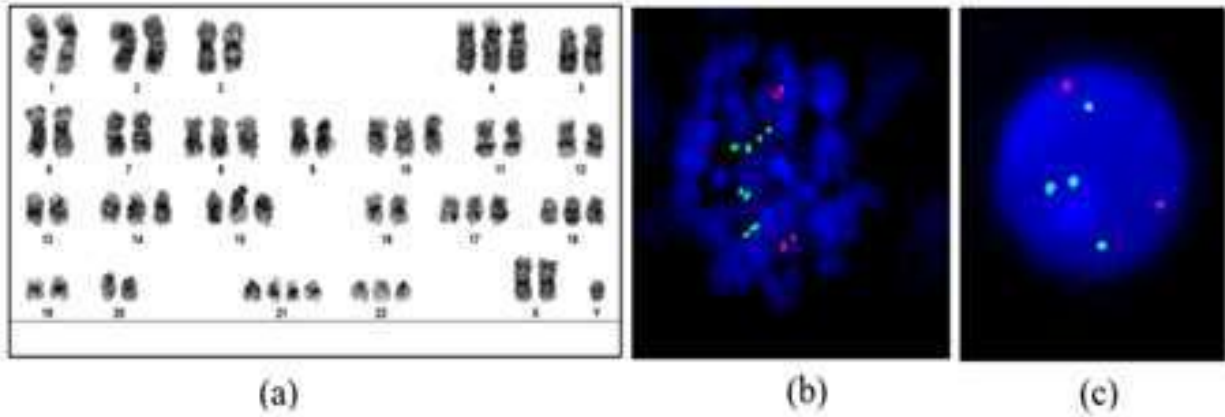


Figure 1. Hyperdiploid karyotype = 57,XXY,+4,+8,+10,+14,+15,+17,+18,+21,+21,+22 (a) Metaphase FISH (b) and interphase FISH (c) showing four green signals for chromosome 21.



Figure 2. Hyperdiploid karyotype of a male child with additional Y chromosome

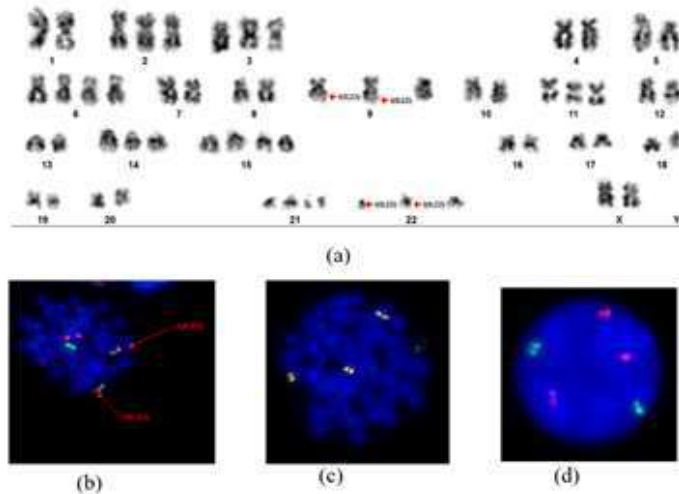


Figure 3. Karyotype of adult female showing Hyperdiploidy with positive double Philadelphia chromosome (a), Metaphase FISH showing positive BCR/ABL1 gene fusion (b), Metaphase FISH with three yellow signals for chromosome 11 at MLL breakpart (c), Interphase FISH with three signals for chromosome 21 (d)



Figure 4. Hyperdiploid karyotype of a male child with additional Y chromosome and gain of X Chromosome

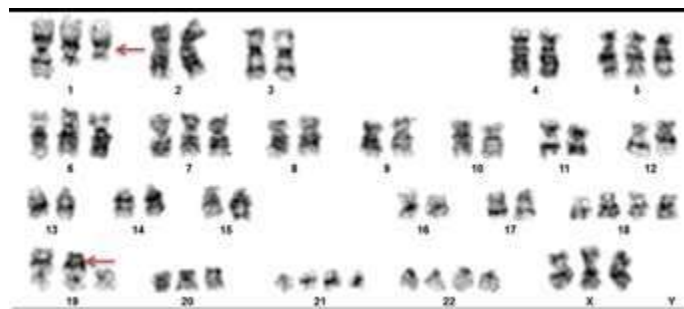


Figure 5. Hyperdiploid karyotype of a female child with double t(1;19).

Discussion

Conventional karyotyping is a gold standard technique in detection of chromosomal abnormalities in patients diagnosed with leukemia. Hyperdiploidy is a numerical chromosomal abnormality commonly seen in patients with acute lymphoblastic leukemia. In present study, hyperdiploidy was present in 15% of cases diagnosed with B cell ALL. In this FISH was an additional tool used to detect hyperdiploidy where karyotyping showed few numbers of spreads. Hyperdiploidy as a sole abnormality is considered as good prognostic marker. However when it is combined with structural abnormalities like t(9;22) the treatment outcome will differ. In present study, we observed that most of cases had only hyperdiploidy as seen in Figure 1.

In two cases there was addition (Figure 2) and loss of Y chromosome (Figure 4) which is rare finding in literature. This suggests increase and decrease in sex chromosomes are also seen in B cell ALL which should be taken into consideration during treatment. One case of adult ALL had double Philadelphia chromosome which might have a variable outcome (Figure 3). Even though t(1;19) is a common structural abnormality in B cell ALL, one of our cases had double t(1;19) (Figure 5) which is a rare finding. This shows that along with increase in normal chromosomes there is tendency for cancer cells to multiply translocated chromosomes as well during mitotic event. This also increases gene dosage which might call for alteration in chemotherapy. But in general, most of studies showed good response to

chemotherapy in patients who had hyperdiploid chromosomes.

According to previous studies, hyperdiploid karyotype was present in 23-42% of newly diagnosed cases of ALL [5,6,7]. Onordera et al discussed mechanism of formation of hyperdiploid karyotype. They used restriction fragment length polymorphism in 15 patients with hyperdiploidy to understand pathophysiology. They concluded that it happens due to sudden gain in number of multiple chromosomes [2].

In a study done by Kaspers et al., on 74 patients, 22% had hyperdiploid ALL. They observed that number of cells in S phase of cell division are more in hyperdiploid patients when compared to non hyperdiploid cases. They also studied drug sensitivity of hyperdiploid cells towards standard chemotherapeutic agents. They concluded that patients with hyperdiploidy had increased sensitivity towards antimetabolites, glucocorticoids and l-asparaginase when compared to non hyperdiploid patients probably hinting towards more number of cells in S phase [3].

Chikako Ito et al., stated that hyperdiploid cells have marked intensity to undergo apoptosis since they rapidly died in stromal cultures. They concluded that pathogenesis of hyperdiploid ALL could involve molecular defects leading to both DNA content abnormalities and a propensity to undergo apoptosis [8].

In a review done by Barbara Gibbons, author stated that presence of hyperdiploidy is dependent on age of patient. As age of patient advances chances of hyperdiploidy decreases. Also they mentioned

hyperdiploidy is a secondary change and structural abnormalities like translocations are primary event which will lead to increase in number of chromosomes [9].

Anthony V. Moorman et al., did a study on ALL patients in which 32% had hyperdiploidy karyotype. In 8 cases along with hyperdiploidy additional structural abnormalities were present. Number of associated structural abnormalities with hyperdiploid karyotype was lower as observed in our study[10].

Ritterbach et al., used FISH as a quick screening method for identification of hyperdiploid karyotypes. They specifically used DNA probes for chromosomes 6, 10, 17, and 18. 28.8% patients had high hyperdiploid karyotype. FISH is a quick screening technique but using DNA probes for all chromosomes is not cost effective also it fails to detect any structural abnormalities if critical region /fusion probes are not used. [11]

Limitation of our study includes there is no correlation of our results with treatment, prognosis relapse of patients whom we have included in our study. Also, further studies are required to understand these abnormalities at molecular level by next generation sequencing.

Conclusion

We conclude that karyotyping and FISH are useful diagnostic tools in detecting hyperdiploidy in patients with B cell ALL. Further molecular studies need to be done to understand pathogenesis as well as reason for increased sensitivity of leukemic cells to chemotherapy.

Conflicts of interest

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

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References

1. Borowitz M, Chan J, Downing J, LeBeau M, Arber D. B-lymphoblastic Leukemia/Lymphoma with Recurrent Genetic Abnormalities. In: Swerdlow S, Campo E, Harris N, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised, 4th edn. Lyon: International Agency for Research on Cancer (IARC); 2017.
2. Onodera N, McCabe NR, Rubin CM. Formation of a hyperdiploid karyotype in childhood acute lymphoblastic leukemia. *Blood*. 1992 Jul 1;80(1):203-8.
3. Kaspers GJ, Smets LA, Pieters R, Van Zantwijk CH, Van Wering ER, Veerman AJ. Favorable prognosis of hyperdiploid common acute lymphoblastic leukemia may be explained by sensitivity to antimetabolites and other drugs: results of an in vitro study. *Blood*. 1995 Feb 1;85(3):751-6.
4. Marilyn S. Arsham, Margaret J. Barch, Helen J. Lawce. The AGT Cytogenetics Laboratory Manual. Hoboken, New Jersey: Wiley-Blackwell, 2017.
5. Kaneko Y, Rowley JD, Variakojis D, Chilcote RR, Check I, Sakurai M: Correlation of karyotype with clinical features in acute lymphoblastic leukemia. *Cancer Res* 42:2918,1982.
6. Heerema NA, Palmer GG, Baehner RL Karyotypic and clinical findings in a consecutive series of children with acute lymphoblastic leukemia. *Cancer Genet Cytogenet* 17:165, 1985.
7. Fletcher JA, Kimball VM, Lynch E, Donnelly M, Pavelka K, Galber RD, Tantravahi R, Sallan SE: Prognostic implications of cytogenetic studies in an intensively treated group of children with acute lymphoblastic leukemia. *Blood* 74:2130,1989.
8. Ito C, Kumagai M, Manabe A, Coustan-Smith E, Raimondi SC, Behm FG, Murti KG, Rubnitz JE, Pui CH, Campana D. Hyperdiploid acute lymphoblastic leukemia with 51 to 65 chromosomes: a distinct biological entity with a marked propensity to undergo apoptosis. *Blood*. 1999 Jan 1;93(1):315-20.
9. Gibbons B. High hyperdiploid acute lymphoblastic leukaemia. *Atlas Genet Cytogenet Oncol Haematol*. 1999; 3(3):145-146.
10. Moorman AV, Richards SM, Martineau M, Cheung KL, Robinson HM, Jalali GR, Broadfield ZJ, Harris RL, Taylor KE, Gibson BE, Hann IM, Hill FG, Kinsey SE, Eden TO, Mitchell CD, Harrison CJ; United Kingdom Medical Research Council's Childhood

- Leukemia Working Party. Outcome heterogeneity in childhood high-hyperdiploid acute lymphoblastic leukemia. *Blood*. 2003 Oct 15;102(8):2756-62.
11. Ritterbach J, Hiddemann W, Beck JD, Schrappe M, Janka-Schaub G, Ludwig WD, Harbott J, Lampert F. Detection of hyperdiploid karyotypes (>50 chromosomes) in childhood acute lymphoblastic leukemia (ALL) using fluorescence in situ hybridization (FISH). *Leukemia*. 1998 Mar;12(3):427-33.



ORIGINAL ARTICLE

A study on challenges and perceptions of schoolteachers towards online classes during COVID 19 pandemic

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Abstract

Introduction: India, with its massive population, witnessed a surge in COVID-19 cases leading to a nationwide lockdown, profoundly affecting the education sector. The closure of schools for an extended period exacerbated the learning gap among students, prompting a swift transition to online education. This abrupt shift posed challenges for teachers unfamiliar with e-learning methods, necessitating a paradigm shift in teaching approaches. While virtual classrooms introduced logistical hurdles, they also spurred innovations like state-run education TV channels and doorstep education schemes. **Materials and Methods:** Ethical clearance was obtained, and a mixed-method survey was conducted among government and private school teachers in Western Tamil Nadu, using online platforms. The questionnaire covered teaching styles, online teaching difficulties, impact on physical well-being, gadget usage, and more. Data from 44 participants were analyzed using SPSS version 27, employing descriptive statistics, Chi-square tests, and Mann-Whitney U tests. **Results:** Of the 44 participants, 84.1% were females, and 61.4% were above 40 years. A majority (95.4%) taught in private schools, and 70.4% taught state board syllabus. While 72.7% spent 0-2 hours daily on online classes, 88.6% preferred live online classes. Network issues (75.7%) were the primary difficulty faced, and 56.8% felt the need for technology training. Health-wise, 47.7% spent 6-10 hours on gadgets, and 90.9% invested in gadgets for online classes. **Conclusion:** The study identified age-associated perceptions in schoolteachers regarding online teaching challenges but found no significant association between age and health issues due to increased screen time.

Keywords: School Teachers, COVID 19, Online Teaching

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Graphical Abstract

Title: A study on challenges and perceptions of schoolteachers towards online classes during COVID 19 pandemic.

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Background: India, with its massive population, witnessed a surge in COVID-19 cases leading to a nationwide lockdown, profoundly affecting the education sector. The closure of schools for an extended period exacerbated the learning gap among students, prompting a swift transition to online education. This abrupt shift posed challenges for teachers unfamiliar with e-learning methods, necessitating a paradigm shift in teaching approaches. While virtual classrooms introduced logistical hurdles, they also spurred innovations like state-run education TV channels and doorstep education schemes. The study focuses on the challenges faced by schoolteachers in Western Tamil Nadu during online teaching amid the COVID-19 pandemic.

Materials and methods: Ethical clearance was obtained, and a mixed-method survey was conducted among government and private school teachers in Western Tamil Nadu, using online platforms. The questionnaire covered teaching styles, online teaching difficulties, impact on physical well-being, gadget usage, and more. Data from 44 participants were analyzed using SPSS version 27, employing descriptive statistics, Chi-square tests, and Mann-Whitney U tests.

Table depicting various perceptions of online teaching among young vs middle aged schoolteachers

Perceptions	All teachers (N=44)	Young schoolteachers (Age less than 40 years) (n=27)	Middle aged schoolteachers (Age more than 40 years) (n=17)	P value (Fishing Exact Wilcoxon U test)
It's difficult to make content generated in online teaching	0.0	0.0	0.0	0.100
They students find it difficult to sit and concentrate	0.0	0.0	0.0	0.100
They spend more time in preparation for online class compared to traditional classroom teaching	0.0	0.0	0.0	0.100
Most students had no initial difficulty to cope up with online class	0.0	0.0	0.0	0.100
Students can manage the online class effectively nowadays	0.0	0.0	0.0	0.100
It's difficult to monitor each student while taking online classes	0.0	0.0	0.0	0.100
My workload has increased due to online teaching	0.0	0.0	0.0	0.100
The stress due to children has increased a lot nowadays	0.0	0.0	0.0	0.100
Online teaching program is not as effective as classroom teaching	0.0	0.0	0.0	0.100
Unable to supervise and guide the activities and assignments done by the students	0.0	0.0	0.0	0.100
Facing difficulty in managing technology	0.0	0.0	0.0	0.100

Conclusion: The study concluded that perception factors like, "students faced initial difficulty to cope up with online teaching", "workload of teachers were increased upon implementation of online teaching practices", "online teaching program is less effective when compared to traditional classroom teaching" and "inability to supervise and guide the activities and assignments done by the students" were associated with the age of schoolteachers. However, there was no association with the age of the teachers and the health issues faced due to increased screen time like backache, eye strain, neck pain etc.



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Introduction

India, being the most populous country in the world, faced exponential growth in the number of COVID 19 cases during the pandemic. The government of India, announced a country wide lockdown for 68 days [1] in 4 phases, starting from March 2020 [1]. On 16th March 2020, the union government of India declared countrywide lockdown of schools [2]. It was a crucial time for the school education sector as the lockdown paralyzed the usual school going culture by confining students to their homes. This led to a widening of the learning gap among students. The country faced a major crisis in the educational sector as the schools remained closed beyond a year. This has impacted 99 percentage of country's student population [3].

Owing to the unprecedented closures, with a view to completing the academic year, the educational ministry made the most

striking change overnight by converting traditional face-to-face teacher-student interaction by e-learning. The pandemic has made online education a norm in formal education across the country. However, this adaptation did not simply mean digitizing content, but required teachers to rethink their subjects and create dynamic materials that stimulated interest in the subject through distance learning. Teachers realized to keep students virtually engaged would need a different approach. They also realized that they would lose the personal connection with students that comes from face-to-face interaction. The virtual learning environment also presented clear logistical challenges. This methodical replacement was not an easy nut to crack through. It created unprecedented challenges in getting accustomed to the technologies [4].

On the other hand, the virtual classroom model has stimulated many other

innovations within the educational sector. Every state across the nation came out with innovative approaches in learning. In Tamil Nadu, approaches like state-run “Kalvi Tholaikatchi” (education TV channel), “Illam Thedi Kalvi” scheme (Education at doorsteps) etc were initiated in support of education continuity. Educational institutions reinvented various virtual teaching methods in record time.

School teachers are the custodians of the future generations, and act as mentors to nurture students’ academic growth. COVID-19 has required states to urgently step-up in preparing schoolteachers to adapt to unfamiliar ways of teaching and new modes of delivery in which they had no prior experience [5]. However, many of these schoolteachers in India are hardly exposed to e-learning approaches prior to this pandemic nor were given any prior training. Teachers have to face various challenges and difficulties in performing their role efficiently according to the modern teaching practices which includes, usage of various online teaching platforms (like zoom, Microsoft teams), making teaching materials using power point, conducting exams online, taking attendance virtually, assessing the performance of students via online platforms etc. The current study investigated the challenges faced by the schoolteachers in Western Tamilnadu during delivering online teaching during the COVID 19 pandemic.

Methods

A quantitative and qualitative survey was conducted across government and private school teachers in Western Tamil Nadu between August and September 2020.

Owing to COVID restrictions, the data collection was made in the form of an online survey. The survey tool was created using google forms and disseminated via social platforms. A total of 43 responses were received. A questionnaire for teachers was developed consisting of 47 items covering a variety of subjects like, teaching styles, difficulties and challenges faced during teaching online, influence of online teaching on physical well-being, purchase and utilization of gadgets, etc. Data was entered into Microsoft excel and all the statistical analysis was performed using SPSS version 27. Categorical variables have been summarized in the form of frequencies and percentages and continuous variables summarized as median with interquartile range. Chi square test was used to check association for health issues faced due to increased screen time and the age of teacher. Results were expressed as crude and adjusted odds ratio (OR) with 95% confidence intervals. A p value < 0.05 was considered statistically significant.

Mann Whitney U test was used to check for statistically significant difference in various perception of online teaching among different age group.

Results

A total of 44 participants participated in the study. Table 1 depicts that, among all the participants, 37 (84.1%) of the participants were females and the rest 7 (15.9%) were males. 27 (61.4%) of the participants were more than 40 years of age and 17 (38.6%) were less than 40 years of age. 30 (69.8%) of the teachers were taking classes for elementary classes, 9 (20.9%)

were teaching secondary classes and the rest 4 (9.3%) were taking classes for both elementary and secondary classes. 42(95.4%) teachers were employed in private schools and 2 (4.6%) teachers were employed in government schools. 31 (70.4%) were teaching state board syllabus, 7 (15.9%) were teaching CBSE syllabus, 4 (9.1%) were teaching matriculation syllabus and 2 (4.6%)

were teaching ICSE syllabus. With respect to years of teaching experience, 22 (50%) were teaching for 10 years or less, 15 (34.1%) were teaching from 11-20 years and 7 (15.9%) were teaching for 21-30 years. 36 (81.8%) were aware of the technology and 8 (18.2%) had limited or no awareness about technology.

Table 1: Demographic profile of respondents (N=44)

Demographic profile	Sub classification	Number (n)	Proportion (%)
Gender	Male	7	15.9
	Female	37	84.1
Age group (in years)	Less than 40	17	38.6
	More than 40	27	61.4
Taking classes for	Elementary	30	69.8
	Secondary	9	20.9
	Both	4	9.3
Type of institution	Government	2	4.6
	Private	42	95.4
Syllabus	State board	31	70.4
	CBSE	7	15.9
	Matriculation	4	9.1
	ICSE	2	4.6
Years of teaching experience	Up to 10 years	22	50
	11-20 years	15	34.1
	21-30 years	7	15.9
Awareness about technology	Yes	36	81.8
	No	8	18.2

Table 2 depicts that, 37(84.1%) had no prior online teaching experience and 7 (15.9%) had prior online teaching experience. 31 (70.4%) were taking online classes for more than 6 months and 13 (29.6%) were taking online classes for less than 6 months. 32 (72.7%) of the teachers spend an average of 0-2 hours in online classes every day, 7 (15.9%) spend 2-4 hours every day and the rest 5 (11.4%) spend more

than 4 hours per day. When questioned about the preferred/comfortable method of e-learning, 33 (75%) said live online classes, 9 (20.5%) preferred sharing of teaching materials via WhatsApp and 2 (4.5%) preferred to send the recorded class via email. 39 (88.6%) conducted online classes from their home and 5 (11.4%) conducted online classes from office. Among the teachers who conducted online classes from home, 62.5%

had a dedicated/ favorable environment for conducting online classes and 37.5% did not have a proper workspace for conducting online classes from home. Of the 44 participants, 37 (86%) faced some or the other difficulty in teaching online and 7 (14%) did not face any difficulty. Among the 37 participants who faced difficulty, 75.7%

faced network issues and 8.1% faced electricity fluctuations, 8.1% faced difficulty to grab students' attention and 8.1% faced difficulty in making teaching materials. 25 (56.8%) of the teachers felt the need for training to improve their knowledge about technology and 19 (43.2%) of the teachers didn't feel the need for training.

