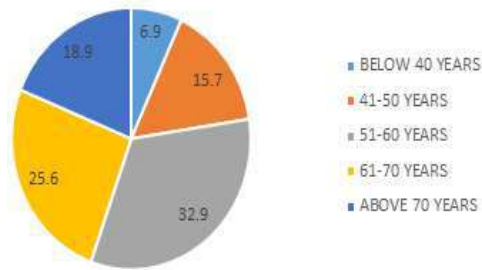




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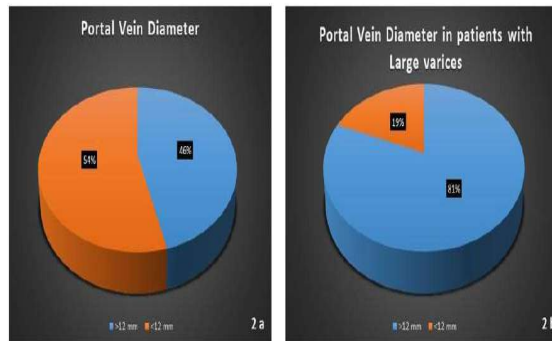


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EDITORIAL

Revelations & Opportunities in Paediatric Surgery

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“Thrive To Set Standards & Not Seek Monopoly”

Paediatric Surgery encompasses a wide spectrum of conditions which essentially include the surgically correctible birth defects but also tumours, trauma and infections. Child is not a mini-adult. Biologically, children's anatomy, physiology, and pathology go through significant changes. Infants and very young children show an increased vulnerability to environmental and other harms, because of their size, immature anatomy and physiology, and differing pharmacodynamics. Organ development determines the patterns of disease that occur in childhood and affects drug treatments and responses to them.

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Pediatric surgeons undertake surgery of congenital malformations, acquired neonatal diseases, common conditions like hernias, undescended testes and appendicitis, but also of the more complex gastrointestinal, broncho-pulmonary or genitourinary conditions, tumors, trauma and solid organ transplantation.

This vast array of interventions, require open, endoscopic and minimally invasive techniques.

The broad spectrum of diseases, often less frequent in incidence, makes training long and hard, but this intensive involvement and care gives the specialty a unique place in academic parlance.

Pediatric surgeons also carry out research work in their field in the quest to seek answers to some hitherto, intriguing biological behaviour of birth defects.

The specialty has the age group of patients which ranges from neonates to up to 18 years of age. Thereby, the specialty is unique, as, the Paediatric surgeons:

1. Get to see disease spectrum presenting in their wide range of natural history because parents seek treatment often late
2. Follow up to see their patients after surgery for long periods, thereby, allowing assessment of the procedures which they have performed.

Thus, it provides an opportunity to do course correction when needed.

Congenital malformation also present in different shades of spectrum and therefore, surgical procedures, too, have to be modified to offer the best correction in a given case.

Some of the examples of various surgical procedures performed by Paediatric surgeons in their long careers are:

Replacement of oesophageal defects by various types of replacements, spina bifida, anorectal malformations, congenital uropathies- pelviureteric junction obstruction, vesicoureteric reflux, posterior urethral valves, bladder exstrophy, hypospadias & neurogenic bladder, to name a few.

Several sub-specialties have emerged from this general spectrum. These are:

1. Urology
2. Gastro Intestinal Surgery
3. Hepatobiliary surgery
4. Neurosurgery
5. Thoracic surgery
6. Trauma

Following areas are integral to each of the above broad ones & performed by all:

- a. To be done by all specialists by rotation
 - I. Neonatal surgery
 - II. Laparoscopy
 - III. Surgical oncology
 - IV. Organ transplant
 - V. Basic Paediatric Surgery: hernia, hydrocoele, cleft lip & palate, malignancies of non-specialized field prescribed above;
 - VI. Foetal surgery

In summary, Paediatric Surgery is a stimulating, academic & research oriented specialty which makes the Paediatric Surgeons the most versatile among their peers & with an unmatched finesse in their skills.



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ORIGINAL ARTICLE

Emphasise the effect of Covid-19 patients on antihypertensive drugs in a tertiary care hospital – a cross sectional study

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Abstract

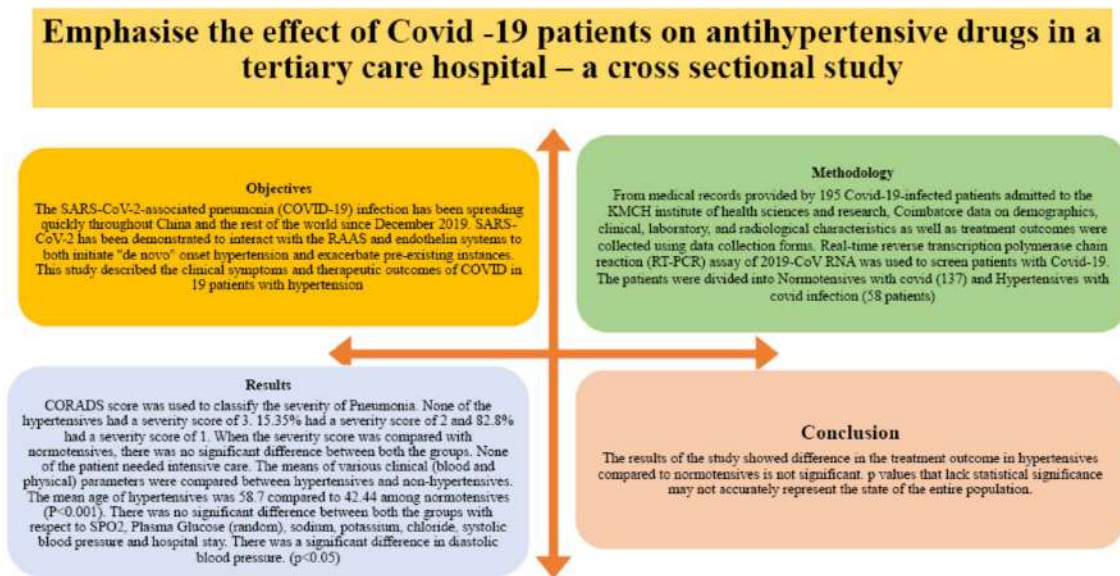
Objectives: The SARS-CoV-2-associated pneumonia (COVID-19) infection has spread quickly throughout China and the rest of the world since December 2019. SARS-CoV-2 has been demonstrated to interact with the RAAS and endothelin systems to both initiate "de novo" onset hypertension and exacerbate pre-existing instances. This study described the clinical symptoms, therapeutic outcomes of COVID in 19 patients with hypertension. **Methods:** Data collection forms were used to gather information on demographics, clinical, laboratory, radiological parameters and treatment outcomes from the medical records provided by 195 Covid-19-infected patients admitted to the KMCH institute of health sciences and research in Coimbatore. The 2019-CoV RNA real-time reverse transcription polymerase chain reaction (RT-PCR) assay was developed to test patients with Covid-19. The patients were split into normotensives (137) and hypertensives (58) with covid infection. **Results and Discussion:** CORADS score was used to classify the severity of Pneumonia. None of the hypertensives had a severity score of 3. 15.35% had a severity score of 2 and 82.8% had a severity score of 1. When the severity score was compared with normotensives, there was no significant difference among both-the groups. None of the patient needed intensive care. The means of various clinical (blood and physical) parameters were compared between hypertensives and non-hypertensives. The mean age of hypertensives was 58.7 compared to 42.44 among normotensives (P<0.001). No significant difference among both the groups with respect to SPO₂, Plasma Glucose (random), sodium, potassium, chloride, systolic blood pressure and hospital stay. There was a significant difference in diastolic blood pressure. (p<0.05). **Conclusion:** Results of this study showed difference in the treatment outcome in hypertensives compared to normotensives is not significant. *p* values that lack statistical significance may not accurately represent the state of the entire population.