Table 2: Current practices and difficulties faced during online teaching during COVID 19

Practices and difficulties faced	Sub classification	Number (n)	Proportion (%)
Online teaching experience prior to COVID	Yes	7	15.9
	No	37	84.1
Since how long you are taking online classes	6 months or less	13	29.6
	More than 6 months	31	70.4
Duration of online session per day	0-2hours	32	72.7
	2-4hours	7	15.9
	More than 4 hours	5	11.4
Method of teaching used for e-learning	Live online classes	33	75.0
	Sharing via WhatsApp groups	9	20.5
	E-mailing recorded lectures	2	4.5
Place from which online class was taken	Home	39	88.6
	Office	5	11.4
Dedicated workspace at home (n=39)	Yes	24	61.5
	No	15	35.5
Favorable environment for teaching (n=24)	Yes	15	62.5
	No	9	37.5
Difficulties faced in teaching online	Yes	37	86.0
	No	6	14.0
If yes, difficulties faced* (n=37)	Network issues	28	75.7
	Electricity fluctuations	3	8.1
	Difficulty to grab students' attention	3	8.1
	Difficulty in making teaching materials	3	8.1
Requirement of training to improve online teaching skills	Yes	25	56.8
	No	19	43.2

Figure 1 depicts that, 21 (47.7%) of the teachers spend 6-10 hours on gadgets, 19 (43.2) spend 1-5 hours on gadgets and the rest 4 (10.1%) spend more than 10 hours on

gadgets every day. 30 (68.2%) of the teachers spent up to 5 hours on gadgets for educational purposes and 14 (31.8%) spent more than 5 hours on gadgets for educational purposes.

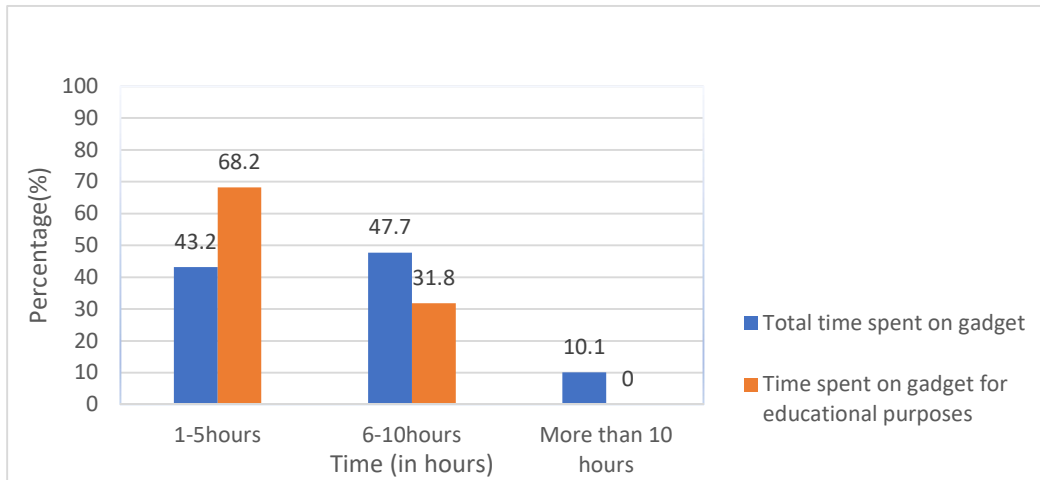


Figure 1. Time spent on Gadgets (N=44)

The data states that 40 (90.9%) of the teachers invested on gadgets for taking online classes and 4 (9.1%) of teachers did not invest on gadgets. Figure 2 depicts that, among the teachers who purchased gadgets,

33.7% invested in Wi-Fi/modem/internet connection, 25.8% invested in mobile/tablets, another 25.8% invested in laptop/desktop and 14.7% invested in furniture like chair/desk/table.

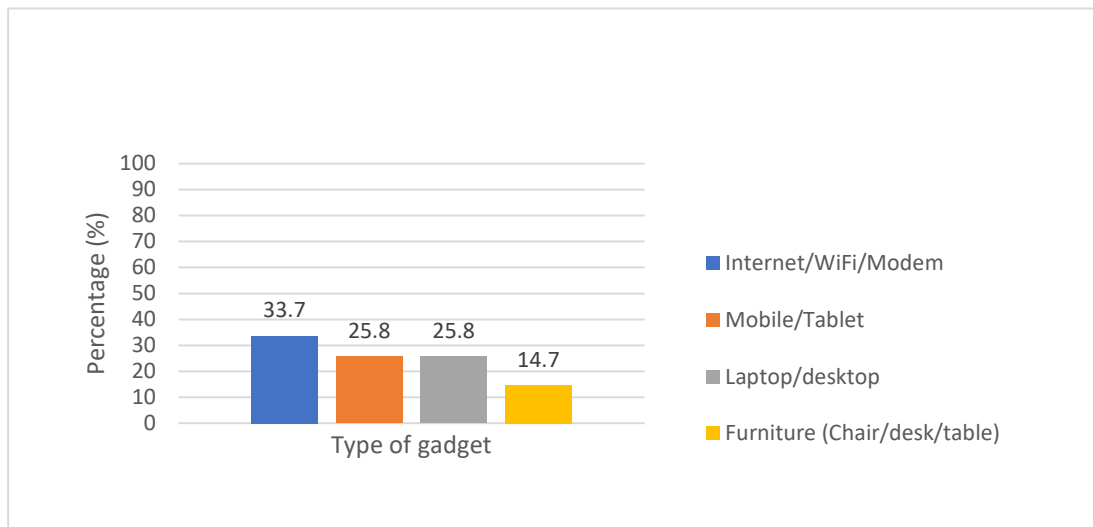


Figure 2. Gadgets purchased by schoolteachers for online teaching

Table 3 depicts the median score for various perceptions about online teaching experiences among young and middle-aged schoolteachers. On using Mann Whitney U

test, there was a statistically significant difference in perceptions like, “most students faced initial difficulty to cope up with online teaching”, “workload of teachers were

increased upon implementation of online teaching practices”, “online teaching program is less effective when compared to traditional classroom teaching”, “unable to

supervise and guide the activities and assignments done by the students” among young schoolteachers and middle aged schoolteachers.

Table 3: Various perceptions of online teaching among young vs middle aged schoolteachers

Perceptions	All teachers (N=44)	Young schoolteachers (Age less than 40 years) (n=17)	Middle aged schoolteachers (Age more than 40 years) (n=27)	P value (Using Mann Whitney U test)
	Median Score (out of 5)			
It's difficult to make students get involved in online teaching	4.0	5.0	4.0	0.094
Many students find it difficult to sit and concentrate	4.0	5.0	4.0	0.164
Must spend more time in preparation for online class compared to traditional classroom teaching	5.0	5.0	5.0	0.887
Most students had an initial difficulty to cope up with online classes	4.5	5.0	4.0	0.004
Students can manage the online classes effectively nowadays	4.0	4.0	4.0	0.959
It's difficult to monitor each student while taking online sessions	5.0	5.0	5.0	0.786
My workload has increased due to online teaching	4.5	5.0	4.0	0.041
The screen time for children has increased a lot nowadays	5.0	5.0	5.0	0.090
Online teaching program is not as effective as classroom teaching	4.0	5.0	4.0	0.018
Unable to supervise and guide the activities and assignments which students do	4.0	5.0	4.0	0.038
Facing difficulty in managing technology	4.0	4.0	4.0	0.959

Table 4 depicts that the odds of having eye strain were 1.1 time more likely (OR 1.143; CI 0.335-3.904) among the middle-aged schoolteacher however the results were not statistically significant (p

value 1.000). Other health issues like anxiety, backache, neck pain, fatigue, dry eye was not statistically significant with the age of schoolteachers.

Table 4: Association between health issues faced due to increased screen time with schoolteachers (N=45)

Health issues faced due to increased screen time*	All teachers		Teachers aged less than 40		Teachers aged more than 40		OR with IQR	P value
	Number (n=120)	Percentage	Number (n=49)	Percentage	Number (n=71)	Percentage		
Anxiety	38	31.7	15	30.6	23	32.4	0.767 (0.124-4.721)	0.774
Backache	28	23.3	12	24.5	16	22.5	0.606 (0.166-2.213)	0.531
Eye strain	19	15.8	7	14.3	12	16.9	1.143 (0.335-3.904)	1.000
Neck pain	15	12.5	6	12.2	9	12.7	0.917 (0.256-3.286)	1.000
Fatigue	11	9.2	5	10.2	6	8.5	0.686 (0.172-2.733)	0.724
Dry eye	9	7.5	4	8.2	5	7.0	0.739 (0.168-3.254)	0.716

*Multiple responses

Discussion

The purpose of this study was to look at the challenges and perceptions faced by the elementary and secondary schoolteachers employed in both the public and private sectors. According to the findings, various health issues like anxiety, back pain and eyestrain were reported by teachers, but the results were not statistically significant with

age. Perceptions on factors like supervising the students, workload of teachers, effectiveness of online teaching, students coping up online teaching strategy showed a statistically significant result with the age of the teachers (p value <0.05).

The present study highlighted that more than 3/4th of the schoolteachers had no prior online teaching experiences before

COVID 19 pandemic and had poor awareness about technology. More than 80% of the schoolteachers faced difficulty in teaching online and more than half of teachers felt the need for training on online teaching practices before commencement of online classes. All the teachers faced some or the other difficulty during online sessions and the most common one was reported as network/internet connectivity issues followed by difficulty in grabbing students' attention and difficulty in preparing the class materials etc.

About 90% had to buy additional gadgets required for the smooth conduct of online classes and the most common gadget purchased was mobile/tablets and laptop/desktop. Teachers adopted various methods to keep students active during the online sessions, the most common one was calling out names in the middle of class and asking questions followed by projecting MCQs in the middle of each section. About 70% of the teachers felt that the students were not as attentive during online classes in comparison to the traditional teaching method. Most of the teachers felt that the academic performance dropped drastically after introducing online teaching and more than 60% teachers felt that the attendance could not be assessed properly in online teaching classes. The most common method of assessing attendance was by downloading the students name list or giving attendance as per the logged in names. About 3/4th of them spent up to 2 hours every day on online teaching.

In the present study, the prevalence of eye strain was 15.8% among teachers and the prevalence was more in teachers aged more

than 40 years. However, the results were not statistically significant (OR 1.143; p value 1.000). In a study done by *Pratyusha Ganne et al* in 2020(6) at India, prevalence of eye strain was reported to be higher among students taking online classes compared to the general public (50.6% vs 33.2%; $\chi^2 = 22.5$, $df = 1$, $p < .0001$). The overall anxiety level in schoolteachers was 31.7% and the prevalence was much higher among teachers aged more than 40 years of age. In a study done by Sowmini et al (2022) (7) in south India on psychological effects of schoolteachers upon reopening schools after COVID, the prevalence of anxiety was 45.2%. This contrasts with the present study, where the prevalence of anxiety was 31.7% among teachers while taking online classes. In a study done by *Tim Pressley et al* (2021) on Teachers stress and anxiety during COVID pandemic [8] it was reported that the stress level increased among teachers in an online teaching environment and the results were statistically significant (P value <0.001) . In the present study, the prevalence of backache was 23.3% (the prevalence was higher among teachers aged less than 40 years) and the prevalence of neck pain was 12.5%. However, the results were not statistically significant. Whereas in a study done by *Alka Pawalia et al* (2022) on the prevalence of musculoskeletal pain and discomfort due to online teaching and learning methods during lockdown in students and teachers [9], 60.8% of the participants experienced some form of musculoskeletal pain out of which 33.4% experienced backpain and 51.3% experiences neck pain.

In a study done by *Sowmini et al* (2022) (10) on perception of teachers towards COVID appropriate behavior for school children in south India, about 30% of the teachers disagreed with the idea of conducting online teaching classes. This result is in line with the present study, where majority of the teachers reported online teaching program as less effective when compared to the offline/ face-to-face teaching and the results showed statistically significant association with age of teachers (P value 0.018)

In a survey done by UNICEF India in 2020, [12] on the rapid assessment of learning during school closures in the context of COVID, 12% of the teachers consider a lack of e-skills. This was in contrast to the present study where 25 (56.8%) teachers, felt the need for conducting training to improve online teaching skills. In the same study, 7% of the teachers reported an additional expenditure as a barrier to online teaching. This contrasted with the present study where (40) 90.9% of the teachers reported to have invested additionally on gadgets for online teaching. The higher prevalence in the present study could be due to the variation in the study setting.

In a study done by *B.V. Rao et al* (2022) [11] on dry eye survey among schoolteachers and students during COVID 19 lockdown, the total screen time was 4-hours for 33.9% of the participants and 2-4 hours for 32.3% of the participants. Whereas in the present study, 47.2% of the teachers spent an average of 6-10 hours on gadgets and 43.2% spend an average of 1-5 hours on gadgets.

In the present study, 21(47.7%) of the teachers spend 6-10 hours on gadgets, 19(43.2%) spend 1-5 hours on gadgets and the rest 4(10.1%) spend more than 10 hours on gadgets every day. 30 (68.2%) of the teachers spent up to 5 hours on gadgets for educational purposes and 14 (31.8%) spent more than 5 hours on gadgets for educational purposes. In a study done by *B.V.Rao et al* (2022) (11) on dry eye survey among schoolteachers and students during COVID 19 lockdown, 60.7% of the participants faced dry eye and the symptom score was worse among the teachers. Whereas in the present study, the prevalence of dry eye among schoolteachers was 7.5%.

In a survey done by UNICEF India in 2020, [12] on the rapid assessment of learning during school closures in the context of COVID, 67% of the teachers perceive students to have fallen behind in their overall progress compared to where they should be pre-COVID if schools were open. This is in line with the perception of schoolteachers of the current study, where the teachers feel that “students find it difficult to cope up with online teaching”, “online teaching program is not as effective as the classroom teaching” and the result is statistically significant with a p value of 0.004 and 0.018 respectively.

In a survey done by UNICEF India in 2020, [12] on the rapid assessment of learning during school closures in the context of COVID, top challenges faced by teachers are the inability to reach students (75 per cent) and lack of class discipline (51 per cent). Whereas perceptions in the present study were, “its difficult to make students get involved in online teaching” and “its difficult to monitor each student while taking online

classes”. However, the results are not statistically significant.

Conclusion

The study concluded that perception factors like, “students faced initial difficulty to cope up with online teaching”, “workload of teachers were increased upon implementation of online teaching practices”, “online teaching program is less effective when compared to traditional classroom teaching” and “inability to supervise and guide the activities and assignments done by the students “were associated with the age of schoolteachers. However, there was no association with the age of the teachers and the health issues faced due to increased screen time like backache, eye strain, neck pain etc.

Since the current study was confined to Western Tamil Nadu, further studies should be conducted among schoolteachers across various states of India to gain a broader and deeper understanding of the online teaching and its effect on the educational system in a developing country like India.

Acknowledgement

We acknowledge all the schools and the participants for the cooperation provided to conduct the study.

Ethical Approval

Ethical clearance for the study was obtained from the Institutional Ethics Committee (IHEC/34/2020) before commencement of the study.

Conflict of interest

None declared.

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Nil

Data availability

The data of the present study is available with the corresponding author and will be shared by the corresponding author on request.

References

1. Ghosh A, Nundy S, Mallick TK. How India is dealing with COVID-19 pandemic. *Sens Int.* 2020 Jan 1;1:100021.
2. Ravi RC. Lockdown of colleges and universities due to COVID-19: Any impact on the educational system in India? *J Educ Health Promot.* 2020 Aug 31;9:209.
3. sg_policy_brief_COVID-19_and_education_august_2020.pdf. Available from: https://www.un.org/development/desa/dspd/wp-content/uploads/sites/22/2020/08/sg_policy_brief_COVID-19_and_education_august_2020.pdf
4. COVID-19 - Higher Education and student related challenges | Bevan Brittan LLP. Available from: <https://www.bevanbrittan.com/insights/articles/2020/covid-19-higher-education-and-student-related-challenges/>
5. Factors influencing university teachers’ use of a mobile technology-enhanced teaching (MTT) platform. DOI: 10.1007/s11423-021-10032-5

6. Ganne P, Najeeb S, Chaitanya G, Sharma A, Krishnappa NC. Digital Eye Strain Epidemic amid COVID-19 Pandemic – A Cross-sectional Survey. *Ophthalmic Epidemiol.* 2021 Jul 4;28(4):285–92.
7. Kamath SP, Mithra P, K J, Kulkarni V, Joshi J, Kamath P, et al. Returning to work at school during the COVID -19 pandemic, is it stressful for schoolteachers? Assessment of immediate psychological effects: a cross sectional study. *F1000Research.* 2022;11:751.
8. Pressley T, Ha C, Learn E. Teacher stress and anxiety during COVID-19: An empirical study. *Sch Psychol.* 2021 Sep;36(5):367–76.
9. Pawalia A, Joshi S, Preeti, Yadav VS. Prevalence of Musculoskeletal Pain and Discomfort Due to Online Teaching and Learning Methods During Lockdown in Students and Teachers: Outcomes of the New Normal. *J Musculoskelet Res* Available from: <https://www.worldscientific.com/worldscinet/jmr>
10. Kamath SP, Mithra P, Joshi J, Kamath P, Unnikrishnan B, K. J, et al. Perceptions of teachers towards COVID appropriate behaviors for school children in coastal South India. *Curr Psychol.* 2022 Nov 1;41(11):8112–22.
11. Rao BV, Bandopadhyay S, Sharma VK, Mishra A, Ambiya V, Sharma N. Dry eye disease survey among schoolteachers and children using visual display terminals during COVID-19 lockdown-CODE study (Covid and dry eye study). *Med J Armed Forces India.* 2022 Aug 1. Available from: <https://www.sciencedirect.com/science/article/pii/S0377123722000648>
12. Report on rapid assessment of learning during school closures in context of COVID-19.pdf. Available from: <https://www.unicef.org/india/media/6121/file/Report%20on%20rapid%20assessment%20of%20learning%20during%20school%20closures%20in%20context%20of%20COVID-19.pdf>



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ORIGINAL ARTICLE

Guy's stone score as a predictor for stone free rate and complications related to PCNL – A retrospective study

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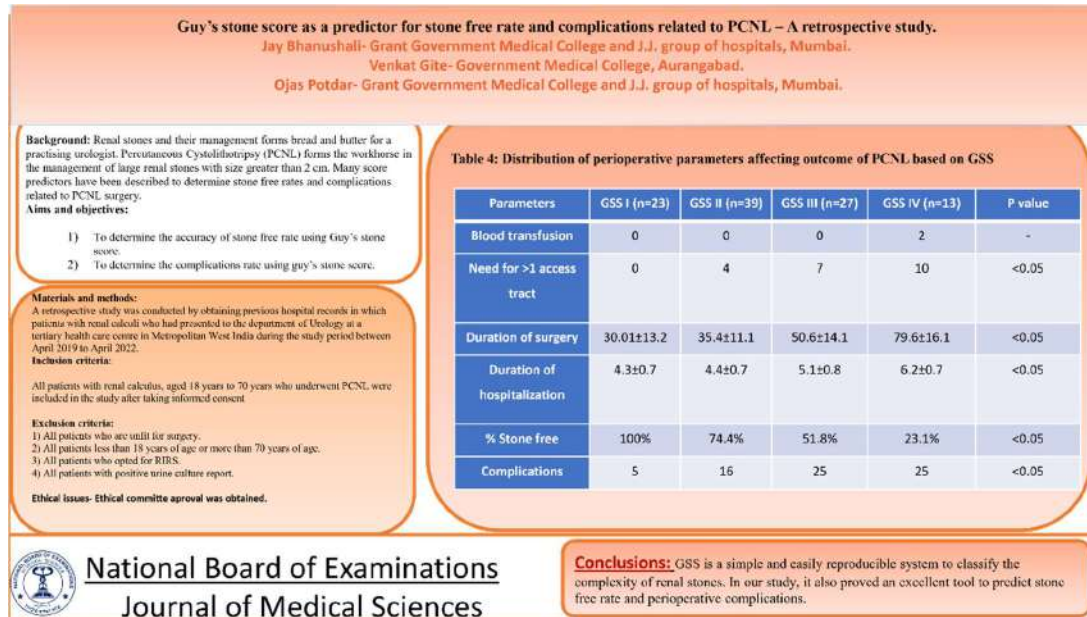
Abstract

Renal stones and their management forms bread and butter for a practising urologist. Percutaneous Cystolithotripsy (PCNL) forms the workhorse in the management of large renal stones with size greater than 2 cm. Many score predictors have been described to determine stone free rates and complications related to PCNL surgery.

Key words: staghorn calculus, guy's scoring system, success and complications

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Graphical Abstract



Introduction

Over the past 20 years, kidney stone illness has become much more commonplace worldwide. The utilization of Percutaneous Nephrolithotomy (PCNL) for the treatment of massive stone burden has increased in tandem with the sharp rise in the incidence and prevalence of stone illness. Even with ongoing advancements in technology and surgical methods, PCNL still has a higher overall complication rate [1,2].

The degree of hydronephrosis, positional distribution, calyceal and anatomical complexity, stone burden and density, and secondary alterations all appear to be significant factors in the outcome of PCNL [3].

After PCNL, the Stone Free Rate (SFR) has been observed to range from 56% to 76% [4]. Comparing different studies, however, is challenging for two reasons. –

- 1) There is no standard grading scheme to classify the difficulty of stones.
- 2) The definition and methodology for evaluating stone clearance are not standardized [5].

Despite being regarded as a minimally invasive surgery, PCNL carries a considerable risk of complications and does not guarantee that the patient will be clear of stones. There are guidelines for PCNL indications, and the Clavien system has been adjusted to grade problems [6].

Moreover, there isn't a widely recognized standard for grading stone complexity that would enable relevant study comparisons. A validated, user-friendly stone score would be helpful for outcome comparison and possibly for informing patients about their chances of achieving a "Stone Free" outcome after surgery.