Keywords: COVID-19, Hypertension, Clinical profile, Treatment outcome

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Graphical Abstract



Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the virus that is causing the aggressive coronavirus disease (COVID-19) pandemic. SARS-CoV-2 disease is renamed to COVID-19 on February 11, 2020 by the World Health Organization (WHO). The majority of the biomedical scientific community's research efforts have been focused on understanding the etiology, epidemiology, diagnosis, and treatment of COVID-19 pandemic, and a plethora of new information is currently being gleaned daily about the sickness [1]. COVID-19 has tropism for ACE2 receptors present in most of the organ system and produces molecular and macroscopic changes. Arterial hypertension appears to have received less attention than the other post-COVID indications and symptoms documented in the literature. Doctors frequently minimize arterial hypertension relevance and danger, despite of one of the factor for nearly all known adverse

cardiovascular events, renal illness, and end organ damage. Unfortunately, research conducted after COVID has also revealed this tendency to overlook one of the biggest silent killers in history [2]. Even though it has been shown that COVID-19 interacts with the RAAS and endothelin systems to both cause obesity, drugs and endocrine related hypertension and worsen cases of pre-existing cases, only few results are available in the literature [3,4]. This concern stems from the fact that COVID-19 patients who suffer unfavourable outcomes are more likely to be hypertensives and other cardiovascular comorbidities. Hypertension is a common non-communicable condition. On a prescription, ACEI, ARB, Calcium channel blockers, and Beta blockers are frequently used to treat it. Most of the hypertensive patients with other comorbidities like heart failure, coronary artery disease, and renal illness are prescribed ACE inhibitors and ARBs. Because it is assumed that people who use these medications during the

COVID-19 outbreak have a poor prognosis, both patients and their healthcare providers have expressed a great deal of concern [5,6]. On the other hand, it is well known that quitting these medications suddenly may have a detrimental effect on cardiovascular results. Additionally, there is a lot of debate regarding the advantages of ACE-Is and ARBs, which are supported by biological veracity, animal research, and human trials on individuals with various respiratory infections due to viral etiology. Patients with diabetes or hypertension may have an increased chance of infection with a severe COVID-19 sickness, according to data reported in China during the COVID-19 pandemic. ACE 2, a SARS-Cov2 receptor responsible for binding and cell entry, expression is boosted by the administration of ACEI or ARB in these circumstances. However, following lung injury due to acute infection, elevated ACE2 levels and/or decreased renin-angiotensin system (RAS) activation may be protective [7,8]. This study aims to shed light on hypertension patients with COVID-19 by analysing the details of both their general characteristics (such as age or gender) and specific clinical entities (Blood pressure, serum electrolytes, co-morbid conditions, antihypertensive drug therapy). It is debatable how ACEI and ARB function when COVID-19 is present. The clinical profile and outcome of COVID-19 infection with different antihypertensives must therefore be investigated. This study's main aim is to evaluate the clinical characteristics and outcomes of COVID patients with and without hypertension.

Materials & Methods

The Institutional Human Ethics Committee approved this study. This cross-sectional study was conducted at the

KMCH Institute of Health Sciences and Research in Coimbatore from October 2020 to April 2021. 195 COVID-19 patients of both sexes participated in this trial, 58 of them had hypertension and were using oral antihypertensive medications. All the patient information was kept confidential. The study did not include any COVID-19-positive children aged less than 18 years.

Methodology

Anonymized data from the medical records of all COVID-19 patients, were then entered and analysed using a data collection tool. The cases were divided into hypertensive and non-hypertensive groups based on the patient's medical history at the time of admission, and the variation between the groups was compared. The patient data recorded were clinical profile (symptoms, comorbidities, O₂ saturation, plasma glucose, HbA_{1c}, serum electrolytes, hospital stay, systolic and diastolic blood pressure, CORADS score) and treatment outcome (i.e. ICU admissions, severity, death).

Statistical Analysis

The data were evaluated using SPSS software, version 27. Descriptive analysis was performed on the clinical profiles and results of patients with and without hypertension.

Results

A total of 195 COVID patients were analysed, and out of them 58 (29.7%) were hypertensives. The characteristics of hypertensive patients were separately analysed and presented as follows. The Study participants ranged from 18 to 85 years with a mean age of 51.39 years. Less than 7% were below 40 years. 48.6% were between 40 to 60 years. Another 25.6%

were between 61-70 years. The rest 18.9% were above 70 years. (Fig 1) Of the study participants, 63.7% of the hypertensives were males and the rest 36.3% were females. 41.37% of the hypertensives had Diabetes. RTPCR was positive in 93.1% of the hypertensives. 96.6% of the hypertensives had a travel history. All the hypertensives recovered and were discharged. 3.4% had taken one dose of vaccine.

CORADS score was used to classify the severity of Pneumonia. None of the hypertensives had a severity score of 3. 15.35% had a severity score of 2, and 82.8% had a severity score of 1. When the severity score was compared with normotensives, there was no significant

difference between both groups. (Table 1). None of the patients needed intensive care. The means of various clinical (blood and physical) parameters were compared between hypertensives and non-hypertensives. The mean age of hypertensives was 58.7 compared to 42.44 among normotensives (P<0.001). There was no significant difference between the groups with respect to SPO2, Plasma Glucose (random), sodium, potassium, chloride, systolic blood pressure and hospital stay. There was a significant difference in diastolic blood pressure. (74.96 Vs 78.45) (Table 2). No significant difference in treatment outcomes with various antihypertensives.

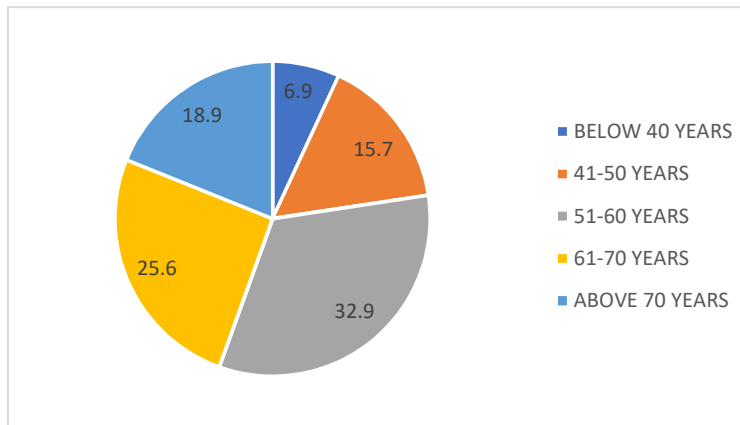


Figure 1. Distribution of study population according to age

Table 1. Distribution of the study population according to various clinical profiles and treatment outcome parameters

Parameter	Normotensives	Hypertensives
Age(years)	48.24 ±16.18	58.70 ± 12.74***
SpO2(%)	96.07 ±2.33	95.56 ±3.57
Plasma glucose(mg/dl)	147.53 ±64.70	160.67 ±89.50
Sodium(mEq/L)	136 ±4.91	137.10 ±5.50
Potassium(mEq/L)	3.97 ± 0.47	4.04±0.44
Chloride(mEq/L)	96.67 ± 3.58	96.43±3.74

Systolic Blood pressure(mmHg)	118.69±15.66	122.76±14.60
Diastolic blood pressure(mmHg)	74.96±9.86	78.45±10.56*
Hospital stay (Days)	5.66±3.21	5.29±3.23

Data are expressed in Mean ±SD. p value *p<0.05, **p<0.01, ***p<0.001

Table 2. Distribution of the study population according to symptoms, severity & comorbidity

Parameter	Normotensives (137)		Hypertensives (58)	
	Number	%	Number	%
Fever	117	85.40	48	82.7
Sore throat	120	87.59	50	86.20
Cough	110	80.29	28	48.27
Headache	54	39.4	15	25.86
Loose stools	30	21.89	20	34.48
Loss of taste and smell	95	69.34	52	89.6
Fatigue	48	35.03	29	50.0
Breathlessness	20	14.59	20	34.48
0	1	0.7	1	1.7
1	120	87.6	48	82.8
2	13	9.5	9	15.5
3	3	2.2	0	0
Mild	120	87.59	48	82.75
Moderate	17	12.40	10	17.24
Severe	0	0	0	0
Diabetes	33	24.08	24	41.37
Bronchial asthma	5	3.64	3	5.172
Coronary artery disease	14	10.21	20	34.48
Chronic kidney disease	0	0	2	3.44

Data is expressed in percentage.