In 2007 UK National PCNL audit by British Association of Urological Surgeons (BAUS) identified 'inability to stratify stone complexity' as a significant barrier towards derivation of meaningful audit conclusions [7].

Two major scoring system categories that attempt to be connected to SFR following PCNL have been described [8-10].

First, Ordinal Scoring Systems were developed from single institution analysis. They classified calculi into "Ordered" classes of increasing difficulty, primarily

based on characteristics that experts believed (with the help of historical data) determined SFR. These grades were then further tested statistically.

Thomas et al. (2011) [8] described Stone Scoring System, "Guy's Stone Score" (GSS), which comprises 4 grades based upon renal anatomy, number of stone and patient factors. Okhunov et al. (2013) [14] proposed S.T.O.N.E. [stone size (S), tract length (T), obstruction (O), number of involved calices (N), and essence or stone density (E)]. It provides an overall view of the surgical procedure's complexity by integrating five components measured from preoperative CT imaging and quantitatively characterizing the stone state [9].

The second type, Smith et al. (2013) [10] proposed CROES (Clinical Research Office of the Endourological Society) nomogram for PCNL success. Regression modeling produced from many institutions serves as the foundation for the statistically determined data-driven risk estimator model known as CROES. With the explanatory variables of stone burden, case volume, previous stone treatment, staghorn stone, stone placement, and stone count, it provides a continuous score that can "predict" the dependent result of SFR. The greatest indicator of the stone-free rate was stone burden (Chi-square =30.27, p=0.001) [10].

With the use of high resolution spatial imaging provided by CT, it is possible to accurately characterize the size and distribution of stones, the anatomy of the pelvic floor, abnormalities, and anatomical linkages that may determine the viability and risks of various treatment methods. With these quantifiable stone and patient characteristics, the GSS [8], S.T.O.N.E. nephrolithometry [4] and the CROES nephrolithometry nomogram [10] were implemented in order to evaluate kidney stones in a methodical and quantitative manner. These models consider co-morbidities that influence the course of the disease in addition to imaging features [8-10]. In order to enhance patient

counseling and surgical planning, the surgeon can more precisely predict PCNL outcomes by using the score systems as disease stratification tools [8-10].

Standardized reporting across several series is another possible benefit of scoring systems. Due to a lack of generally recognized guidelines, comparison testing of urolithiasis treatments has not yet been possible and user-friendly stone scoring standardization system [5]. This was a retrospective study which evaluated the Guy's scoring system not only in predicting the stone free rate and complications, but also in evaluation of the intraoperative events during PCNL.

Aims and objectives:

- 1) To determine the accuracy of stone free rate using Guy's stone score.
- 2) To determine the complications rate using guy's stone score.

Materials and methods

A retrospective study was conducted by obtaining previous hospital records in which patients with renal calculi who had presented to the department of Urology at a tertiary health care centre in Metropolitan West India during the study period between April 2019 to April 2022.

Inclusion criteria

All patients with renal calculus, aged 18 years to 70 years who underwent PCNL were included in the study after taking informed consent.

Exclusion criteria

- 1) All patients who are unfit for surgery.
- 2) All patients less than 18 years of age or more than 70 years of age.
- 3) All patients who opted for RIRS.
- 4) All patients with positive urine culture report.

Information was obtained from hospital previous records which included basic demographic data like age and sex, detailed clinical history on basis of

symptoms and its duration, associated comorbidities, past calculus history, previous surgical intervention (especially urological) and family history of calculus disease, diabetes, hypertension, malignancy and clinical examination findings. Investigations included basic preoperative investigations and imaging in the form of Non contrast Computerised Tomography of Kidney, Ureter and Bladder (NCCT KUB).

This radiological imaging provided for details of stone location, site, size, number, stone density, calyceal involvement, dilated system and associated congenital & anatomical abnormalities.

In all study cases, Guy's stone score was calculated as follows:

PCNL had been performed in all these patients and their operative details were obtained from the previous records and noted.

Peri-operative variables included Operative side (Laterality of stones), Stone location, Stone size, Number of calyces involved, Anatomy of kidney (normal or abnormal) operative time, analgesic and blood requirement, length of hospital stay were noted and surgical complications (intraoperative and postoperative) according to modified Clavien system were also obtained from the records. Post operatively Stone Free Status was assessed by X-Ray KUB on the first postoperative day and findings were recorded.

A patient was considered to be in a stone-free status if there were no stones at all or clinically insignificant residual fragments (CIRF) that were smaller than 4 mm and did not indicate an obstruction, infection, or need for additional care.

The postoperative complications of PCNL were assessed using the **modified Clavien grading** scale [5].

All the data obtained was tabulated and results analysed.

Materials and methods

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This radiological imaging provided for details of stone location, site, size, number, stone density, calyceal involvement, dilated system and associated congenital & anatomical abnormalities.

In all study cases, Guy's stone score was calculated as follows (Table 1):

Table 1. Guy's Stone Score

Grade	Description
Grade I	A solitary stone in the mid/lower pole with simple anatomy OR A solitary stone in the pelvis with simple anatomy
Grade II	A solitary stone in the upper pole with simple anatomy OR Multiple stones in a patient with simple anatomy OR Any solitary stone in a patient with abnormal anatomy
Grade III	Multiple stones in a patient with abnormal anatomy OR Stones in a calyceal diverticulum OR Partial Staghorn Calculus
Grade IV	Staghorn Calculus OR Any stone in a patient with spina bifida or spinal injury

PCNL had been performed in all these patients and their operative details were obtained from the previous records and noted.

Peri-operative variables included Operative side (Laterality of stones), Stone location, Stone size, Number of calyces involved, Anatomy of kidney (normal or abnormal) operative time, analgesic and blood requirement, length of hospital stay were noted and surgical complications (intraoperative and postoperative) according to modified Clavien system were also obtained from the records. Post operatively Stone Free Status was assessed by X-Ray KUB on the first postoperative day and findings were recorded.

A patient was considered to be in a stone-free status if there were no stones at all or clinically insignificant residual fragments (CIRF) that were smaller than 4 mm and did not indicate an obstruction, infection, or need for additional care.

The **modified Clavien grading system** was used to evaluate postoperative complications of PCNL [5].

All the data obtained was tabulated and results analysed.

Results

The study included a total of 102 patients in which 62 were males and 40 were females. The mean age of patients was 43.2 (± 13.2) years. The age distribution of patients is depicted in Table 2.

Table 2. Distribution of age groups based on gender of patients

Age groups (Years)	Males (n ₁ /%)	Female (n ₂ /%)	Total no. of patients (N/%)
18-30	8 (7.8%)	7 (6.9%)	15 (14.7%)
30-39	10 (9.8%)	5 (4.9%)	15 (14.7%)
40-49	24 (23.6%)	13 (12.7%)	37 (36.3%)
50-59	11 (10.8%)	9 (8.8%)	20 (19.6%)
>60	9 (8.8%)	6 (5.9%)	15 (14.7%)
Total	62 (60.8%)	40 (39.2%)	102 (100%)
Mean ±SD	50.6±14.1	41.6±15.3	43.2±13.2
Min-Max	18-70 years	P value	0.07^{NS}

Out of 102 patients studied, majority belonged to the age group 40 to 49 years old (37 cases, 36.3%), followed by 20 patients (19.6%) aged between 50 to 59 years of age and 15 patients (14.7%) each of age between 18 to 30, 30 to 39 and above 60 years old.

Youngest patient admitted was 18 years old male while oldest patient admitted was 70 years old female.

Mean age of male and female patients was 50.6±14.1 years and 41.6±15.3 years respectively. Mean age of patients was found to be 43.2±13.2 years. It can be seen that mean age of male and female patients did not differ significantly (p=0.07) (Figure 1 and Table 3).

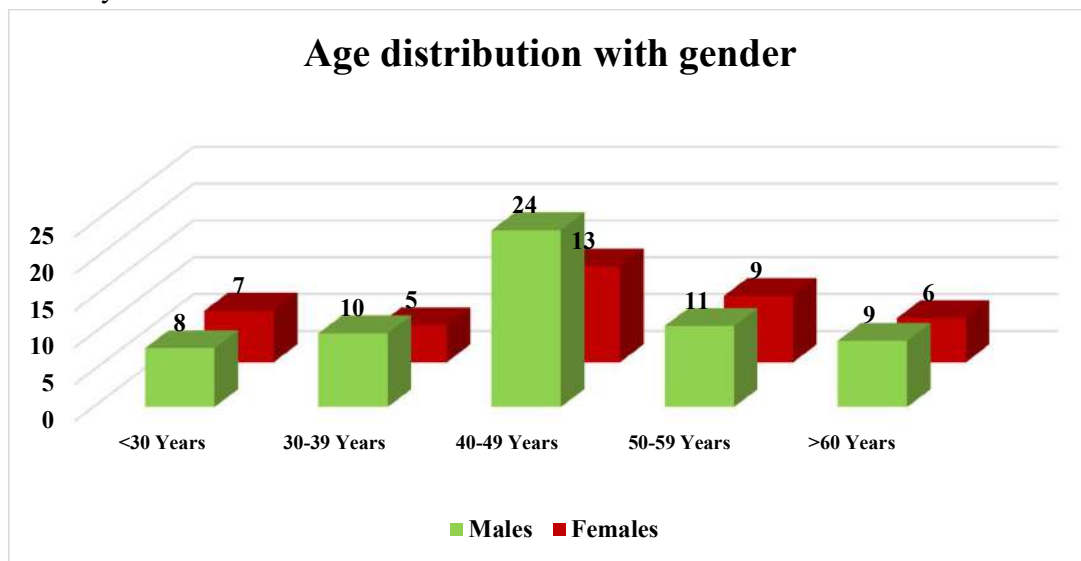


Figure 1. Distribution of age groups based on gender of patients

Table 3. Distribution of stone free rate based on Guy Stone’s Score

Guy Stone’s Score	Stone free (n1/%)	Residual stone (n2/%)	Total (N/%)	% Free
I	23 (22.6%)	0	23 (22.6%)	100%
II	35 (34.3%)	4 (3.9%)	39 (38.2%)	89.7%
III	20 (19.6%)	7 (6.9%)	27 (26.5%)	74.1
IV	5 (4.9%)	8 (7.8%)	13 (12.7%)	38.7%
Total	83 (81.4%)	19 (18.6%)	102 (100%)	P<0.05*

According to the GSS there were 23 (22.6%), 39 (38.2%), 27 (26.5%) and 13 (12.7%) patients in GSS I, II, III and IV groups, respectively. GSS I (n=23) included 13 pelvic, 2 mid-pole and 8 inferior pole calculi. GSS II (n=39) included 30 multiple calculi, 4 upper-polar calculi and single pelvic calculus with pelviureteric junction obstruction in 5 renal unit. All GSS III (n=27) included 27 partial

staghorn calculi. All renal units in GSS IV (n=13) had complete staghorn calculus.

About 19 (18.6%) patients still had residual stones while 83 patients (81.4%) were stone free. For renal units with GSS I, II, III and IV, 100%, 89.7%, 74.1% and 38.7% of renal units respectively were stone-free. There was a significant inverse correlation between GSS grade and Stone free rate (p < 0.05) (Figure 2 and Table 4).

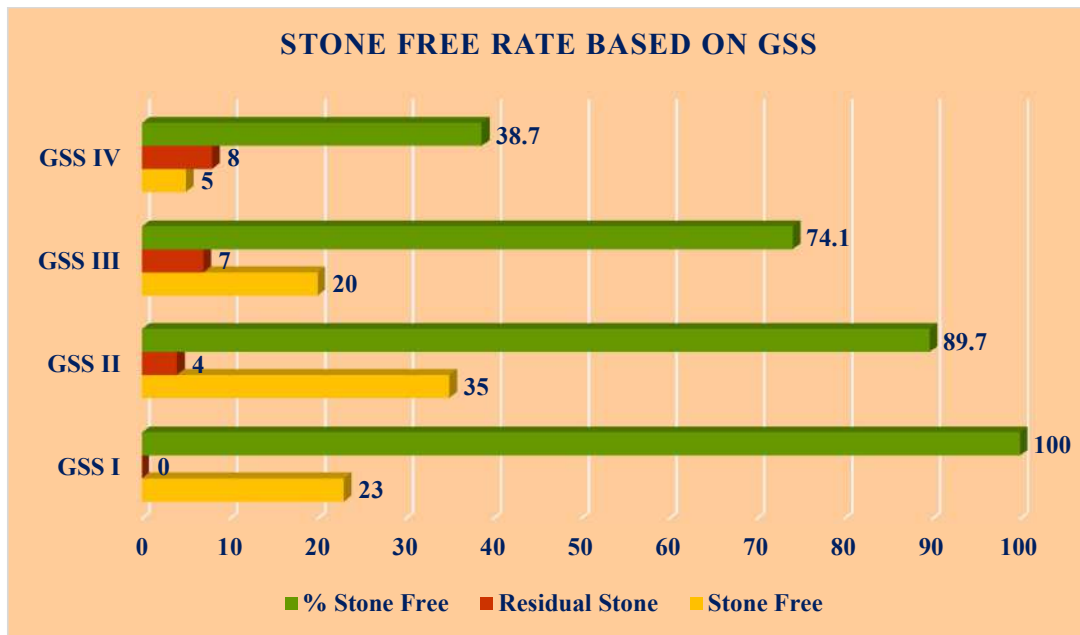


Figure 2. Distribution of stone free rate based on Guy Stone’s Score

Table 4. Distribution of complications based on Clavien Dindo grading system among GSS groups

Clavien grading	GSS I	GSS II	GSS III	GSS IV	Total complications (N/%)
1	4 (5.6%)	11 (15.6%)	13 (18.3%)	9 (12.7%)	37 (52.2%)
2	1 (1.4%)	1 (1.4%)	3 (4.2%)	5 (7%)	10 (14%)
3a	0	4 (5.6%)	7 (9.9%)	8 (11.3%)	19 (26.8%)
3b	0	0	1 (1.4%)	2 (2.8%)	3 (4.2%)
4a	0	0	1 (1.4%)	1 (1.4%)	2 (2.8%)
4b	0	0	0	0	0
5	0	0	0	0	0
Total	5 (7%)	16 (22.6%)	25 (35.2%)	25 (35.2%)	71 (100%)

A total 71 complications were seen in 102 patients studied. The occurrence of complications in patients with various GSS grades was compared and is shown in above table. Majority of complications were seen

in grade III and grade IV (25 cases each, 35.2%). All grades of complications were more common in patients with GSS III and IV ($P < 0.05$) (Figure 3 and Table 5).

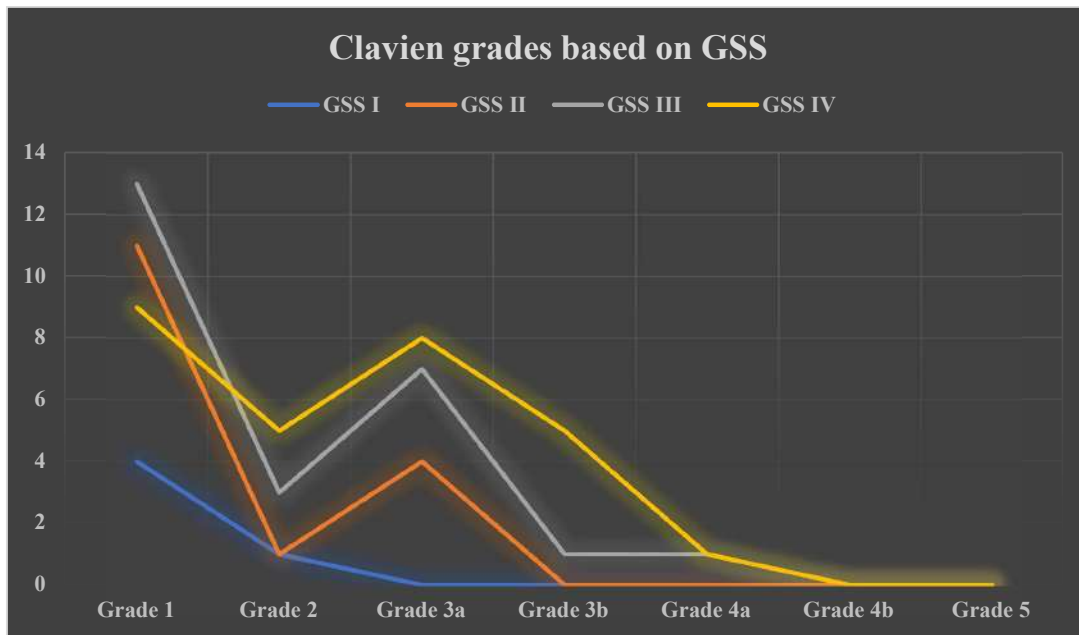


Figure 3. Distribution of complications based on Clavien grading system among GSS groups

Table 5. Distribution of perioperative parameters affecting outcome of PCNL based on GSS

Parameters	GSS I (n=23)	GSS II (n=39)	GSS III (n=27)	GSS IV (n=13)	P value
Blood transfusion	0	0	0	2	-
Need for >1 access tract	0	4	7	10	<0.05
Duration of surgery	30.01±13.2	35.4±11.1	50.6±14.1	79.6±16.1	<0.05
Duration of hospitalization	4.3±0.7	4.4±0.7	5.1±0.8	6.2±0.7	<0.05
% Stone free	100%	74.4%	51.8%	23.1%	<0.05
Complications	5	16	25	25	<0.05

Blood transfusion was needed in 2 patients with GSS IV. In 4 patients of GSS II, 7 patients with GSS III and 10 patients with GSS IV more than one access tract was needed to complete the procedure. Duration of surgery and hospitalisation in GSS I was 30.01±13.2 and 4.3±0.7, in GSS II was 35.4±11.1 and 4.4±0.7, in GSS III was 50.6±14.1 and 5.1±0.8 and that of in GSS IV was 79.6±16.1 and 6.2±0.7 respectively. Stone free rate in GSS I, GSS II, GSS III and GSS IV was 100%, 89.7%, 74.1% and 38.7%. Complications were seen in 5, 16, 25 and 25 patients with GSS I, GSS II, GSS III and GSS IV respectively.

The GSS grade and Stone free rate had a significant inverse connection ($p < 0.05$). GSS grades III and IV had a considerably increased rate of problems using the Clavien grading system ($p < 0.05$). The frequency of blood transfusions, the requirement for more than one access tract, and the duration of surgery and duration of hospitalization.

Discussion

Over the previous forty years, there has been a threefold increase in kidney stone incidence and prevalence. Researchers have worked hard to build a standard system that can identify patients who may require a staged procedure or other alternative procedure, be more susceptible to complications, or have residual stone burden following PCNL. This will aid in patient counseling and clinical decision-making.

In 2008, Tefekli et al. attempted to establish a connection between the rate of complication and stone complexity, but they were unable to produce any meaningful results.

In their investigation, De la Rosette et al. discovered a significant correlation between operative time and stone burden, although they did not identify any relationship between stone burden and complications.

A noteworthy correlation between stone size and problems was discovered by Michel et al.

Standardization of the preoperative data was lacking in all earlier studies and subsequent ones on preoperative variables

to predict the stone free rate and outcome following PCNL.

The S.T.O.N.E. score system was created by Okhunov et al. [16] and is based on non-contrast CT (NCCT). A lower number indicates a higher rate of stone clearance. The score ranges from 5 to 13, taking into account several factors.

Increased estimated blood loss (EBL), longer operating times (OT), and longer lengths of stay (LOS) are among the major problems that are linked to higher S.T.O.N.E. scores. Smiths et al.'s CROES nomogram was derived from a global database analysis involving 5830 patients. This nomogram has six characteristics: stone burden, number, location, multiple, staghorn, and institute-level case volume. It is cucumber-sized and requires a lot of work, yet it achieved an impressive 76% prediction accuracy.

Numerous research works have contrasted these scoring systems' prognostic abilities in post-PCNL SFR. The majority of research has looked at how well these scoring systems function in terms of SFR prediction, but not in terms of complications prediction.

Every scoring system has limitations or drawbacks. For instance, the term "partial staghorn stone" was ambiguous in Guy's scoring system. Preoperative CT is the only source of data used in the S.T.O.N.E. Score scoring system.

The CROES nomogram requires data (case volume and treatment history) that may not be easily accessible.

Percutaneous Nephrolithotomy (PCNL) has become the accepted standard treatment of choice for large and difficult kidney stones. It is a minimally invasive procedure with a good safety record and success rate. Variable outcomes related to renal anatomy, the number of stones, calcification involvement, stone burden, complexity, and other variables are also linked to PCNL. A number of Stone Scoring Systems have been implemented to evaluate and validate predictive

nomograms, which can greatly improve patient counseling and preoperative treatment planning.

Higher grades are linked to lower SFR. Thomas et al. (2011) [4] established the GSS per grading to predict SFR based on stone complexity. Ingimarson et al. (2014) [16] verified the GSS.

The calyceal diverticulum, aberrant renal architecture, and the quantity of stones are included in the Guy's Score. A stone complexity metric is included in each grading system. Staghorn or partially staghorn stone formation is a variable in the GSS that is primarily used to highlight a stone's intricacy [13,15]. Subjective interpretations of stone burden and position can lead to variances in scores for certain grading systems [13,16].

For comprehensive reporting and comparison, the ideal scoring system must be easily implementable, reproducible, and sufficiently detailed. The sole assessment needed to determine the GSS score is renal imaging, which may be completed at facilities with CT access. Complication prediction is linked to GSS. In comparison, it is less laborious.

Numerous published studies have confirmed the GSS as having good inter-rater concordance [16].

In our study, we found direct correlation between GSS and increased complication rate. This may be attributable to higher stone burden leading to need for multiple punctures and higher technical complexity and longer intraoperative time [17].

Conclusion

The GSS is a straightforward and repeatable method for grading the difficulty of kidney stones. In our study, it also proved an excellent tool to predict stone free rate and perioperative complications. Ultimately, meticulous pre operative planning aided by a thorough evaluation of patients using GSS and radiological investigations accompanied by preoperative counselling is key to success

in management of renal stone disease and obtain favourable outcome while minimising morbidity of the patient.

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Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

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Consent for publication

Consent for publication has been given by all the authors mentioned in the study.

Availability of data and material:

The data and material required for the conduct of the study was collected by filing out case proforma sheets and use of hospital information system to collect patient related reports and other related data required for the study after obtaining consent from the patient and the hospital administration.

References

1. Turk C, Knoll T, Petrik A, Sarica K, Skolarikos A, Straub M, et al. European Association of Urology. EUA Guidelines on Urolithiasis.
2. de la Rosette J, Assimos D, Desai M, Gutierrez J, Lingeman J, Scarpa R, et al. The Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study: Indications, complications, and outcomes in 5803 patients. *J Endourol.* 2011; 25:11–7.
3. C.W. Jeong, J.W. Jung, W.H. Cha, B.K. Lee, S. Lee, S.J. Jeong, S.K. Hong, S.S. Byun, S.E. Lee; Seoul National University renal stone complexity score for predicting stone-free rate after percutaneous nephrolithotomy *PLoS One*, 8 (6) (2013), p. e65888, 10.1371/journal.pone.0065888.
4. Thomas K, Smith NC, Hegarty N, Glass JM. The Guy's stone score – Grading the complexity of percutaneous nephrolithotomy procedures. *Urology.* 2011; 78:277–81.
5. A. Tefekli, M. Ali-Karadag, K. Tepeler, E. Sari, Y. Berberoglu, M. Baykal, et al. Classification of percutaneous nephrolithotomy complications using the modified Clavien grading system: looking for a standard *Eur Urol*, 53 (2008), pp. 184-190.
6. Preminger GM, Assimos DG, Lingeman JE et al: Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J Urol* 2005; 173:1991.
7. Ghani KR, Sammon JD, Bhojani N et al: Trends in percutaneous nephrolithotomy use and outcomes in the United States. *J Urol* 2013; 190:558.
8. Sivalingam S, Cannon ST and Nakada SY: Current practices in percutaneous nephrolithotomy among endourologists. *J Endourol* 2014; 28: 524.
9. Shahrour K, Tomaszewski J, Ortiz T et al. Predictors of immediate postoperative outcome of single-tract percutaneous nephrolithotomy. *Urology.* 2012; 80:19-25.
10. Hyams ES, Bruhn A, Lipkin M, Shah O. Heterogeneity in the reporting of disease characteristics and treatment outcomes in studies evaluating treatments for nephrolithiasis. *J Endourol.* 2010; 24:1411-4.
11. Graefen M. The modified clavien system: A plea for a standardized

- reporting system for surgical complications. *Eur Urol* 2010; 57:387-9.
12. The British Association of Urological Surgeons. PCNL Audit 2007. Available at: <http://www.baus.org.uk/Resources/BAUS/Documents/PDF%20Documents/Sections/Endourology/PCNL%20Audit%202007.pdf>. Accessed May 18, 2014.
 13. Thomas K, Smith NC, Hegarty N et al: The Guy's stone score grading the complexity of percutaneous nephrolithotomy procedures. *Urology* 2011; 78:277.
 14. Okhunov Z, Friedlander JI, George AK et al: S.T.O.N.E. nephrolithometry: novel surgical classification system for kidney calculi. *Urology* 2013; 81:1154.
 15. Smith A, Averch TD, Shahrour K et al: A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy. *J Urol* 2013; 190:149.
 16. Ingimarsson JP, Dagrosa LM, Hyams ES et al; External validation of a preoperative renal stone grading system: reproducibility and inter-rater concordance of the Guy's stone score using preoperative computed tomography and rigorous postoperative stone-free criteria. *Urology*. 2014; 83:45-9.
 17. Tailly T, Okhunov Z, Nadeau BR et al. Multi-Centre External Validation and Comparison of Stone Scoring Systems in Predicting Outcomes after Percutaneous Nephrolithotomy. *J Endourol*. Epub 2016 Feb 5.



ORIGINAL ARTICLE

Prediction Strength of Some Risk Factors for Severe COVID-19 Course at hospital Admission in Al-Nasiriyah City -Iraq : A Cohort Retrospective Single center Study

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Abstract

Background: The early prediction of the clinical course of COVID-19 helps health professionals to discriminate the severe cases that need ICU admission from those with no risk of worsening outcomes.

Materials & methods: This cohort retrospective study included 389 COVID-19 patients admitted to Al-Hussein Teaching Hospital during the period from March to August 2021. Demographic characteristics, clinical symptoms, and laboratory findings upon hospital admission were analyzed by univariate analysis to determine their association with the severity of COVID-19; only those variables with ($P > 0.05$) were included in the multivariable logistic regression to find the strong predictors of severity in term of Odd ratios.

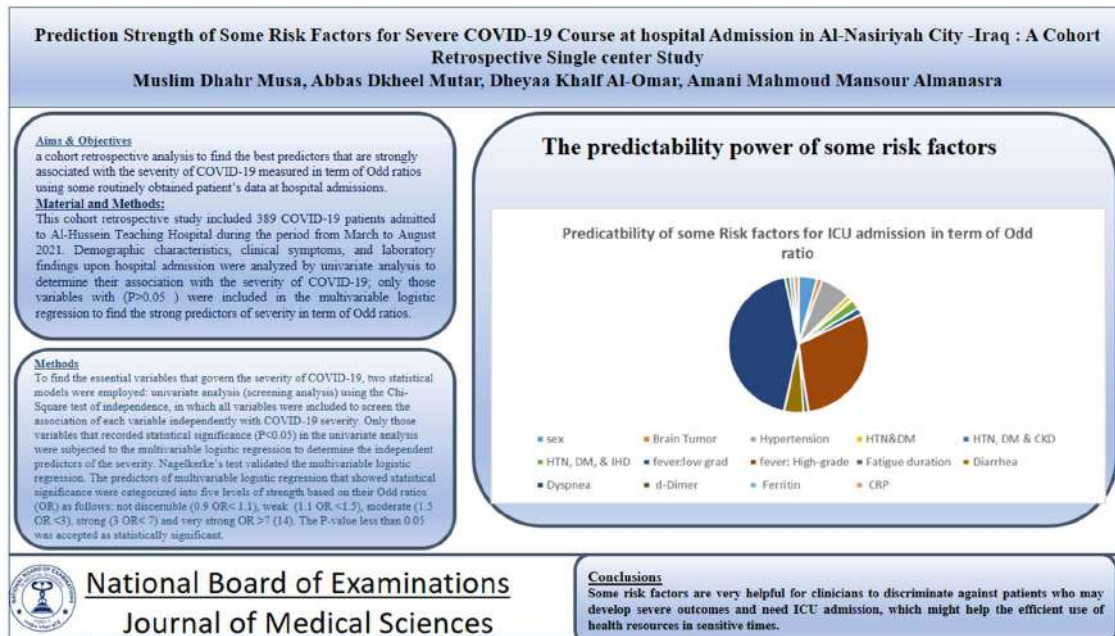
Results: The mean age of the 389 patients was 33.6 ± 14.8 ; there were 231(59.4%) severe cases (admitted to ICU), and 158(40.6%) were non-severe cases (admitted to regular wards). Univariate analysis revealed that gender (male) presence of co-morbidities and all clinical symptoms and laboratory findings were associated with severe outcomes of COVID-19. However, multivariate logistic regression revealed that dyspnea [O.R 42.58 (12.22; 148.36)] and high grad fever [O.R 29.25 (5.34; 160.24)] were very strong predictors for severity, while male gender [O.R 4.26 (1.95; 9.33)] and hypertension [O.R 6.83 (2.4; 19.54)] were strong predictors of the severity. On the other hand, Ferritin gave an indiscernible predictive value [O.R 1.003 (1.001; 1.006)].

Conclusion: Some risk factors are very helpful for clinicians to discriminate against patients who may develop severe outcomes and need ICU admission, which might help the efficient use of health resources in sensitive times.

Keywords: Risk factors, Severity, COVID-19, Iraq

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Graphical Abstract



Introduction

Late 2019 was an extraordinary global event in public health; the emerging new respiratory viral disease, COVID-19, caused by *betacoronavirus* SRAS-Cov-2, began in China and spread worldwide, hitting 229 countries and leaving behind more than 6 million deaths [1]. The clinical presentation of the disease is widely varied from asymptomatic/mild to fatal respiratory distress and multi-organ failure [2,3]. Although about 80% of infected patients experienced mild symptoms, resolved entirely by the end of the disease course, a subset of the patients developed severe symptoms [4,5]. However, due to the surge in the number of patients, especially during the first and second waves of the pandemic, this subset of severe patients constitutes a massive burden on health systems, even those in developed countries, particularly the intense care units (ICU) [6]. One of the biggest challenges was the early prediction of the clinical course or identifying the risk

factors that worsened the clinical course. The importance of early prediction of the clinical course helps health professionals to arrange their priorities in dealing with the vast numbers of hospital attendances and to discriminate the severe cases that need ICU admission from those with no risk of worsening outcome [7]. Additionally, strengthening early prediction of COVID-19 severity is one of the fundamental approaches for lowering the death rate [8]. Since then, many efforts have gone into determining the best risk factors the clinician can use to assess the severity of hospital admission. Many previous studies have undertaken the topic of risk factors for severe forms of COVID-19 using demographic, clinical, and laboratory results variables. Nevertheless, most of those studies only apply their prediction models to estimate in-hospital mortality [7,9]. Other studies used the prediction models to assess the severity upon hospital presentation; however, these studies' results are difficult to generalize due to

small sample sizes or variations in the demographic characteristics of populations in different countries [7-12]. Studying the possible risk factors that may play a role in the path of COVID-19 clinical course in the Iraqi population has not been fully covered; thus, in this study, we perform a cohort retrospective analysis to find the best predictors that are strongly associated with the severity of COVID-19 measured in term of ICU admission using some routinely obtained patient's data at hospital admissions.

Materials and Methods

Study Design and Setting

This retrospective cohort study included 389 COVID-19 patients admitted to Al-Hussien Teaching Hospital (the main hospital for COVID-19 management) in Thi-Qar province, south of Iraq, for five months (March to August 2021). The outcome of the study was the severity of the disease defined in terms of clinical symptoms at hospital admission time according to WHO, 2021 [13], and the demand for ICU admission based on the decisions of emergency physicians; thus, the study population divided into two groups as severe cases and non-severe cases

Definitions

- *Severe cases*: are those patients that are characterized by low oxygen saturation (<90%) on room air, low respiratory rate (<30 breaths/minute), and signs of respiratory distress, besides the physician's decision to ICU admission.
- *Non-severe cases* are those patients without any criteria signs as mentioned above of severe cases; thus, the physician decides to be admitted to regular hospital wards.

- *Primary education*: patients who have accomplished primary school.
- *Intermediate education*: patients who have accomplished secondary school.
- *High education*: patients who have a Bachelor's or higher degrees.

Data collection

All data were obtained retrospectively from the biostatic department of Al-Hussien Teaching Hospital, based on approved written permission from the Thi-Qar Health Directory. Each participant had three parts of information: demographic included; age, gender, smoking habit, residence (stratified into rural and urban), education levels (stratified into primary, intermediate, and high), blood group, and presence of comorbidities; hypertension (HTN), diabetes mellitus (DM), ischemic heart diseases (IHD), chronic kidney diseases (CKD), and cancers. The clinical information included fever, fatigue duration, dyspnea, and diarrhea. The laboratory data included D-dimer, Ferritin, and CRP serum levels. All patients' data regarded the clinical symptoms, and the laboratory findings represented the patient's health status during the first 24 hours of hospital admission.

Statistical Analysis

Descriptive statistics were conducted to illustrate the characteristics of the cohort. Categorical variables were expressed as numbers and percentages (%). Continuous variables were expressed as mean and standard deviation (SD) or median (IQR: Inter-quartile Range) based on the normality test (Kolmogorov-Smirnov). To find the essential variables that govern the severity of COVID-19, two

statistical models were employed: univariate analysis (screening analysis) using the Chi-Square test of independence, in which all variables were included to screen the association of each variable independently with COVID-19 severity. Only those variables that recorded statistical significance ($P < 0.05$) in the univariate analysis were subjected to the multivariable logistic regression to determine the independent predictors of the severity. Nagelkerke's test validated the multivariable logistic regression. The predictors of multivariable logistic regression that showed statistical significance were categorized into five levels of strength based on their Odd ratios (OR) as follows: not discernible ($0.9 < \text{OR} < 1.1$), weak ($1.1 < \text{OR} < 1.5$), moderate ($1.5 < \text{OR} < 3$), strong ($3 < \text{OR} < 7$) and very strong ($\text{OR} > 7$) (14). The P-value less than 0.05 was accepted as statistically significant.

Results

Cohort characteristics

The cohort characteristics are illustrated in Table 1. Our cohort included 389 patients; 231 (59.4%) were severe cases (admitted to ICU), and 158 (40.6%) were recognized as non-severe cases (admitted to regular wards). The mean age of the entire cohort was 36.6 ± 14.8 ranging from 7 years to 78 years old. Most of the cohort 255 (65.6%) were in the age group 19-40 years old, while only 18 (4.6%) were older than 65 years. Most participants, 238 (61.2%), lived in urban regions. Regarding education levels, most participants (48.6%) have a high education level. The majority of individuals, 244 (62.7%), were non-smokers. Thirty-four percent of the cohort had comorbid conditions; the most common were HTN & DM (13.4%) and HTN alone (13.1%), whereas brain tumors were the least common, reported in 0.8% of cases. Patients with over three comorbidities (DM, HTN, IHD, and CKD) constitute 2.3% of the study population.

Table 1. The Demographic Characteristics, Clinical Features and Laboratory findings of the Study Cohort

Type of character	Characters	Categories	No (%)
Demographic	Age Mean \pm SD (Min-Max)	33.6 ± 14.8 (9-78)	
	Age categories	≤ 18 years	22 (5.7%)
		19-40 years	255 (65.6%)
		41-64 years	94 (24.2%)
	Gender	≥ 65 years	18 (4.6%)
		Male	189 (48.6%)
	Residence	Female	200 (51.4%)
		Rural	151 (38.8%)
	Education levels	Urban	238 (61.2%)
		Primary	66 (17%)
Intermediate		134 (34.4%)	
Smoking status	High	189 (48.6%)	
	Smoker	79 (20.3%)	

Clinical Symptoms		Non-Smoker	244(62.7%)
		X-Smoker	66 (17%)
	Blood Group	A	105 (27%)
		AB	76 (19.5%)
		B	72 (18.5%)
		O	136 (35%)
	Co-Morbidity	Without Co-Morbidity	256 (65.8 %)
		With Co-morbid	133(34.2%)
		Brain Tumor	3 (0.8 %)
		HTN	51 (13.1 %)
		HTN&DM	52 (13.4 %)
		HTN, DM, CKD	4 (1 %)
		HTN, DM, IHD	14 (3.6 %)
		HTN, DM, IHD, CKD	9 (2.3 %)
	Fever (°C) Mean ± SD (Min-Max)	38.8 ± 0.6 (38- 40)	
Fever categories	No fever	40 (10.3%)	
	Low grade (38-39.3)	281 (72.2%)	
	High grade (>= 39.4)	68 (17.5%)	
	Fatigue duration (days) Mean ± SD (Min-Max)	18.9 ± 8.2 (3-35)	
Fatigue categories	Less than one week	6 (1.5%)	
	1-2 weeks	79 (20.3%)	
	2-3 weeks	171 (44%)	
	More than three weeks	133 (34.2%)	
Diarrhoea	Yes	153 (39.3%)	
	No	236 (60.7%)	
Dyspnea	Yes	161 (41.4%)	
	No	228 (58.6%)	
Severity	Yes	231 (59.4%)	
	No	158 (40.6%)	
Laboratory findings	d-Dimer (µg/ml)	Median (IQR)	680 (230-1600)
	Ferritin (ng/ml)	Median (IQR)	460 (260-840)
	CRP (mg/l)	Median (IQR)	46 (24-96)

Regarding the patient's clinical symptoms, most study participants (89.7%) had a fever. Most of them (72.2%) have a low-grade fever. The highest recorded fever was 40°C. Additionally, 60.7% reported having diarrhea. All the study participants reported being fatigued, with the mean duration of fatigue 18.9±8.2 days.

The largest group (44%) reported fatigue for two to three weeks. Dyspnea was reported among 41.4% of the cohort. The laboratory findings included the CRP, d-Dimer, and ferritin values. Their median readings were 46 mg/l, 680 g/ml, and 460 ng/ml.

The Association of the variables with the severity

The univariate analysis illustrated in Table 2 revealed that among seven demographic variables, only gender and the presence of co-morbidities were significantly associated with severe cases (P -value =0.001). As among 231 severe cases, 135 (58.4%) accounted for male's sex, while 96 (41.6%) were females. For the age variable, although 145 (62.8%) of the severe cases belonged to the age group (19-40 years old), no significant association was found (P -value 0.47). Nearly two-thirds (61.5%) of the patients with severe infection lived in urban regions. Yet, the association between the geographic region and the symptoms' severity was insignificant (P value 0.88). Regarding the education levels, higher education levels were found to have more severe infections as nearly half (48.9%) of those severe cases were among this category and the lowest group (18.6%) of severe cases were primarily educated. Again, the relationship between education and severity was insignificant (P -value 0.45). Surprisingly, the non-smoker was found to have a more severe infection (61%) when compared with both the smoker (22.5%) and X-Smoker groups (16.5%). However, the association was not significant (P -value 0.42). Similarly, patients with different blood groups tend to have different responses to the COVID infection, as our study reported that those with blood group O were more likely to have a severe infection (37.2%) when compared with other groups, followed by blood group A (25.1%), moreover, blood group AB and B nearly making the same contribution among the severe group, (19%) and (18.6%) respectively. Nevertheless, the association was not

statistically significant (P -value 0.64). Patients without underlying comorbidities were found to have a higher percentage (79.7%) in the non-severe group than in the severe group (56.3%). Yet, the percentage of patients without comorbidities was still higher than those with comorbidities in the severe group. Among patients with underlying diseases, those with double burden (DM & HTN) and those with HTN alone contributed to 17% and 16% of the severe group. Those with HTN, DM & IHD constituted nearly 5% of the severe group. Patients with HTN, DM, IHD and CKD contribute to approximately 4% of the severe group, and the lowest group was those with a brain tumour. Regarding the clinical features, fever found to be significantly associated with the severity of infection, as 97% of the patients with severe infection were had fever at presentation (P value .00). Those with low-grade fever (less than 39.4 C) constituted the majority of the severe group (69.3%). Additionally, increasing the duration of fatigue was found to be significantly associated with the severity of COVID-19 infection (P value 0.00), as those who reported being fatigued for more than three weeks were found to be the largest contribution to the severe group (52.8%), followed by those whose duration of fatigue was between 2-3 weeks (38.5%), and none of those whose fatigue duration was less than one week found to have a severe infection. Patients with diarrhoea similarly being more likely to have a severe infection (50.2%), and the association is statistically significant (P value 0.00). Dyspnea was linked with COVID severity, and the relationship is statistically significant (P value 0.00) as 65.4% of the severe group had dyspnea.

Table 2. Univariate analysis of fourteen variables that included in this study

Variable	Categories	Non-severe (Regular ward) n= 158	Severe (ICU admitted) n= 231	P-value
Demographic characteristics				
Age categories	<= 18 years	8 (5.1%)	14 (6.1%)	0.47
	19-40 years	110 (69.6%)	145 (62.8%)	
	41-64 years	35 (22.2%)	59 (15.1%)	
	>= 65 years	5 (3.2%)	13 (5.6%)	
Gender	Male	54 (34.2%)	135 (58.4%)	0.00
	Female	104 (65.8%)	96 (41.6%)	
Geographic region	Rural	62 (39.2%)	89 (38.5%)	0.88
	Urban	96 (60.8%)	142 (61.5%)	
Education level	Primary education	23 (14.6%)	43 (18.6%)	0.45
	Intermediate education	59 (37.3%)	75 (32.5%)	
	High-level education	76 (48.1%)	113 (48.9%)	
Smoking status	Smoker	27 (17.1%)	52 (22.5%)	0.42
	Non-Smoker	103 (65.2%)	141 (61%)	
	X-Smoker	28 (17.7%)	38 (16.5%)	
Blood Group	A	47(29.7%)	58 (25.1%)	0.64
	AB	32 (20.3%)	44 (19%)	
	B	29 (18.4%)	43 (18.6%)	
	O	50 (31.6%)	86 (37.2%)	
Co-Morbidity	Brain Tumor	1(0.6%)	2 (0.8%)	0.00
	HTN	14 (8.9 %)	37 (16%)	
	HTN&DM	13 (8.2 %)	39 (16.9%)	
	HTN, DM, CKD	1(0.6 %)	3 (1.3%)	
	HTN, DM, IHD	3 (1.9 %)	11 (4.8%)	
	HTN, DM, IHD, CKD	0 (0 %)	9 (3.9%)	
	No comorbidity	126 (79.7%)	130 (56.3%)	
Clinical features*				
Fever categories	No fever	33 (20.9%)	7 (3%)	0.00
	Low grade (38-39.3)	121 (76.6%)	160 (69.3%)	
	High grade (>= 39.4)	4 (2.5%)	64 (27.7%)	
Fatigue categories	Less than one week	6 (3.8%)	0 (0%)	0.00
	1-2 weeks	59 (20.3%)	20 (8.7%)	
	2-3 weeks	82(51.9%)	89 (38.5%)	
	More than three weeks	11(7%)	122 (52.8%)	
Diarrhoea	Yes	37 (23.4%)	116 (50.2%)	0.00
	No	121 (76.6%)	115 (49.8%)	
Dyspnea	Yes	10 (6.3%)	151 (65.4%)	0.00
	No	148 (93.7%)	80 (34.6%)	

Laboratory Findings			
D-Dimer (µg/ml), Mean value	618.2	1435.8	0.00
Ferritin (ng/ml), Mean value	386.9	721.6	0.00
CRP (mg/l), Mean value	37.6	73.9	0.00

When comparing the two groups (severe and non-severe) based on their laboratory findings, we found that the mean of d-Dimer for the severe group is 1435.8 µg/ml, which is significantly higher than the mean of the non-severe group 618.2 µg/ml ($t = 879.6$, $P = -8.036$, $P < .001$). Similarly, among the severe group, the mean of the ferritin level is 721.6 ng/ml, which is significantly higher than the mean for the non-severe group, 386.9 ng/ml ($t = 376.9$, $P = -9.65$, $P < .001$). The CRP level was also considerably higher among the severe group, 73.9 mg/l versus 37.6 mg/l for the non-severe group ($t = 377.9$, $p < .001$).