Discussion

As a "silent killer," hypertension is a condition whose consequences and severity are not noticed until the disease has progressed. Literature search showed that incidence of arterial hypertension post COVID-19 was assessed to be between 9 and 12%. It has been well observed that hypertension worsens the condition and increases mortality in patients with

COVID-19. In our study, patients with hypertension were over 55 years old on average significantly older than patients without the condition [9,10]. We also observed that fever, sore throat, and loss of taste and smell were the most prevalent signs of hypertensive patients infected with COVID -19. In hypertensive patients low to moderate grade fever with minor systemic symptoms were common. The

hypertensives included in this study were commonly treated with ACE inhibitors, Angiotensin receptor blockers and calcium channel blockers. No significant difference was observed in treatment outcome related to drugs. Ang II was reportedly converted by ACE2 into Angiotensin (1–7), which protects lungs and also prevent or decrease lung failure due to acute infection according to certain studies. Their higher risk of severe COVID-19 development may be attributed to the expression of ACE 2. But research has also demonstrated that the ACE2 receptor is the route by which SARS-CoV-2 penetrates human cells [11,12]. Additionally, research has demonstrated that various antihypertensive medications, including ACEI and ARBs, may raise the level of ACE2 expression on the cell surface. Theoretically people with hypertension treated with ACEI or ARBs would become more susceptible [13].

However, research has demonstrated that reducing angiotensin II levels can lessen the immediate lung harm caused by the deletion of ACE2 following SARS - CoV infection. As a result, the lung damage caused by SARS-CoV-2 may be partially mitigated by the elevated expression of ACE2 caused by therapy with ACEI/ARBs. [14,15]. Since there was no discernible difference in our study between the normotensives and hypertensive groups on ACEI/ARBs, it can be assumed, that COVID-19-infected hypertension patients can continue with ACEI/ARBs [16,17].

According to certain studies, SARS-CoV-2 may function similarly to SARS-CoV in primarily affecting lymphocytes, particularly T cells. Through the respiratory mucosa, the virus multiplies and affects other cells [18]. Additionally, it results in a cytokine storm and a string of

immunological reactions that change immune cells mainly lymphocytes and white blood cells. T cells produce the crucial lymphokine IL-6. It directly mediates immune system reactions and plays a crucial role in prognosis of viral infection. [19,20]. We found that the serum electrolyte levels (Na, K, Cl) were not statistically different between individuals with and without hypertension. At the same time, chronic hypertension can readily harm target organs like the kidneys, heart, and brain. Because of this, the vital organs of individuals with hypertension lose their ability to compensate during the systemic inflammatory response and cannot respond fast to the inflammatory storm [21,22]. However, several studies have discovered that the primary causes of death for COVID-19 individuals are old age and comorbidities. More than 60 years was the average age of hypertensive patients. The identified risk may be connected to hypertension, which, together with other comorbidities, influences mortality in older persons. [23]. We need age-adjusted studies to identify the clinical predictors of severe and fatal COVID-19.

Conclusion

The outcome of the study showed difference in the treatment outcome in hypertensives compared to normotensives is not significant. p values without statistical significance might not be a reliable indicator of the condition of the entire population. A larger sample size is thus necessary.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable

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ORIGINAL ARTICLE

A Prospective comparative study of Incidence of early Suture site infection following incisional negative pressure wound therapy and Povidone-iodine dressing in a post-operative emergency non-traumatic exploratory laparotomy

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Abstract

Aims and Objectives: The study aimed to assess the efficacy of incisional negative pressure wound therapy (iNPWT) in reducing the risk of suture site infections (SSI) in patients undergoing post-operative emergency non-traumatic laparotomy.

Materials and Methods: A cross-sectional observational prospective study was conducted in a tertiary care setup in a rural area between March 2018 and July 2018. Fifty emergency exploratory laparotomies performed for non-traumatic reasons were included. Patients were randomized into two groups: one receiving conventional povidone-iodine dressing and the other receiving iNPWT over the main wound. After 7 days, SSI was assessed using the center for disease control and prevention's criteria.