Predictors of COVID-19 Severity

The multivariable logistic regression model was created with the following variables: sex, co-morbidities, fever, fatigue duration, diarrhoea, dyspnea, CRP, ferritin, and D-Dimer levels. In general, the model's overall classification accuracy was 85.9%, and Nagelkerke's R² was .715, which suggests that the model explains roughly 71.5% of the variation in the outcome. Also, there is no multicollinearity between the independent variables.

The results showed that among the nine included variables, eight were statistically significant independent predictors of COVID-19 severity, as illustrated in Table 3. Developing severe

COVID-19 infection was significantly higher among male patients; the odds of developing severe infection were more than four times that of the female group (OR 4.5, [95% CI 2.05; 9.87]). Among comorbid patients, HTN was the only comorbidity found to be a statistically significant predictor in that developing severe infection among patients with HTN was more than six times (OR 6.83, [95% CI 2.4; 19.54]). Additionally, fever was a significant predictor of the severity of COVID-19 infection. Patients with high-grade fever were 29 times more likely to develop a severe infection when compared with patients without fever (OR 29.3, 95% CI 5.34; 160.24). Similarly, diarrhoea and dyspnea were found to be a statistically significant predictor of COVID-19 severity as they increased the odds of developing a severe infection by more than 4, 42, and 18 times (ORs 4.4, 42.6, 18.4), respectively, when compared with the reference groups (No diarrhoea, No dyspnea). Increasing fatigue duration was also a significant predictor of the severity of COVID-19 infection, as it increased the odds of severity by 8% (OR 1.08, 95% CI 1.01; 1.16). Of the three studied laboratory findings, elevated ferritin level was a significant predictor of the severity of infection. As for every one ng/ml increase in ferritin level, the odds of severity are increased by 0.3 (OR 1.003, 95% CI 1.001; 1.006).

Table 3. Multivariable binary logistic regression of ten risk factors for the severe course of COVID-19 in the study cohort

Variable	β Coefficient	SE	P value	Odds Ratios (95% CI)
Sex (Female = reference)	1.45	.40	.000*	4.26 (1.95; 9.33)
Underlying disease (No= reference)			.019	
Brain Tumor	.12	1.94	.952	1.12 (.03; 49.97)
Hypertension	1.92	.54	.000*	6.83 (2.4; 19.54)
HTN&DM	.12	.54	.823	1.13 (.39; 3.27)
HTN, DM & CKD	-1.63	2.50	.515	.196 (.001; 26.32)
HTN, DM, & IHD	.81	1.06	.446	2.24 (.28; 17.9)
Fever categories (No fever= reference)			.000	
Low-grade fever	.43	.60	.478	1.53 (.47; 4.96)
High-grade fever	3.3	.87	.000*	29.25 (5.34; 160.24)
Fatigue duration (continuous)	.080	.034	.021*	1.08 (1.01; 1.16)
Diarrhea (No diarrhea = reference)	1.47	.44	.001*	4.36 (1.85; 10.28)
Dyspnea(No dyspnea = reference)	3.75	.64	.000*	42.58 (12.22; 148.36)
d-Dimer ($\mu\text{g/ml}$)	.000	.000	.377	1.00 (.99; 1.00)
Ferritin (ng/ml)	.003	.001	.013*	1.003 (1.001; 1.006)
CRP (mg/l)	-.012	.01	.198	.99 (.97; 11.01)
Constant	-2.92	1.11	.008	

To summarise, the logistic regression model identified that male gender, HTN as underlying disease, high-grade fever, increasing fatigue duration, diarrhoea, dyspnea, and higher ferritin level were significantly associated with the severity of COVID-19 infection, and indeed can explain 67.2 % of the variance in outcome. Furthermore, sorting the significant predictors based on their odds ratios revealed that dyspnea and high grad fever were very strong predictors of severity. At the same time, male gender and hypertension were strong predictors of severity. On the other hand, Ferritin gave indiscernible predictive value.

Discussion

This study focuses on the predictability of some routinely and easily obtained patient data upon hospital admission that might govern the severity of

COVID-19 in an attempt to early discrimination between the severe and non-sever cases. Since it is not reasonable to perform physical examinations and laboratory tests for the vast numbers of hospital-attending individuals, it is important to find the strong predictors of the possibility of getting a severe course and required ICU admission.

Different previous studies documented that older age (above 60 years) has been associated with the worse outcome; however, in our research and through univariate analysis, the age variable did not show a significant association with the severity. Our cohort characteristics can account for this inconsistency, as the older participants (above 65 years) constitute only 4%, and the cohort mean age is 33.6 years. This study found that male gender was the important risk factor for a severe course of

the disease; in this regard, our finding was in agreement with a large-scale global study conducted by Peckham and his colleagues, 2020 (15), who found that male gender was significantly associated with severe outcome measured in term of ICU admission with $OD=4.26$ (1.95; 9.33); furthermore, Jin et al., 2020(16) conclude that male gender was a significant risk factor and independent of age and susceptibility to COVID-19 infection; also many other global studies stated the association of gender (male) with severe cases of COVID-19 [8,10,17,18]. However, in contrast to our findings, other studies found no significant association of the gender variable with the severe course of the disease [10,12,19]. The gender-biased prognosis is attributed to the gender differences in the genetic makeup, hormonal factors and immune response. Male gender had a higher expression level of TMPRSS2, the main protease involved in SARS-Cov-2 entry, many genes that play a crucial role in both innate and adaptive immune responses are located on the chromosomes X since females have two X chromosomes; they are protected from an inherent mutation in contrast to males that have only one chromosome [20]. Estrogen may also protect females against worse outcomes [21,22]. Regarding the immunological aspect, the differences between males and females accounted for the females' advantages, as a higher number of CD4-T cells and increased B-cell production of antibodies were found in females [23].

For smoking status, in this study, the univariate analysis found no significant differences between smokers, non-smokers, and X-smokers regarding COVID-19 severity; a similar finding was also reported previously [24,25]; ABO-

system has been linked to the susceptibility and severity of many infectious diseases like; Rotavirus, Norovirus Malaria, Cholera and *E.coli* [26]. Nevertheless, the results of previous studies that proposed such an association with COVID-19 severity were heterogeneous. Our study found that blood group O was more likely to have a severe infection (37.2%); however, no statistical significance between the blood groups and the severity of COVID-19 was found. Our finding in this regard was in line with [27]. In agreement with our result, Almadhi et al., 2021 [28] found that the ABO-blood groups were not ideal predictors of severity. Regarding the co-morbidities, previous studies [29-32] showed a higher prevalence of hypertension than other comorbidities. However, our study's prevalence rate of hypertension was 13.1% lower than what was previously documented in international studies [8,10,17]. It has been stated that the prevalence rates of hypertension among COVID-19 patients varied from 15% [29] to 58% [30]. To explain this difference, the age variable should be considered, as there is a high correlation between older ages (above 65 years) and hypertension. Furthermore, the prevalence of hypertension is affected by the age of the patients included [31], with the keeping in mind that the mean age of our cohort was 33.6 years, lower than the mean ages (>65 years) of previous studies.

The univariate analysis of the current study indicated a significant association of the co-morbidities with the severity; this finding was in line with many severity prediction studies [10,17,32,33]. However, the multivariable logistic regression model indicated that only hypertension was the solid independent

risk factor of severity (OR. 6.83), a finding that was also recorded in China (8,30), USA [34], Spain [22] and Bangladesh [35]. Hypertension has been considered a risk factor for the poor prognosis of COVID-19 in many previous meta-analysis studies [36,37]. It is widely accepted that some comorbidities frequently coexist, and the best example is the coexistence of hypertension with diabetes, which was noticed in this study. However, in contrast to Guan et al. (2020) [33], who found a correlation between the number of comorbidities and the severity of COVID-19, such a finding was not recorded in our study. Our results indicated that the prevalence of CKD and tumors among COVID patients were relatively low in consistency with other reports [33,35,38]. The association of the comorbidities with the severe outcome in this study represents an interesting finding since the confounding effect of age did not exist.

Regarding the clinical features at presentation, this study found that dyspnea, and high-grade fever, were very strongly (OR >7) predicted the severe outcome. Previous meta-analysis studies also recorded a similar finding [39-41]. The result of this study in this regard is significant since both dyspnea and fever can easily be measured at the house, and the patient can judge if they need hospitalization or not. Ding, 2021 [42] documented that fever significantly predicted longer hospitalization. Gastrointestinal symptoms, particularly diarrhea, have frequently been reported among COVID-19 patients; in our study, the prevalence of diarrhea was 30.3%. Although the prevalence of diarrhea among the COVID-19 population was subjected to regional variation, sample size, and the number of involved study sites, our finding

was within the global prevalence range (10-50%) of diarrhea among COVID-19 patients stated in the previous meta-analysis studies [43-45]. Several studies have associated diarrhea with a severe course of COVID-19; our study found that diarrhea increases the chance of a severe course about four times [OR: 4.36 (1.85; 10.28)]. However, our finding was in line with [45,46]. Gastrointestinal symptoms are not uncommon in COVID-19 patients since the SARS-Cov-2 receptors, ACE2, are expressed on the enterocytes of the ileum and colon; attachment of the virus to enterocytes causes alteration in the absorption function through dysregulation of the sodium-dependent glucose transport and hence diarrhea ensues [47]. The association of diarrhea with the severe COVID-19 course could be explained as the massive release of proinflammatory cytokines during cytokine storms could damage the digestive tract [48].

Regarding the laboratory findings, in the current study, the univariate analysis revealed a significant association between laboratory findings and the COVID-19 severity as the levels of d-Dimer, ferritin and CRP in the severe group were higher than those of the non-severe group (1435.8, 721.6 and 73.9 vs 618.2, 386.9 and 37.6), findings were agreed with previous studies [7,49-52]. On the other hand, Multivariable logistic regression showed that only ferritin level was significantly associated with the severity of COVID-19; moreover, the prediction strength of all laboratory findings (measured by OR) was not Discernable. In this regard, our results disagreed with a previous Iraqi study conducted by Mohammed et al. (2022) [51] as they found that the elevated levels of biomarkers (Ferritin, CRP, and d-Dimer) are essential predictors of severity;

this disagreement could be attributed to differences in the statistical models as they used only one statistical model (Two Step Cluster analysis) while in our study, two tests were used (Univariate and Multivariable logistic regression), in addition we used 14 different types of variable (demographic, clinical presentation and laboratory findings), while they used only laboratory findings of some biomarkers, so the confounding effect of other variables was considered in our study. It has been stated that no reliable biomarkers can be used for precise prediction of the prognosis and the severity of COVID-19 [53]. However, in agreement with our study, Omran 2021 [10] and Zayed 2022 [54] documented ferritin as a significant predictor for severe COVID-19 [10]. In the same context, [55] concluded that early assessment of ferritin level may help identify the patients with increasing risk of poor outcomes. The high level of proinflammatory cytokines (IL-6) stimulates the production of hepcidin, which regulates the ferritin level [56].

The strength of this study was: I- the use of routinely obtained patient data at hospital admission time (within the first 24 hours) that are applicable in different hospitals. II- Relatively good sample size, representative of the entire population of Al-Nasiriyah city, since the study was conducted in the main COVID-19 hospital specialized for diagnosing and managing COVID-19. III- The study was conducted during peak COVID-19 cases recorded in the city. IV- in contrast to many previous studies, which used only demographic or clinical signs or laboratory findings to predict the severity, our study combined all demographic, clinical symptoms, and laboratory findings in which the confounding effects of different variables

were considered. V- Since the age variable was not included in our logistic regression model, the prediction power of comorbidities was isolated from the confounding effect of the age. VI- Instead of previous predicting studies, which only named the risk factors without determining the strength of prediction, this study arranged the risk factors according to their power of prophecy in terms of OR. However, the interpretation of the findings of this study should consider the following limitations that could not be overcome, including the I-missing of some important host-specific data like; MI and some essential clinical symptoms like cough and radiological findings. The laboratory findings represented the patient's status within the first 24 hours of admission. Our study did not include mortality due to the study design focusing on hospital admission, not follow-up studies.

Conclusions

In this study, some risk factors are found to have strong prediction power for the severity of COVID-19; these factors include; high grade fever, dyspnea, male gender, diarrhoea and presence of comorbidities, particularly hypertension. This work is constructive for clinicians to early discriminate the patients who may develop severe outcomes, which might help efficiently use health resources in sensitive times.

Aknowlegemet

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Ethical Approval

This study was approved by the scientific committee of the community health department of AL-Nasiriyah Technical Institute/ Southern Technical University and the scientific committee of the College of Medicine/ Thi-Qar University. The data were collected according to written approval permission from the Thi-Qar Health Directory. Patient's consensuses were not required as personal information was unidentified.

Competing Interests and Funding

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References

1. WHO. COVID-19 Weekly Epidemiological Update. 2023. Available from: <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-may-2023>
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497–506.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507–13.
4. Epidemiological Group of Emergency Response Mechanism of Novel Coronavirus Pneumonia CC for DC and P. Analysis of Epidemiological Characteristics of Novel Coronavirus Pneumonia. *Chinese Journal of Epidemiology*. 2020;41(02):145–51. Available from: doi: 10.3760/cma.j.issn.0254-6450.2020.02.003
5. Wang Y, Wang Y, Chen Y QQ. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol*. 2020;92(6):568–76.
6. Requia WJ, Kondo EK, Adams MD, Gold DR, Struchiner CJ. Risk of the Brazilian health care system over 5572 municipalities to exceed health care capacity due to the 2019 novel coronavirus (COVID-19). *Science of the Total Environment*. 2020;730.
7. Pramono A, Setiawan YB, Maryani N. Risk Factors for Mortality in Indonesian COVID-19 Patients. *Open Access Maced J Med Sci*. 2022;9(T5):181–4.
8. Fang L, Xie H, Liu L, Lu S, Lv F, Zhou J, et al. Early predictors and screening tool developing for severe patients with COVID-19. *BMC Infect Dis*. 2021;21(1):1–8. Available from: <https://doi.org/10.1186/s12879-021-06662-y>
9. Abolfotouh MA, Musattat A, Alanazi M, Alghnam S, Bosaeed M. Clinical characteristics and outcome of Covid-19 illness and predictors of in-hospital mortality in Saudi Arabia. *BMC Infect Dis*. 2022;22(1):1–11. Available from: <https://doi.org/10.1186/s12879-022-07945-8>
10. Omran D, Soda M Al, Bahbah E, Esmat G, Shousha H, Elgebaly A, et al. Predictors of severity and development of critical illness of Egyptian COVID-19 patients: A multicenter study. *PLoS One*. 2021;16(9 September):1–15. Available from: <http://dx.doi.org/10.1371/journal.pone.0256203>
11. Alrajhi AA, Alswailem OA, Wali G, Alnafee K, Alghamdi S, Alarifi J, et al.

- Data-Driven Prediction for COVID-19 Severity in Hospitalized Patients. *Int J Environ Res Public Health*. 2022;19(5).
12. Cantero-Quintero S, Sáez-Martínez M, Castellanos-Garrido AB. Risk factors for severity and mortality in adults testing positive for COVID-19 in the VI Health Area of Albacete. *Enferm Clin*. 2022;32(4):217–24.
 13. WHO. Clinical management Clinical management Living guidance COVID-19. 2021B. 2021;(January):16–44.
 14. Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D, et al. Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. *Cancer Causes and Control*. 2000;11(6):477–88.
 15. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun*. 2020;11(1):1–10. Available from: <http://dx.doi.org/10.1038/s41467-020-19741-6>
 16. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Health*. 2020;8(April):1–6.
 17. Martínez-Martínez MU, Alpízar-Rodríguez D, Flores-Ramírez R, Portales-Pérez DP, Soria-Guerra RE, Pérez-Vázquez F, et al. An Analysis COVID-19 in Mexico: a Prediction of Severity. *J Gen Intern Med*. 2022;37(3):624–31.
 18. Chen J, Bai H, Liu J, Chen G, Liao Q, Yang J, et al. Distinct Clinical Characteristics and Risk Factors for Mortality in Female Inpatients with Coronavirus Disease 2019 (COVID-19): A Sex-stratified, Large-scale Cohort Study in Wuhan, China. *Clinical Infectious Diseases*. 2020;71(12):3188–95.
 19. Ramadan HK-A, Mahmoud MA, Aburahma MZ, Elkhawaga AA, El-Mokhtar MA, Sayed IM et al. Predictors of Severity and Co-Infection Resistance Profile in COVID-19 Patients: First Report from Upper Egypt. *Infect Drug Resist*. 2020;13:3409–3422. Available from: <https://doi.org/10.2147/IDR.S272605>
 20. Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: Sex differences in immune response and cardiovascular comorbidities. *Cardiovasc Res*. 2020;116(14):2197–206.
 21. Roved J, Westerdahl H HD. Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. *Horm Behav*. 2017;88:95–105.
 22. Klein SL FK. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16:626–38.
 23. Abdullah M et al. Gender effect on in vitro lymphocyte subset levels of healthy individuals. *Cell Immunol*. 2012;272:214–219.
 24. Rachmawati E, Nurmansyah MI, Suraya I, Listiowati E, Kurniawan DW, Ahsan A. Association between cigarette smoking patterns and severity of COVID-19: Findings from a study in 15 private Hospitals in Indonesia. *Tob Induc Dis*. 2023;21:2021–4.
 25. Ismail N, Hassan N, Abd Hamid MHN, Yusoff UN, Khamal NR, Omar MA, et al. Association of Smoking and Severity of Covid-19 Infection Among 5,889 Patients in Malaysia: a Multi-Center Observational Study. *International Journal of Infectious Diseases*. 2022;116(February 2020):189–96. Available from: <https://doi.org/10.1016/j.ijid.2022.01.011>
 26. L. C. Blood groups in infection and host susceptibility. *Clin Microbiol*. 2015;28(3):801–70.

27. Kabrah SM, Kabrah AM, Flemban AF AS. Systematic review and meta-analysis of the susceptibility of ABO blood group to COVID-19 infection. *Transfusion and Apheresis Science*. 2021;60(4):103169.
28. Almadhi MA, Abdulrahman A, Alawadhi A, Rabaan AA, Atkin S, AlQahtani M. The effect of ABO blood group and antibody class on the risk of COVID-19 infection and severity of clinical outcomes. *Sci Rep*. 2021;11(1):19–23. Available from: <https://doi.org/10.1038/s41598-021-84810-9>
29. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*. 2020;382(18):1708–20.
30. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - Journal of the American Medical Association*. 2020;323(11):1061–9.
31. Sisniegues CEL, Espeche WG, Salazar MR. Arterial hypertension and the risk of severity and mortality of COVID-19. *European Respiratory Journal*. 2020;55(6):6–9. Available from: <http://dx.doi.org/10.1183/00000000.00000000>
32. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. *Clinical Immunology*. 2020;217(May):108509.
33. Guan WJ, Liang WH, Zhao Y et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a Nationwide Analysis. *Eur Respir J*. 2020;55(5):2000547. Available from: [doi:10.1183/13993003.00547-2020](https://doi.org/10.1183/13993003.00547-2020)
34. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. *The BMJ*. 2020;369.
35. Ganguli S, Howlader S, Dey K, Barua S, Islam MN, Begum A, et al. Association of food habit with the COVID-19 severity and hospitalization: A cross-sectional study among the recovered individuals in Bangladesh. *Nutr Health*. 2022;28(4):771–82.
36. Fathi M, Vakili K, Sayehmiri F, Mohamadkhani A, Hajiesmaeili M, Rezaei-Tavirani M, et al. The prognostic value of comorbidity for the severity of COVID-19: A systematic review and meta-analysis study. *PLoS One*. 2021;16(2 February):1–25. Available from: <http://dx.doi.org/10.1371/journal.pone.0246190>
37. Yang J. et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *International Journal of Infectious Diseases*. 2020;
38. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. 2020;133(9):1025–31.
39. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *International Journal of Infectious Diseases*. 2020;94:91–5.
40. Jain V, Yuan J min. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission : a systematic review and meta- analysis. *Int J Public Health*. 2020;65(5):533–46. Available from: <https://doi.org/10.1007/s00038-020-01390-7>

41. Hu X, Hu C, Yang Y, Chen J, Zhong P, Wen Y, et al. Clinical characteristics and risk factors for severity of COVID-19 outside Wuhan: a double-center retrospective cohort study of 213 cases in Hunan, China. *Ther Adv Respir Dis.* 2020;14(April):1–15.
42. Ding FM, Feng Y, Han L, Zhou Y, Ji Y, Hao HJ, et al. Early Fever Is Associated With Clinical Outcomes in Patients With Coronavirus Disease. *Front Public Health.* 2021;9(August).
43. Klopfenstein, T.; Kadiane-Oussou, N.D.J.; Royer PYD. Diarrhea: An underestimated symptom in Coronavirus disease 2019. *Clin Res Hepatol Gastroenterol.* 2020;44:282–283.
44. Ozkurt, Z.; Çınar Tanrıverdi E. Gastrointestinal manifestations, liver injury and recommendations. *World J Clin Cases.* 2022;10:1140–1163.
45. Ghimire S, Sharma S, Patel A, Budhathoki R, Khan HM, Lincoln M, et al. Diarrhea Is Associated With Increased Disease Severity in COVID-19: Systematic Review and Meta-Analysis. *American Journal of Gastroenterology.* 2020;115(1):S68–S68.
46. Dhakal S, Charoen P, Pan-ngum W, Luvira V, Sivakorn C, Hanboonkunupakarn B, et al. Severity of COVID-19 in Patients with Diarrhoea: A Systematic Review and Meta-Analysis. *Trop Med Infect Dis.* 2023;8(2).
47. Gu, J., Han, B., & Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission See. *Gastroenterology.* 2020;7(2):33–48. Available from: http://repository.radenintan.ac.id/11375/1/PERPUS_PUSAT.pdf⁰<http://business-law.binus.ac.id/2015/10/08/pariwisata-syariah/>⁰<https://www.ptonline.com/articles/how-to-get-better-mfi-results/>⁰<https://journal.uir.ac.id/index.php/kiat/article/view/8839>
48. Wang, M.-K.; Yue, H.-Y.; Cai J. COVID-19 and the digestive system. *World J Clin Cases.* 2021;9:3796–3813.
49. Assal HH, Abdel-hamid HM, Magdy S, Salah M, Ali A, Elkaffas RH, et al. Predictors of severity and mortality in COVID-19 patients. *The Egyptian Journal of Bronchology.* 2022;16(1). Available from: <https://doi.org/10.1186/s43168-022-00122-0>
50. Cueto-Manzano AM, Espinel-Bermúdez MC, Hernández-González SO, Rojas-Campos E, Nava-Zavala AH, Fuentes-Orozco C, et al. Risk factors for mortality of adult patients with COVID-19 hospitalised in an emerging country: A cohort study. *BMJ Open.* 2021;11(7):1–9.
51. Mohammed SK, Taha MM, Taha EM, Mohammad MNA. Cluster Analysis of Biochemical Markers as Predictor of COVID-19 Severity. *Baghdad Science Journal.* 2022;19(6):1423–9.
52. Ghweil AA, Hassan MH, Khodeary A, Mohamed AO, Mohammed HM, Abdelazez AA, et al. Characteristics, outcomes and indicators of severity for covid-19 among sample of esna quarantine hospital's patients, egypt: A retrospective study. *Infect Drug Resist.* 2020;13:2375–83.
53. Yan L, Zhang HT, Goncalves J, Xiao Y, Wang M, Guo Y, et al. An interpretable mortality prediction model for COVID-19 patients. *Nat Mach Intell.* 2020;2(5):283–8. Available from: <http://dx.doi.org/10.1038/s42256-020-0180-7>
54. Zayed NE, Abbas A, Lutfy SM. Criteria and potential predictors of severity in patients with COVID-19. *The Egyptian Journal of Bronchology.* 2022;16(1). Available from: <https://doi.org/10.1186/s43168-022-00116-y>

55. Para O, Caruso L, Pestelli G, Tangianu F, Carrara D, Maddaluni L, et al. Ferritin as prognostic marker in COVID-19: the FerVid study. *Postgrad Med.* 2022;134(1):58–63. Available from: <https://doi.org/10.1080/00325481.2021.1990091>
56. Velavan TP MC (Mild versus severe COVID-19): laboratory markers. *Int J Infect Dis.* 2020;95:304–7.



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CASE REPORT

Primary Umbilical Endometriosis: A Rare Entity

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Abstract

Umbilicus is a rare site of endometrioma. Spontaneous or primary umbilical endometrioma are still rarer. A 41years old primipara presented with 1.5 years history of nodular umbilical swelling with cyclical pain and increase in size occurring more pronounced during menses with no prior history of any abdominal surgery or procedure or abdominal trauma. Clinical history gave a likely possibility of umbilical endometrioma. Surgical excision was done as she had not responded to prior hormonal treatment and histopathology confirmed the diagnosis.

Keywords: Endometriosis, Umbilical endometrioma, infertility

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Introduction

Endometrioses are functional endometrial glands and stroma outside the uterine cavity. It commonly occurs in pelvic organ presenting as secondary dysmenorrhoea, menorrhagia, pelvic pain and infertility [1]. Presence at site other than pelvic organ in abdomen or genital usually results because of any obstetrical or gynaecological procedure. However spontaneous primary endometriosis superficial to peritoneum are rare. Cutaneous or umbilical endometriomas are rare with estimated incidence of 0.5-1% but those without any prior history of laparoscopic or other surgical procedure are even rarer [1]. Primary cutaneous lesion is <30% of all cutaneous endometriosis. Umbilicus is most common site of primary cutaneous endometriosis accounting for 0.4-4% of all endometriosis [2]. Cutaneous endometriosis usually occurs on abdominal or pelvic scar of gynaecological surgeries such as hysterectomy, episiotomy, caesarean section or laparoscopy [3]. Umbilical endometriosis (UE) was first described by Villar hence also known as Villar's Nodule [2].

Case Presentation

A 41-year-old female para 1 living 1 abortion 1 (P₁ L₁ A₁) presented with history of swelling at umbilical region for 1 and half years associated with pain during menses. There was no history of associated discharge

or bleeding from umbilicus during menses, no history of increase in size during coughing, rather the swelling increased in size during menses. She denied any other gynaecological complain. There was no preceding history of abdominal trauma or any abdominal surgical intervention, no history of contraceptive use. She had an ultrasound showing blood collection at umbilical region. She had taken symptomatic medical treatment for above symptoms but had no relief. On examination an indurated raised area 5*5 cm was present around umbilicus. In view of her clinical presentation, examination and sonographic findings a clinical diagnosis of primary umbilical endometrioma was made and planned for surgical excision as prior medical treatment had failed. Excision of umbilicus enbloc along with fat tissue and fibrous nodular swelling was done until normal tissue visible at margin and sent for histopathological examination followed by closure of umbilical defect. There was no communication with peritoneal cavity. On histopathology gross finding suggested cystic spaces filled with blood. On microscopy sub epithelial tissue showed cystically dilated endometrial glands with inflammatory infiltrate in glandular endometrial lumen along with haemorrhage with hemosiderin laden macrophages in surrounding stroma, these finding were consistent with umbilical endometriosis (Figures 1 and 2).

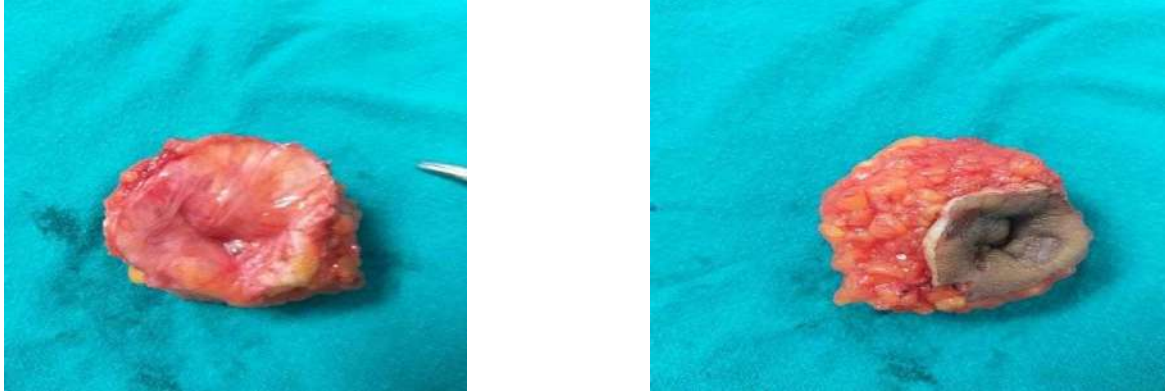


Figure 1. Excised Specimen

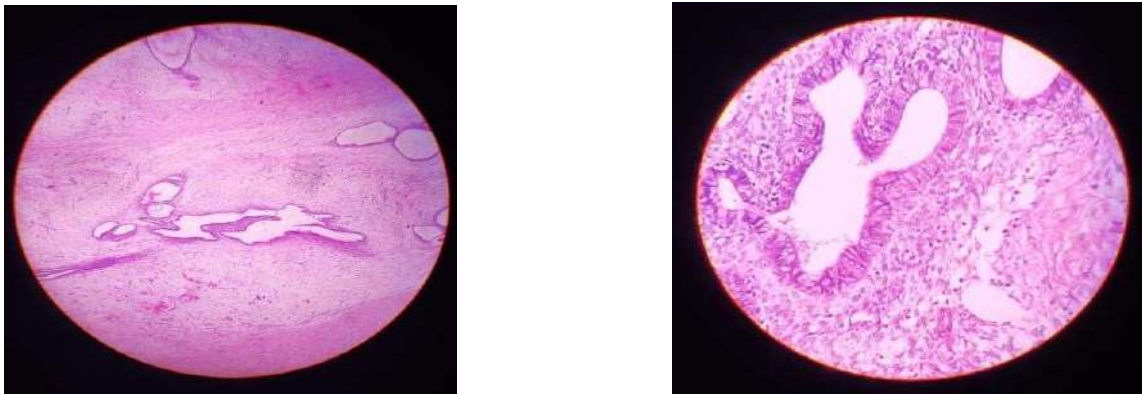


Figure 2. Histopathology images showing endometrial like glands and endometrial stroma

Discussion

Pelvic endometriosis commonly occurs in ovaries, uterosacral ligament, cul-de-sac, bladder as postulated by Sampson's retrograde theory of menstruation. Extra pelvic site like genital organs, skin, lungs or brain may occur due to lymphatic/haematogenous dissemination postulated by Halban. Ectopic endometrium behaves in same way as when present in utero. Hormone level causes thickening, breakdown and bleeding leading to swelling, pain and or bleeding. Umbilical endometriosis may present similarly as pain, swelling or nodule, discolouration/ bleeding which aggravates during menstruation.

Pathogenesis of secondary UE is easy to explain as it follows procedure like laparoscopy or open surgery like caesarean section, amniocentesis etc. or may be associate with pelvic endometriosis but for primary UE there is unclear pathogenic mechanism. Hypothesis proposed are embryonal rest theory of Wolfian or Mullerian remnant as described by Latcher classification of all theories for endometriosis, the transplantation theory in which ectopic endometrial tissue harbours from retrograde menstruation or haematogenous lymphatic dissemination, or both [4,5]. Other hypothesis include the coelomic metaplasia or induction theory,

suggest that sloughed endometrium produces substance that form endometriosis induced by hormonal manipulation, inflammation or trauma or a recent theory of cellular immunity proposed cellular proliferation of ectopic endometrial cells wherein umbilicus acts as physiological scar with predilection for endometrial tissue [6].

Diagnosis of UE can be made by dermoscopy wherein cytologic smear reveals high cellularity with haemosiderin laden macrophages and sheets of stromal and epithelial cells on haemorrhagic background [1]. USG/ MRI usually helps to rule out another differential. FNAC is not conclusive. Histopathology where two of three findings i.e endometrial like glands, endometrial stroma or hemosiderin pigment confirms diagnosis. IHC confirm diagnosis by showing positivity for both oestrogen and progesterone receptors and for antigen CD 10, a marker for stromal cells in endometriosis [7].

Swelling at umbilical region must be differentiated from other possible differentials which either presents as swelling like lipoma, sarcoma, primary/ metastatic cancer, cyst, hernia or differentials which may presents as skin discoloration like pyogenic granuloma, nodular melanoma, primary/metastatic adenocarcinoma, residual

embryonic tissue and cutaneous endosalpingiosis [1,3].

Management of UE is also not clear. Hormonal treatment with progesterone, danazol, GnRH analogues are usually not successful though provide a temporary relief in symptom and size providing a better assess to surgical treatment or they may be less responsive. Hence surgical treatment with either complete umbilical resection with/ without repair of underlying fascia or local resection of nodule are preferred approach². It also helps in appropriate histopathology and exclude unusual cutaneous malignancies. Surgery should ideally be done with at least 1 cm normal margin to prevent local recurrence. Surgery usually done in post menstrual phase to avoid extensive excision.

Conclusion

UE should be considered in any women presenting with clinical pain, swelling, discharge or bleeding or discoloration of umbilicus even in absence of any prior abdominal surgery intervention. Total resection of umbilicus is preferred treatment and also avoid local recurrences.

Conflict of Interest -Nil

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Ethical Considerations: Addressed by the authors.

REFERENCES:

1. Efremidou E I, Kouklakis G, Mitrakas A, Liratzopoulos N, Polychronidis A Ch. Primary umbilical endometrioma: a rare case of spontaneous abdominal

wall endometriosis Int J of General Medicine. 2012; 5:999-1002

2. Fancellu A, Pinna A, Manca A, Capbianco G, Porcu A. Primary umbilical endometriosis. Case report and discussion on management option.

- Int J of Surgery Case Report. 2013; 4:1145-1148
3. Egin S, Pektas B A, Hot S, Mihnanli V. Primary umbilical endometriosis: A painful swelling in the umbilicus concomitantly with menstruation. Int J of Surgery Case Report. 2016; 8:78-80
 4. Pallavi VB, Giurguis M M. Menstruating from the umbilicus as a rare case of primary umbilical endometriosis: a case report. J Med Case Rep. 2009; 3:9326
 5. Kyamidis K, Lora V, Kanitakis J. Spontaneous cutaneous umbilical endometriosis; report of new case with immunohistochemical study and literature review. Dermatol Online J. 2011; 17:5
 6. Chatzikokkinou P, Thorfinn J, Angelidis I K, Papa G, Trevisan G. Spontaneous endometriosis in an umbilical skin lesion. Acta Dermatovenerol Alp Panonica Adriat. 2009; 18:126-130
 7. Capobianco G, Wenger J M, Marras V, Cosmi E, Ambrosini G, Dessole M, et al. Immunohistochemical evaluation of epithelial antigen BER-EP4 and CD 10: new marker for endometriosis. Eur J Gynaecol Oncol.2013;3:254-256



CASE REPORT

A rare case of Colovesical fistula in a middle-aged man managed successfully by conservative management

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Abstract

Colovesical fistula is an improper connection between the urinary bladder and intestinal tract. Although there are many possible causes of colovesical fistula, Chen et al. have classified them into five main classes: congenital, traumatic, tumor, inflammatory, and other. Intestinal diverticulitis accounts for 50–70% of cases in Western countries, and nearly all of them are related to colonic or bladder fistulas. Malignant tumors (20%) rank second in Western countries as the most common cause, which are situated largely in the large intestine. Other related tumours include bladder, cervical, ovarian and prostate cancers, and non-Hodgkin's lymphoma in the small intestine. The third most prevalent cause is Crohn's disease (10%), which occurs mainly in the ileum. "Other causes" include iatrogenic injury; trauma; foreign bodies in the intestinal tract; radiotherapy; chronic appendicitis

Keywords: colovesical, fistula, conservative, cystoscopy.

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Introduction

Colovesical fistula is an improper connection between the urinary bladder and intestinal tract [1]. Although there are many possible causes of colonovesical fistula, Chen et al. [2] have classified them into five main classes: congenital, traumatic, tumor, inflammatory, and other. Intestinal diverticulitis accounts for 50–70% of cases in Western countries, and nearly all of them are related to colonic or bladder fistulas [3]. Malignant tumors (20%) rank second in Western countries as the most common cause, which are situated largely in the large intestine. Other related tumours include bladder, cervical, ovarian and prostate cancers, and non-Hodgkin's lymphoma in the small intestine. The third most prevalent cause is Crohn's disease (10%), which occurs mainly in the ileum. "Other causes" include iatrogenic injury; trauma; foreign bodies in the intestinal tract; radiotherapy; chronic appendicitis [4]; tuberculosis; and syphilis. The male-to-female ratio is 3: 1. The lower prevalence in females is owing to interposition of the uterus between the bladder and sigmoid colon, but higher rates of both colovesical and colovaginal fistula have been reported in females who have previously undergone a hysterectomy [5].

We put forth a case of a middle-aged male with Colovesical fistula which was managed conservatively and recovered successfully.

Case presentation

A middle-aged man of 31 years of age presents to the urology outpatient department of a tertiary care centre with complaints of passing faecal material while passing urine since a period of 15 days. Patient reports history of anorectal malformation with colonic pouch for which ileo-anal anastomosis was done at the age of 2 years in childhood. Patient also reports history of recurrent urinary tract infections in the last 6 months. On examination, patient was clinically afebrile and on local examination, external genitalia examination and perineum was normal. Patient was then further evaluated by laboratory investigations and an ultrasound of the pelvis and abdomen, which showed 1.2 mg/dl of serum creatinine and a normal complete blood count ultrasound revealed bilateral normal kidneys with bladder wall thickening. Patient then underwent Computerised Tomography of abdomen and pelvis with oral contrast which revealed rectosigmoid junction adherent to the left postero-lateral wall of bladder (Figures 1 and 2).

The patient then underwent Barium enema study which revealed a fistulous communication seen between rectosigmoid junction and left posterolateral wall of urinary bladder (Figure 3).

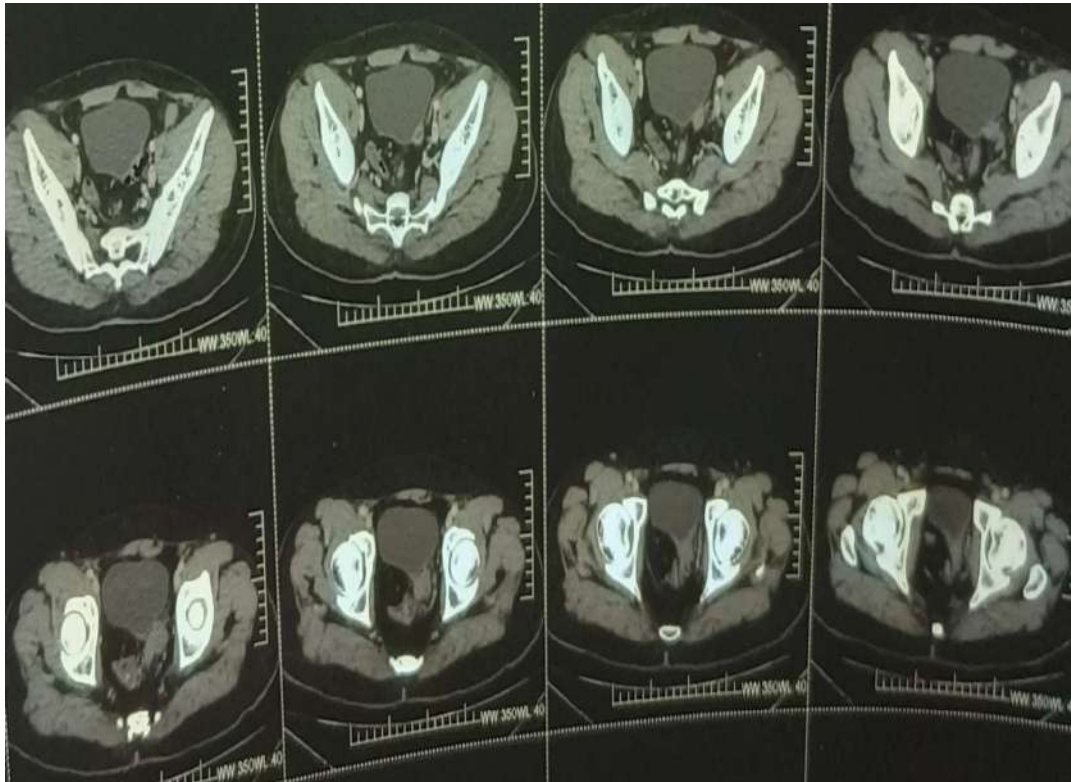


Figure 1. Serial axial sections of CT scan of the patient showing adherent rectosigmoid junction adherent to the left posterolateral wall of bladder.

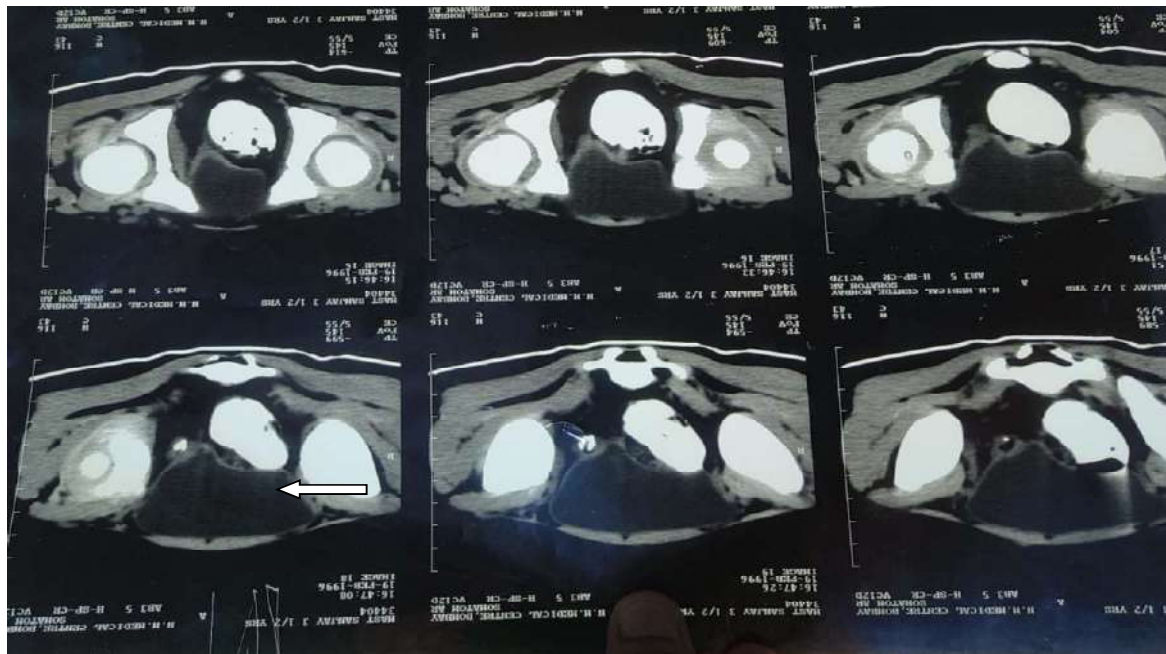


Figure 2. Serial axial sections of CT scan with oral contrast showing the fistulous communication of Colovesical fistula.