Results: iNPWT demonstrated a significant reduction in the risk of SSI development when compared to conventional povidone-iodine dressing ($p < 0.001$) within a 95% confidence interval. The odds of SSI development with conventional povidone-iodine dressing were found to be 8.48 times higher compared to iNPWT. The 95% confidence interval for the odds ratio was 2.21-32.45.

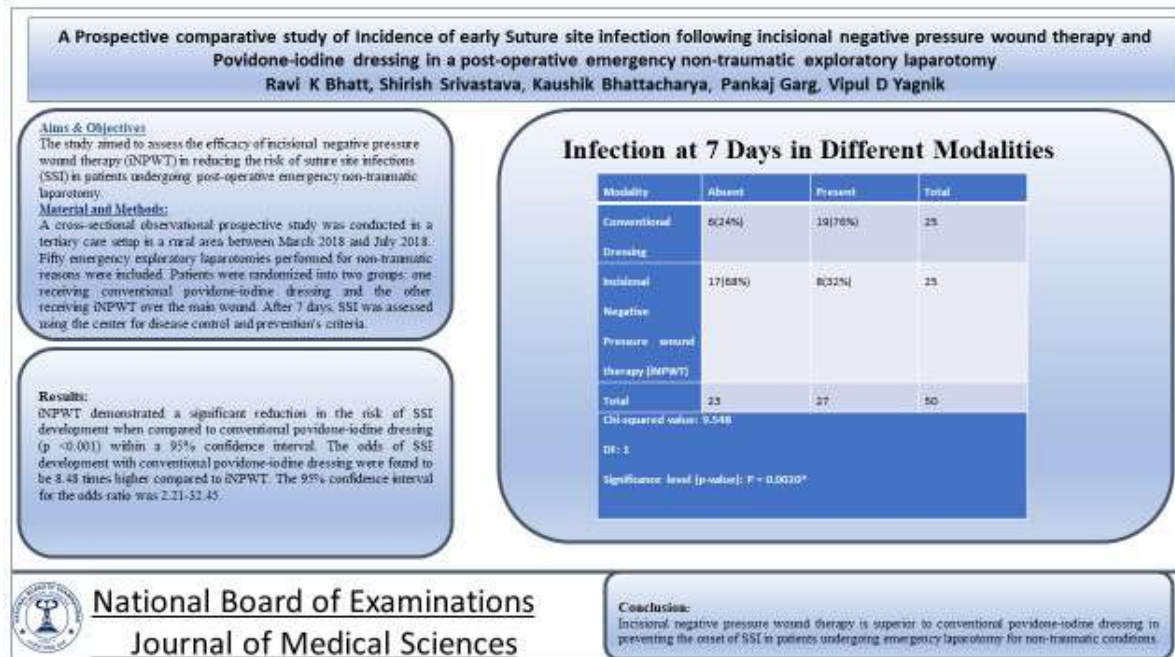
Conclusion: Incisional negative pressure wound therapy is superior to conventional povidone-iodine dressing in preventing the onset of SSI in patients undergoing emergency laparotomy for non-traumatic conditions.

Keywords: incisional negative pressure wound therapy, Suture site infection, povidone-iodine dressings

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Graphical Abstract



Introduction

Suture site infection accounts for roughly 20% of hospital-acquired infections (HAIs), with reports ranging from 274,000 to 600,000 cases annually in the US [1]. High rates of SSI are reported for similar operations in the United States and other countries. The increasing complexity of SSI, especially those involving implanted materials or devices, often requires prolonged courses of antibiotics and additional surgery. Prolonged, frequent, and repetitive antibiotic use facilitates antibiotic resistance [2-4]. Patients who undergo emergency laparotomies have a higher risk of SSI, wound dehiscence, pulmonary embolism, and renal failure. SSI significantly increases rates of ICU admission and readmission [5]. SSI carries a 29% risk of ICU admission. Readmission rates approach 41% in patients with SSI, compared to only 7.4% in non-infected patients. SSI also prolongs hospital stays, with average increases across specialties of 9.7 days [5], thereby increasing the cost to the patient.