Figure-3: Barium enema showing evidence of colovesical fistula.

A diagnostic cystoscopy was done along with instillation of Betadine stained solution through a tube inserted into the rectum to aid in the identification of the fistula which revealed infratrigonal single

fistulous opening on the left side of the urinary bladder of size 1cm * 0.5 cm which was seen to exude betadine stained fluid confirming the presence of Colovesical fistula (Figure 4).



Figure 4. Diagnostic Cystoscopy image showing evidence of colovesical fistula after betadine instillation through a per rectal tube.

The patient was supervised carefully with antibiotics and avoiding constipation. Over a period of 4 weeks, the symptoms entirely resolved with no active intervention and the patient was discharged. The patient has been on regular follow up till a period of 1 year and has no recurrence of complaints.

Discussion

Colovesical fistula presents clinically as passage of foul-smelling urine along with passage of gas and stool particles in urine. Recurrent urinary tract infections can also be a presentation. For the diagnosis of Colovesical fistula, traditional diagnostic methods such as cystoscopy, barium enemas, colonoscopy and cystography are used. Barium enemas shall be used to show the primary lesion although there is a negative of the contrast agent into the bladder. But barium enemas only sensitivity ranges from 20–35% [6].

According to Gruner et al., radiography of centrifuged urine samples taken right after a barium enema (Bourne test) can increase the diagnostic accuracy to 90%. Diagnosis cannot be made with simple bladder imaging. Cystography can be performed to show that contrast is passing outside the bladder, but this won't be accurate if the bladder's underfilling or inflammatory oedema causes the fistula's outlet to close. Cystography only reveals gas and an increase in the bladder wall where it attaches. If the patient's position is altered to enhance abdominal pressure or if there is a significant obstruction of the urine outlet, the diagnostic accuracy of cystography increases. Because cystography can detect fistula and be used to rule out urological malignancies, bladder stones, and interstitial cystitis, several authors saw it as a necessary diagnostic procedure. A localized region with erythema, oedema, and congestion is a common finding in the

early stages of fistula. Following this, a fistula is surrounded by bullous oedema and mucosal papillomatous hyperplasia. Occasionally, floating masses, such as faecal waste, are also visible. Nonetheless, more than 50% of patients have a cystoscopy fail to find a fistula; instead, the procedure merely reveals intravesical oedema, which suggests a fistulous tract, mucus, and feces in the bladder. Colonoscopy is not very reliable in identifying fistulas. Nonetheless, colonoscopy is sensitive in identifying underlying colon cancer, particularly those linked to diverticular illness. Research on the use of MRI to diagnose fistulas has been lacking. Given that CT imaging is more widely available, MRIs should be utilized as a second-line inquiry for the diagnosis of colovesical fistulas, such as in the imaging of complex fistulae, as it is unclear whether MRIs provide any appreciable advantages over CT scans [6]. A CT scan is the most sensitive and non-invasive test available, with a 60–100% diagnosis accuracy [3]. The diagnosis of the condition can be aided by observing the contrast agent in fistulae on enhanced CT scans. The location of fistulae can be aided by cystoscopy in conjunction with the detection of a mass outside the bladder wall, local thickening of the bladder wall, and thickening of the nearby bowel wall. A CT scan has the following benefits: it can reveal abscess formation, identify intestinal diverticula, identify adhesions between the intestine and the bladder, show accompanying soft tissue masses forming the fistula between the bladder and the bowel, and enable tumour staging for surgical management. The most typical findings are gas in the bladder, localized bladder wall thickening, neighboring bowel wall thickening, and soft tissue masses adhering to the bladder

wall's outside [8,9]. To prevent bladder opacification, some writers choose for an oral contrast agent instead of an intravenous one [3,10]. Occasionally, the viscosity of the contrast agent prevents it from fitting through a tiny fistula. In certain situations, conservative management may be effective. Surgical management still the most effective technique to treat the illness. There is no standard surgical treatment and hence, the treatment is individualised according to the clinical presentation of the patient. The most commonly employed method for the surgical treatment of this condition is to separate the fistula formed by the impacted bladder and bowel walls, and subsequently fix the lesion. However, if there is underlying malignancy, then the patient will require partial or total remodelling along with chemotherapy and regular review [11].

Conclusion

Colovesical fistula presents a unique challenge to a practising urologist. Various management options are available for its management. Our case report demonstrates how a small Colovesical fistula can be managed successfully by conservative management.

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Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

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Statement on ethical clearance and consent for participation:

Patient consent was obtained for publication of the case report.

Statement on Data availability

It is a case report and data was obtained from the hospital records.

References:

1. Kavanagh D, Neary P, Dodd JD, Sheahan KM, O'Donoghue D, Hyland JM. Diagnosis and treatment of enterovesical fistulae. *Colorectal Dis* 2005; 7: 286–91.
2. Chen WS, Hsieh JH, Jiang JK, Lin JK, Hsu H, Lin TC. Enterovesical fistula: 10 years experience. *Chin Med J* 1997; 59: 283–8.
3. Scozzari G, Arezzo A, Morino M. Enterovesical fistulas: diagnosis and management. *Tech Coloproctology* 2010; 14: 293–300.
4. Gross M, Peng B. Appendico-vesical fistula. *J Urol* 1969; 102: 697–8.
5. Pontari MA, McMillen MA, Garvey RH, Ballantyne GH. Diagnosis and treatment of enterovesical fistulae. *Am Surg* 1992; 58: 258–63.
6. Holroyd DJ, Banerjee S, Beavan M, Prentice R, Vijay V, Warren SJ. Colovaginal and colovesical fistulae: the diagnostic paradigm. *Tech Coloproctol* 2012; 16: 119–26. doi: <https://doi.org/10.1007/s10151-012-0807-8>.
7. Gruner JS, Sehon JK, Tohnson LW; Diagnosis and management of enterovesical fistulas in patients with Crohn's disease. *AM; J Surg* 2002; 68: 714–8.
8. Mosner A, Probst M, Jonas D, Beecken WD.; A easy method to localize the vesical opening of an enterovesical fistula. *J Urol* 2002; 167: 1794.
9. Jarrett TW, Vaughan ED.; Accuracy of computerized tomography in the diagnosis of colovesical fistula secondary to diverticular disease. *J Urol* 1995; 153: 44–6. doi: <https://doi.org/10.1097/00005392-199501000-00018>.
10. Goldman SM, Fishman EK, Gatewood OM, Jones B, Siegelman SS, Olga MB. CT in the diagnosis of enterovesical fistulae. *AJR Am J Roentgenol* 1985; 144: 1229–33. doi: <https://doi.org/10.2214/ajr.144.6.1229>
11. He wei-yang, Gou xin, Wang ming, yuan-zhong D, Tang shao-bing. Diagnosis and treatment of enterovesical fistula; *Journal of Chongqing Medical University* 2010; 35.



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CASE REPORT

An atypical case of neurobrucellosis: intracranial mass lesion mimicking tuberculosis clinically and on imaging

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Abstract

Brucellosis is the most common bacterial zoonosis and it causes approx half million human infections per year worldwide. Neurobrucellosis should be considered as possible differential diagnosis when a patient presents with symptoms of neuropsychiatric spectrum and fever. We report a case of neurobrucellosis in a patient who presented with headache, vomiting and an episode of generalized tonic clonic seizure.

Keywords: Brucella, Neurobrucellosis, Zoonosis

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Introduction

Brucellosis is the commonest bacterial zoonosis and it causes approx half million human infections per year worldwide [1]. It is caused by the gram negative, facultative intracellular coccobacilli of the Brucella species. Human brucellosis is a multisystem disease that can present with a broad spectrum of manifestations and various complications; It has a wide spectrum of clinical manifestation due to possibility of extensive involvement of organ systems. It comes under the WHO list of the neglected tropical zoonosis. The common symptoms are fever, myalgia, arthralgia, night sweats and weight loss.

Brucellosis can develop at any stage of the disease and have variable manifestations which include meningoencephalitis, encephalitis, myelitis, subarachnoid hemorrhage, radiculitis, neuropathies and psychiatric manifestations [2,3,4]. In the various literatures, diagnosis of the neurobrucellosis is problematic. Some authors suggest diagnosis of brucellosis is based on neurological symptoms while some suggest diagnosis is based on the microbiological and biochemical evidence [5,6]. A positive response to treatment is very important marker for diagnosis. So, examining the patient's complete history such as occupation, travel history and similar complain in family member can be very helpful to reach the diagnosis.

Case Report

A 17-year-old female patient presented to the Emergency Room with complaints of headache and two episodes of

vomiting. Her headache was predominantly in frontal region and throbbing in nature. Her caretaker gave history of single episode of GTCS 3 days ago. Her caretaker has also informed that she has slightly altered behavior since last 5-6 day with slightly slurred speech. On examination it was revealed that she has mild fever (101 F). The fever is not associated with chills and rigors. There was no history of photophobia, blurred vision, motor weakness, abnormal movements, gait problem syncope, tremors or sensory loss.

On examination, her blood pressure was 136/88 mmHg, pulse rate of 88 beats per minute, and respiratory rate of 19 breaths/min. There was no pallor, icterus, lymphadenopathy, clubbing or cyanosis. Per abdominal examination and auscultation findings were normal. There were no cranial nerve abnormalities. Motor examination showed normal muscle bulk normal reflexes and generalized rigidity. Examination of other system did not reveal any abnormality.

Her hemogram revealed mild elevation of WBC count of 11500 per cumm, however rest of the hemogram renal function test renal function test and thyroid function test were normal. Sputum microscopy turned out to be negative for acid fast organism, so was genexpert PCR. Inflammatory markers including ESR and c reactive protein were slightly raised.

Subsequently Magnetic resonance imaging (MRI) with contrast was done to assess any intracranial space occupying lesion or any other pathology. It showed irregular ill-defined area of heterogeneous hyperintensity on FLAIR & T2W images is seen in right frontal lobe. No obvious diffusion restriction seen. On TIW images,

the lesion appear hypointense. Contrast study showed mild to moderate enhancement in right frontal lobe with few patchy areas in periventricular region in right frontal lobe along with linear leptomeningeal enhancement. Increased vascularity was seen in right frontal lobe with enlarged right internal cerebral vein.

As genexpert was negative, patient underwent CSF analysis and right frontal craniotomy with brain biopsy to evaluate the cause of the lesion and to confirm the diagnosis. The results showed positive Brucella antibodies in serological survey with active chronic inflammation in brain biopsy (Figures 1 and 2).

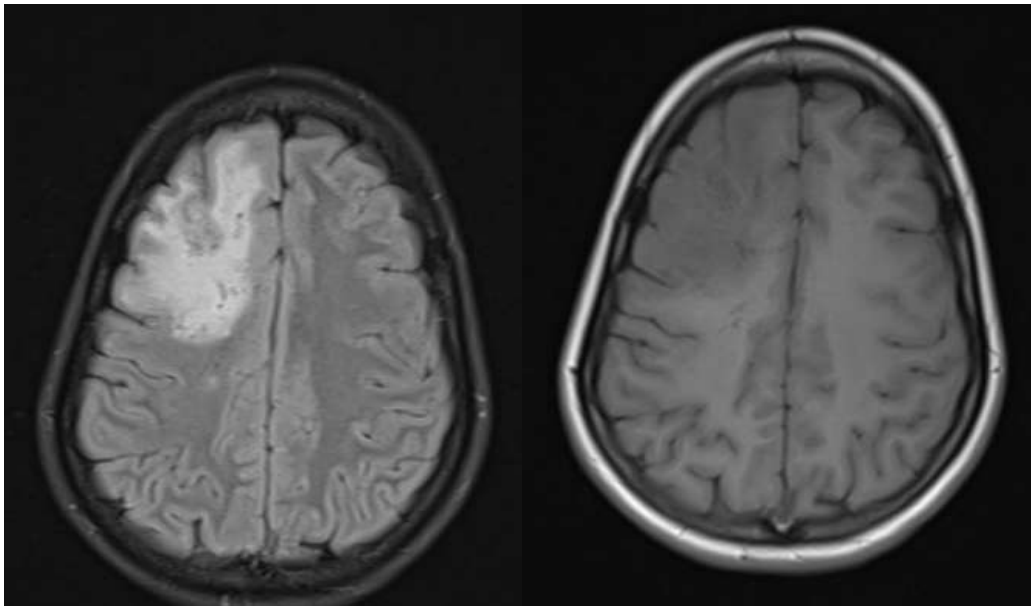


Figure 1. T1 weighted images and FLAIR images of the patient: On flair heterogenous hyperintense lesion noted in right frontal lobe which is hypointense on TIWI

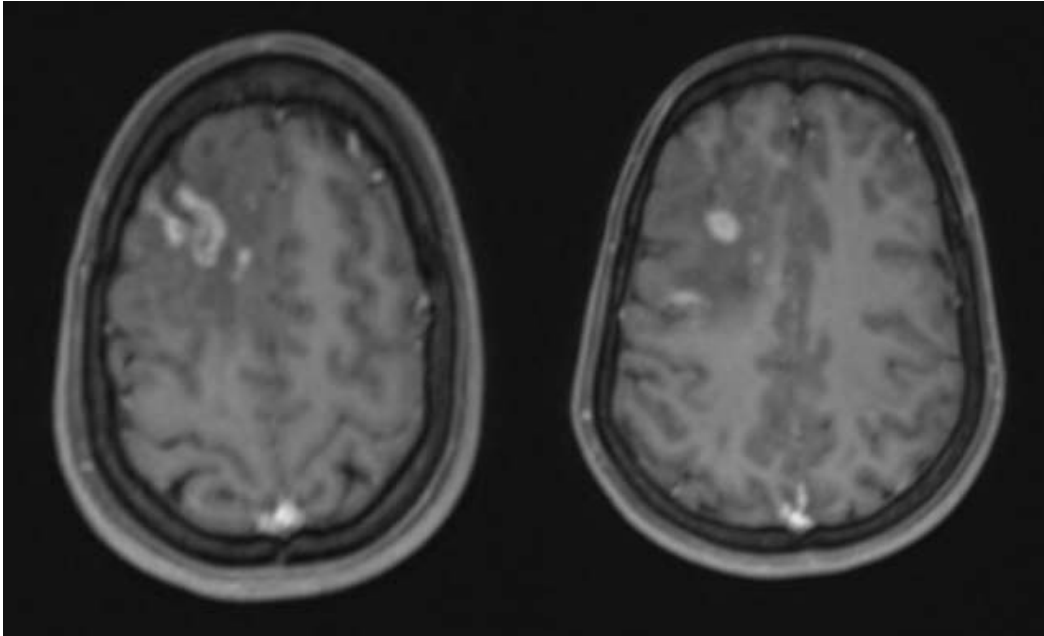


Figure 2. On post-contrast study, moderate areas of enhancement in right frontal lobe with few patchy areas of enhancement in periventricular right frontal lobe along with linear leptomeningeal enhancement

Post-treatment, the patient improved significantly and did not have any complaints. Follow up MRI study with contrast was performed after 40 days which

showed significant reduction in the previously mentioned T2 hyperintensities as well as leptomeningeal enhancement (Figure 3).

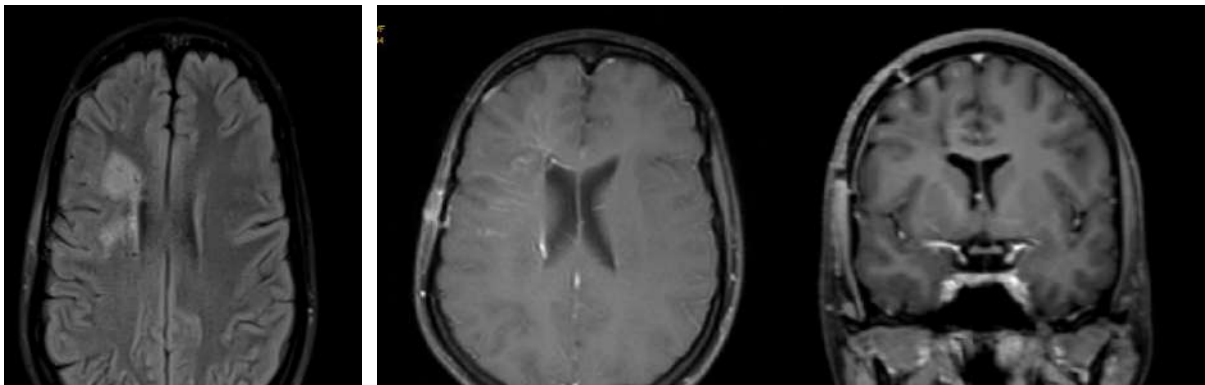


Figure 3. Post treatment follow up MRI suggest significant reduction in the previously mentioned T2 hyperintensities as well as reduced lepto meningeal enhancement on post-contrast study.

Discussion

Brucellosis is a deceptive infectious disease in India, especially due to high prevalence of tuberculosis. There are only few reports on brain involvement of brucellosis, however involvement of cervical cord and vertebral column are more common. Clinical presentation is often variable and depends upon the site of involvement. It is observed that headache, hearing loss, blurred vision, altered behavior and confusion are common association with neurobrucellosis. Along the cranial nerves facial, vestibulocochlear and abducense are more commonly affected than other cranial nerves.

Brucella bacteria can affect the CNS directly or indirectly by result of cytokine and endotoxin release in the neural tissue. Infection triggers the immune mechanism leading to a demyelinating state of brain parenchyma as well as spinal cord [7].

Neurobrucellosis is often a diagnostic puzzle due to lack of proper diagnostic radiological criteria. However, CSF indicating lymphocytic pleocytosis and increased protein with positive CSF culture for brucella organism and positive Brucella IgG with neurological dysfunction not explained by other neurological disease should make high suspicion of neurobrucellosis in a patient in with imaging modalities our suspicious of infective meningitis or meningoencephalitis [8].

Neurobrucellosis on CT scan show diffuse white matter changes with meningeal enhancement. Hydrocephalus with basal ganglia hemorrhage and cerebral edema are other common findings. MRI is better modality, on T1 weighted images changes of arachnoiditis can be seen. T2/ FLAIR

demonstrate diffuse hyperintense lesions commonly affecting the white matter with areas of focal demyelination. Contrast study demonstrate granuloma or abscess with ring enhancement. Changes of meningoencephalitis are also better visualised on contrast study. It is important to note that many of the radiological finding seen in Neurobrucellosis can overlap the findings of CNS tuberculosis and hence it is important that differential diagnosis of neurobrucellosis should be considered in radiologically suspicious CNS tuberculosis patient's in which gene xpert turns out to be negative or there is no favorable response to antitubercular therapy. Other important differential diagnosis is demyelinating disorder like acute disseminated encephalomyelitis and multiple sclerosis; however focal area of demyelination with changes of meningitis and meningoencephalitis should be associated with neurobrucellosis .

Conclusion

Neurobrucellosis has favorable response with drug therapy, so it is important that diagnosis of neurobrucellosis should be considered in clinically and radiologically suspicious cases. Neurobrucellosis should be considered as an important differential diagnosis of various demyelinating disease and tuberculosis in India when there is no favorable response to treatment or serological studies not supporting them. Neurobrucellosis can have wide spectrum of presentation so proper clinical and radiological evaluation become essential for diagnosis of Neurobrucellosis.

Conflicts of interest

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

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References

1. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis*. 2006 Feb;6(2):91-9. doi: 10.1016/S1473-3099(06)70382-6.
2. Zumla A. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. *Lancet Infect Dis*. 2010 May;10(5):303-4. doi: 10.1016/S1473-3099(10)70089-X.
3. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. *New England Journal of Medicine*. 2005 Jun 2;352(22):2325-36.
4. McLean DR, Russell N, Khan MY. Neurobrucellosis: clinical and therapeutic features. *Clin Infect Dis*. 1992 Oct;15(4):582-90. doi: 10.1093/clind/15.4.582.
5. Eren S, Bayam G, Ergönül O, Celikbaş A, Pazvantoğlu O, Baykam N, Dokuzoğuz B, Dilbaz N. Cognitive and emotional changes in neurobrucellosis. *J Infect*. 2006 Sep;53(3):184-9. doi: 10.1016/j.jinf.2005.10.029
6. Bodur H, Erbay A, Akinci E, Colpan A, Cevik MA, Balaban N. Neurobrucellosis in an endemic area of brucellosis. *Scand J Infect Dis*. 2003;35(2):94-7. doi: 10.1080/0036554021000027000.
7. Ceran N, Turkoglu R, Erdem I, Inan A, Engin D, Tireli H, et al. Neurobrucellosis: clinical, diagnostic, therapeutic features and outcome. Unusual clinical presentations in an endemic region. *Braz J Infect Dis*. 2011;15(1):52-9.
8. Kochar D K, Kumawat B L, Agarwal N, Shubhakaran, Aseri S, Sharma B V, Rastogi A. Meningoencephalitis in brucellosis. *Neurol India* 2000;48:170.



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LETTER TO THE EDITOR

The Global “Paraben Toxicity” Discourse: A Call for Indian Doctors and Researchers to Step in

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Parabens (*methylparaben, ethyl paraben, propyl paraben, butyl paraben, heptyl paraben and benzyl-paraben etc.*) are the most widely used preservatives in cosmetic, pharmaceutical, and several other industrial products including food stuffs. The term ‘paraben’ refers to a group of alkyl esters of para-hydroxybenzoic acid, which vary from one another at the para position of the benzene ring due to different chemical substitutions [1]. Since their initial introduction in the early 20th century, parabens have become the most regularly used preservative (not vehicle) in drugs and cosmetics around the world.

In general, parabens may be found in creams, pastes, oils, fats, glues, food, and cosmetic items [2]. Besides water, methyl and ethyl parabens stand out as widely utilized chemicals in cosmetic formulations like moisturisers, emollients, hypopigmentation agents etc. Their use is prevalent because they are cheap, colourless, odourless, and generally presumed to be nontoxic by common population. They possess stability and efficacy across a diverse pH range, coupled with a broad spectrum of antibacterial action. Additionally, their chemical stability and biodegradability further contribute to their appeal and justify their utilization [3].

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The preservative effects of parabens are caused, at least in part, by disruptions in membrane transport and mitochondrial activity in microorganisms, thereby increasing the shelf life of any substance [4]. The toxicological profile i.e. ADME and health effects of parabens are summarized in Figure 1. However, the major routes of exposure to these substances are dermal and oral, especially concerning cosmetic and food products, respectively. Parabens can reach the systemic circulation through oral ingestion or transdermal penetration, as evidenced by the measurement of systemic paraben concentrations after exposure to these chemicals [5]. On the other hand, parabens are quickly converted to p-hydroxybenzoic acid by esterases in the liver and in the skin, followed by elimination via urine [6]. The majority of parabens are excreted as

glycine, sulfate, and glucuronide conjugates [7]. Carboxyl esterase enzymes present in the skin and subcutaneous fat partially metabolize topically applied parabens. These esterases hydrolyse parabens into para-hydroxybenzoic acid and respective side chains [8]. While esterases localized to keratinocytes are more active against parabens with longer chains, the carboxyl esterases found in subcutaneous fat are more active against those with shorter chains. Due to quick intestinal and hepatic metabolism, the topical use of paraben-containing components is more likely to contribute to systemic paraben levels than oral ingestion [9]. This idea is supported by the fact that the majority of human paraben exposure occurs as a result of the widespread use of personal care products.

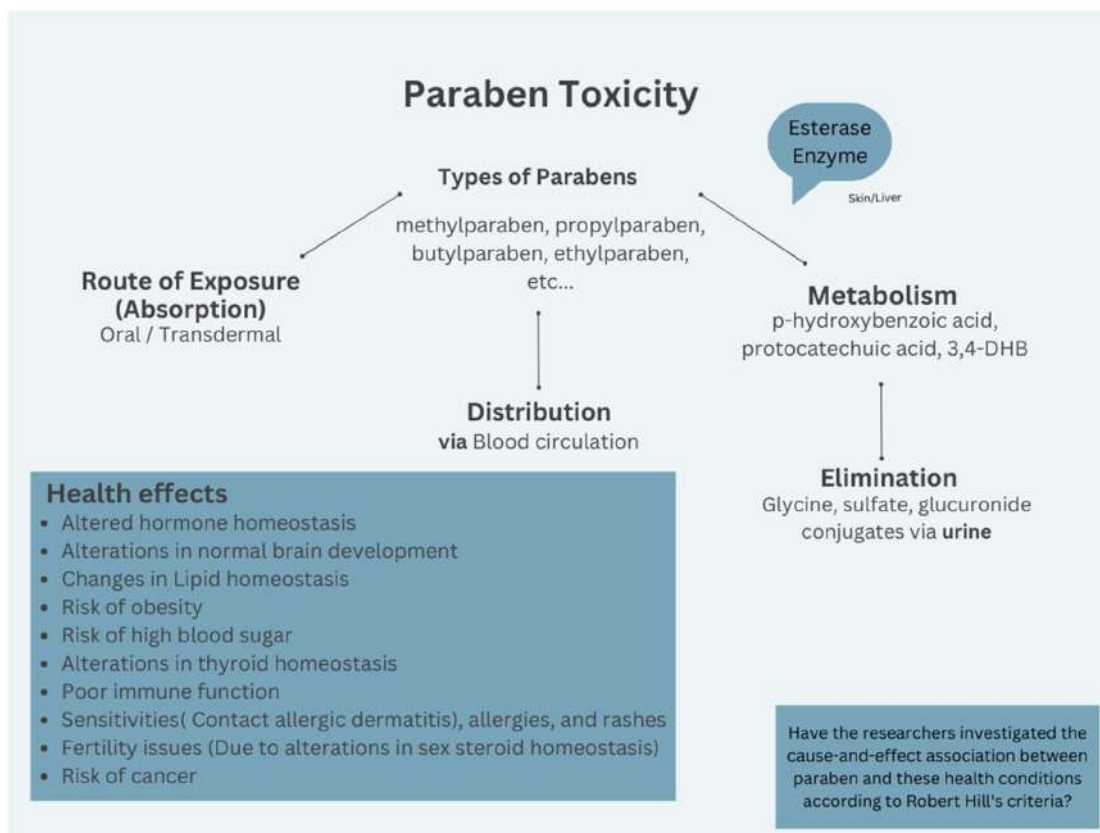


Figure 1. Absorption, Distribution, Metabolism and Elimination of Parabens & Health effects.

It was previously believed that parabens absorbed by the body were completely metabolized by esterases in the liver (and kidney in some animal species), and excreted in the urine, and did not build up within the body. However, in a study, para-hydroxybenzoic acid (PHBA), the primary metabolite of parabens, was found in all patient blood and milk samples, while individual parabens were not found in either [10].

Parabens, recognized as endocrine disruptors, have been extensively studied for their links to disruptions in estrogen hormone action [6]. In recent decades, significant research has focused on their potential estrogenic activities, leading to a concerted effort to replace them with available alternatives [11]. Due to their structural similarity to the estrogen molecule, parabens interfere with nuclear receptors for androgens, estrogens, progesterone, glucocorticoids, and other hormones, classifying them as endocrine-disrupting chemicals (EDCs). Studies on humans and rats have shown how parabens affect steroidogenesis and the activity of enzymes responsible for metabolizing endogenous hormones.

Beyond causing diseases in the reproductive and nervous systems potentially effecting normal development of a foetus, parabens also trigger skin allergies, thyroid-related issues, and malignancies by disrupting hormone function [12,14]. Extensive research in recent decades has linked parabens to disruptions in the activity of the estrogen hormone as already stated [5]. The investigation into their estrogenic properties intensified after the identification of unconjugated parabens in breast cancer cells. This sparked unwarranted concerns and speculation linking parabens with breast cancer [13].

Some studies assessed the risk of propyl- and butylparaben, revealing impacts on testosterone levels and sperm count in rats exposed to these chemicals in their diet for four and eight weeks, respectively. Propylparaben specifically led to a daily decrease in testis sperm production at dosage levels around 10, 100, and 1000 mg/kg bw/day, with the epididymal sperm count affected at 100 mg/kg bw/day [15]. Notably, commonly used parabens exhibit varying degrees of estrogenic activity in different test methods both in vitro and in vivo. Longer paraben chains and branched alkyl chains correspond to increased estrogenic activity. Additionally, PHBA demonstrates estrogenic action in both in vivo and in vitro tests. A uterotrophic experiment in mice investigated sensitivity to butylparaben exposure, considering reported in vivo estrogenic effects and known strain variations in susceptibility to endocrine disruption [16]. Some research reported the ability of propylparaben and butylparaben to cause DNA damage detectable in comet assays and induction of chromosome aberrations together with sister chromatid exchange [5].

Several studies reveal parabens' estrogen agonist properties, androgen antagonist activity and enzyme inhibition. The estrogenic activity of parabens increases linearly from methylparaben to n-butylparaben, and they can inhibit sulfation of estrogen through the inhibition of SULTs (sulfotransferase enzymes). Maternal exposure to butylparaben during gestation and lactation has been linked to reproductive disorders in male offspring [5]. Propylparaben is associated with earlier menstruation, while methylparaben is linked to earlier breast development, pubic hair development, and menstruation in girls aged 9 to 13 [17].

Overall, the impact of parabens on the Hypothalamo-Pituitary-Gonadal-Axis, influencing secondary sexual characteristics, menstruation duration, sperm quality, and their effects on estrogen-dependent breast cancer cells, as well as Hypothalamo-Pituitary-Thyroid axis in pregnant and nursing mothers (resulting in elevated TSH, TT3 levels and higher birth weights in boys concerning), and transplacental spread etc. remains a subject of vigorous debate within the core scientific community and medical fraternities of the Western world. The need for more in-vivo data and well-planned studies had been stressed by researchers and medical doctors time and again [18]. By the same token, there has been enough discussion on the local effects of parabens being used in dermatological and ocular drug preparations. The health issues concerned range from irritation, dermatitis (allergic/contact), a risk factor for depigmentation disorders and skin cancers (basal cell carcinoma and melanomas) [19]. Interestingly, several dermatological associations have advocated the need for research on systemic effects rather than local effects, as parabens rarely cause acute and local effects, and most of the purported effects are chronic and long-term [20-22]. For the sake of clarity, the cutaneous manifestations of toxicity include inflammation, corrosion, contact dermatitis, ageing etc. to name of few.

Similarly, there have been occasional discussions both in favour of and against exploring economically viable and pro-health alternatives to parabens. Simultaneously, there is a cautious approach towards abandoning parabens, given their established relative safety, as toxicology data for newer preservatives is yet to be ascertained. Additionally, the consideration of using paraben free products with a shorter shelf life that are

more human and ecologically friendly has been contemplated; especially during pregnancy and lactation owing the fact that research demonstrated effects of paraben on maternal and child thyroid health. The persistence of parabens in the environment has also been a topic of discussion, including considerations on how to remediate their impact [21,22,23].

Conflicting evidence persists in the literature regarding the impact/effect of parabens on thyroid hormones, with uncertainties surrounding whether they lead to an increase or decrease in hormone levels. Most studies have shown elevated TSH levels in children and decreased T3 and T4 levels in adults. The data on pregnant women is sometimes conflicting at different periods of gestation. For example, some studies indicate raised TSH during early pregnancy and decreased TSH between 16-20 weeks, while a few studies showed increased T3 levels, a majority showed decreased T3 and T4 levels. It is acknowledged, however, that parabens influence thyroid homeostasis. Similarly, their effects, such as pro-estrogenic, anti-androgenic, adipogenic, and carcinogenic impacts in humans, necessitate methodological validation or refutation on a global scale through multilateral cooperation [22].

Although some systematic reviews have been conducted in this area of research, the reliability of results out of these reviews is compromised due to the majority of them lacking specificity for humans. The overall quantity and quality of published literature studying the association between parabens and human health (leaving aside in vitro, in vivo, in silico papers) is insufficient for establishing a higher level of evidence using systematic reviews or meta-analysis. The limited number of clinical studies, mostly comprising birth cohort studies or

investigations on adolescents, expectant and lactating women, focuses on the mere presence of parabens and their metabolites in body fluids and the observed alterations in endocrinological markers, such as hormones and hormone precursors and often times the studies include a cocktail of potential endocrine disruptors.

Some of these studies lack methodological rigor, as they often fail to properly account for very essential 'host' and 'environmental' factors. Moreover, the concept of 'endocrine disruption' may seem just fancy in the realm of 'evidence-based medicine' when a clinical sign/symptom/disease is not evident in the study population. A causal association or potential link goes beyond the mere presence of a substance and changes in hormone levels. Paraben toxicology in medicine requires more emphasis on clinical endpoints rather than solely relying on laboratory values.

The considerable variability in hormone assessment results, at times conflicting, is influenced by factors like the method used, calibration, timing of sample collection, individual health conditions, and various other uncontrolled variables. Unfortunately, many studies have not adequately addressed these factors, compromising their reliability for making assessments or establishing links to specific diseases.

In India, the use of parabens in drugs and cosmetics is governed by BIS Standard IS 4707 (Part 2): 2017, along with relevant provisions of the Indian Pharmacopoeia. Meanwhile, the Food Safety Standards Authority of India (FSSAI) regulates the use of parabens as a food additive in the country. Stricter regulations on parabens are observed in the European Union (for example in the EU: The maximum total concentration allowed in such consumer products is 8 g of parabens

per kg of cosmetic product, with no single paraben having a higher concentration than 4 g/kg. for longer paraben molecules; the maximum concentration of 1.9g/kg)[24], Canada and the USA. These countries have established comprehensive frameworks overseen by regulatory bodies such as the European Commission, the U.S. Food and Drug Administration (FDA), and Health Canada, ensuring adherence to specified limits and safety standards for the use of parabens in drugs, cosmetics, and food products.

Concerns in Indian Context:

1. Limited research has been conducted on the impact of preservatives, such as parabens, in personal care products on the Indian population, as evident in the scarce literature [25]. It is imperative to initiate well-structured studies in our country to comprehensively understand the effects of these preservatives.
2. A comprehensive investigation into chronic paraben toxicity necessitates interdisciplinary collaboration, involving endocrinology, dermatology, paediatrics, and obstetrics departments. Establishing baseline levels of parabens and their metabolites within the Indian population and environment is crucial for informed toxicological assessments.
3. Delving into toxicogenomic considerations pertaining to both dermal and systemic metabolism of parabens specific to the Indian population is vital for unravelling potential genetic susceptibilities.
4. Exploring the potential influence of skin and gut microbiomes on paraben toxicology in the Indian population is paramount for a

holistic understanding of the molecular mechanistic toxicology of parabens.

5. Current regulations lack consideration for cumulative exposure in defining permissible limits for substances. Investigating and rectifying this oversight is essential for a more comprehensive approach to risk management.
6. A multi-centric research initiative at Indian medical colleges is essential to decipher the role of confounding variables influencing associations between parabens and various health conditions.
7. The Department of Health Research, Government of India should consider adopting a comprehensive approach, aligning with Hill's criteria of causation for investigating the association between paraben and putative health conditions. Both clinical and epidemiological datasets are imperative to unravel the intricacies of this subject matter.
8. The professional associations of the specialities of paediatrics, endocrinology, obstetrics, and dermatology should collaborate to establish a working group. This group can issue a position paper, consolidating scientific knowledge on the toxicity of parabens and frame proper research questions and methods to work out them scientifically.
9. In light of the burgeoning industry of paraben-free products in India, research endeavours are warranted to inform public choices and address broader public health concerns.
10. Inclusion of parabens and their toxicology in the medical

curriculum is essential for enhancing the knowledge base of healthcare professionals and researchers in our country.

In conclusion, it is a categorical imperative for our scientific community to actively engage in the ongoing global discourse surrounding paraben toxicity. The existing body of clinical research appears inconclusive and appears to lack the prescribed scientific rigor. We believe that the Indian scientific community, with the collaboration and support of healthcare professionals, is well-positioned to address the unresolved questions pertaining to paraben toxicity. This is not merely an academic debate but holds significant implications for public health, particularly given the substantial population in our context that utilizes cosmetic products, drugs containing parabens as preservatives, and certain foods preserved with parabens. It is high time to prioritize and launch comprehensive research initiatives to guarantee the safety of our citizens, with a particular focus on high-risk groups such as pregnant women and children.

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Conflict of Interest

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References

1. Richardson EL. Up-date frequency of preservative use in cosmetic formulas as disclosed to FDA. *Cosmetic and Toiletries*. FDA Report. 1977;92.
2. Kang SH, Kim H. Simultaneous determination of methylparaben, propylparaben and thimerosal by high-performance liquid chromatography and electrochemical detection. *J Pharm Biomed Anal*. 1997;15(9–10):1359–64. Available from: [http://dx.doi.org/10.1016/s0731-7085\(96\)02031-6](http://dx.doi.org/10.1016/s0731-7085(96)02031-6)
3. Maddox DN. The role of p-hydroxybenzoates in modern cosmetics. *Cosmetic Toiletries*, FDA Report. 1982;97:85–8.
4. Jackson EM. Moisturizers of today. *J Toxicol Cutaneous Ocul Toxicol* [Internet]. 1992;11(3):173–84. Available from: <http://dx.doi.org/10.3109/15569529209042706>
5. Darbre PD, Harvey PW. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. *J Appl Toxicol*. 2008;28(5):561–78. Available from: <http://dx.doi.org/10.1002/jat.1358>
6. Boberg J, Taxvig C, Christiansen S, Hass U. Possible endocrine disrupting effects of parabens and their metabolites. *Reprod Toxicol*. 2010;30(2):301–12. Available from: <http://dx.doi.org/10.1016/j.reprotox.2010.03.011>
7. Ye X, Kuklennyik Z, Bishop A, Needham L, Calafat A. Quantification of the urinary concentrations of parabens in humans by on-line solid phase extraction-high performance liquid chromatography–isotope dilution tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2006;844(1):53–9. Available from: <http://dx.doi.org/10.1016/j.jchromb.2006.06.037>
8. Lobemeier C, Tschoetschel C, Westie S, Heymann E. Hydrolysis of parabens by extracts from differing layers of human skin. *Biol Chem*. 1996;377:647–51.
9. Lakeram M, Lockley DJ, Sanders DJ, Pendlington R, Forbes B. Paraben transport and metabolism in the biomimetic artificial membrane permeability assay (BAMPA) and 3-day and 21-day caco-2 cell systems. *SLAS Discov*. 2007;12(1):84–91. Available from: <http://dx.doi.org/10.1177/1087057106295383>
10. Nakazawa H, Oda H, Fujisima H. Analysis of chlorobenzenes, para-hydroxybenzoic acid esters and herbicide in human subjects using GC/MS.] A report of the Research Fund of Health and Welfare of Japan Tokyo: Ministry of Health and Welfare of Japan. 1999.
11. Sasseville D, Alfalah M, Lacroix J-P. “parabenoia” debunked, or “who’s afraid of parabens?” *Dermatitis*. 2015;26(6):254–9. Available from: <http://dx.doi.org/10.1097/der.000000000000147>
12. Mitra P, Chatterjee S, Paul N, Ghosh S, Das M. An overview of endocrine disrupting chemical paraben and search for an alternative – A review. *Proc Zool Soc*. 2021;74(4):479–93. Available from:

- <http://dx.doi.org/10.1007/s12595-021-00418-x>
13. Darbre PD, Aljarrah A, Miller WR, Coldham NG, Sauer MJ, Pope GS. Concentrations of parabens in human breast tumours. *J Appl Toxicol.* 2004;24(1):5–13. Available from: <http://dx.doi.org/10.1002/jat.958>
 14. Holst JP, Soldin OP, Guo T, Soldin SJ. Steroid hormones: relevance and measurement in the clinical laboratory. *Clin Lab Med.* 2004;24(1):105–18. Available from: <http://dx.doi.org/10.1016/j.cll.2004.01.004>
 15. Oishi S. Effects of propyl paraben on the male reproductive system. *Food Chem Toxicol.* 2002;40(12):1807–13. Available from: <https://www.sciencedirect.com/science/article/pii/S0278691502002041>
 16. Shaw J, deCatanzaro D. Estrogenicity of parabens revisited: Impact of parabens on early pregnancy and an uterotrophic assay in mice. *Reprod Toxicol.* 2009;28(1):26–31. Available from: <https://www.sciencedirect.com/science/article/pii/S0890623809000458>
 17. Harley KG, Berger KP, Kogut K, Parra K, Lustig RH, Greenspan LC, et al. Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys. *Hum Reprod.* 2019;34(1):109–17. Available from: <https://pubmed.ncbi.nlm.nih.gov/30517665/>
 18. Lincho J, Martins RC, Gomes J. Paraben compounds—part I: An overview of their characteristics, detection, and impacts. *Appl Sci (Basel)* [Internet]. 2021 [cited 2023 Dec 31];11(5):2307. Available from: <https://www.mdpi.com/2076-3417/11/5/2307>
 19. Inamadar A, Adya K, Palit A. Paradoxes in dermatology. *Indian Dermatol Online J.* 2013;4(2):133. Available from: <http://dx.doi.org/10.4103/2229-5178.110589>
 20. Fransway AF, Fransway PJ, Belsito DV, Yiannias JA. Paraben toxicology. *Dermatitis* 2019;30:32–45. Available from: <https://doi.org/10.1097/der.0000000000000428>.
 21. Nowak K, Jabłońska E, Ratajczak-Wrona W. Controversy around parabens: Alternative strategies for preservative use in cosmetics and personal care products. *Environ Res.* 2021;198(110488):110488. Available from: <https://www.sciencedirect.com/science/article/pii/S0013935120313852>
 22. Azeredo DBC, de Sousa Anselmo D, Soares P, Graceli JB, Magliano DC, Miranda-Alves L. Environmental endocrinology: Parabens hazardous effects on hypothalamic–pituitary–thyroid axis. *Int J Mol Sci* 2023;24:15246. <https://doi.org/10.3390/ijms242015246>.
 23. Jala A, Varghese B, Dutta R, Adela R, Borkar RM. Levels of parabens and bisphenols in personal care products and urinary concentrations in Indian young adult women: Implications for human exposure and health risk assessment. *Chemosphere* 2022;297:134028.

- <https://doi.org/10.1016/j.chemosphere.2022.134028>.
24. Parabens used in cosmetics. Greenfacts.org 30 Sep 2013 Available from: <https://copublications.greenfacts.org/en/parabens-cosmetics/index.htm> (accessed January 4, 2024).
25. Lincho J, Gomes J, Martins RC. Paraben compounds—part II: An overview of advanced Oxidation Processes for their degradation. Appl Sci (Basel) 2021;11:3556. <https://doi.org/10.3390/app11083556>.