In the past 15 years, there have been significant advances in complex acute and chronic wound management. One of the most significant discoveries was the improvement in wounds with negative pressure-assisted wound closure. With this technology, the surgeon now has additional options in addition to immediate closure of wounds (i.e., adjunctive therapy before or after surgery, or an alternative to surgery in the extremely ill). There have been reports of a decrease in hospital stays and cost with NPWT [6]. Clinical benefits of NPWT have been demonstrated in randomized controlled trials and case-control studies. These benefits include a decrease in wound volume or size, accelerated wound bed preparation, accelerated wound healing, an improved rate of graft take [7], decreased drainage time for acute wounds, reduction of complications, enhancement of the response to first-line treatment, increased patient survival, and decreased cost.

This study aims to study the effect of iNPWT in reducing the risk of the development of suture site infection in post-operative

emergency non-traumatic laparotomy cases. It compares the incidence of the development of SSI with conventional Povidone-iodine dressings and NPWT over the laparotomy incision. The study also assesses the wound for early signs of the development of SSI, which mainly include discharge, gape, erythema, and signs of local site infection at the end of 7 days.

Material and Methods

A cross-sectional observational prospective hospital-based study was conducted in the Department of Surgery at Shree Krishna Hospital of Pramukhswami Medical College, Karamsad. The study aimed to evaluate a new dressing modality for laparotomy wounds in emergency cases without traumatic causes and examine the early changes related to the development of SSIs. We collected data that includes age, sex, risk factors, operation types, post-operative wound status, and on which day the dressing was opened and discharged was present or absent. We also noticed the types of discharge.

During the study period from March 2018 to July 2018, a total of 50 emergency exploratory laparotomies were performed for non-traumatic causes. These cases were randomly allocated to receive either conventional beta-dine dressing (25 cases) or iNPWT (25 cases) on the main wound. We use custom-made Negative pressure wound dressing (Figure 1). In the group undergoing incisional negative pressure wound therapy (NPWT), the fascia is closed using 1-0 PolyDioxanone Suture, followed by skin closure with 2-0 Nylon. For patients with stomas, the dressing is applied before the stoma matures. Routine preoperative antibiotic prophylaxis is given half an hour before surgery, and standard precautions are taken to avoid wound infection. The patients were able to move around the day after surgery. To facilitate their mobility, we removed the tube from the suction device

and reconnected it when they returned to bed. After 7 days, the laparotomy wounds were assessed based on predefined criteria to identify early signs of suture site infection. The study recorded each case's risk factors and diagnosis to determine their impact on the development of SSIs in both treatment groups. The inclusion criteria for the study were as follows: Patients of all age groups who underwent emergency exploratory laparotomy for acute abdomen and cases of emergency non-traumatic laparotomy, regardless of the diagnosis. The following cases were excluded from the study: Exploratory laparotomy performed for blunt abdominal injuries to diagnose hemoperitoneum and manage solid organ injuries and elective exploratory laparotomy carried out for the definitive management of patients with intra-abdominal malignancies and those patients were wound kept open.

Ethical considerations were considered for the study. Ethical clearance was obtained from the Research Ethics Committee prior to conducting the research. Permission was also sought from the management of the hospital. Patients and their relatives or guardians were provided with information about the study's purpose. Since the study involved subjecting the patients to a new and unconventional dressing modality, separate consent was obtained from the guardians/relatives before the operation and from the patients themselves either preoperatively or postoperatively, once their general condition stabilized. The data collected during the study were entered into a data collection tool. The variables studied in the research included age, gender, risk factors, diagnosis, and evidence of surgical site infection in the laparotomy wound after 7 days of surgery. Data processing and analysis involved using descriptive analysis, correlation study, and regression analysis models to examine all the variables.

Results

Table 1. Infection at 7 Days in Different Modalities

Modality	Absent	Present	Total
Conventional Dressing	6(24%)	19(76%)	25
Incisional Negative Pressure wound therapy (iNPWT)	17(68%)	8(32%)	25
Total	23	27	50
<i>Chi-squared value: 9.548</i>			
<i>DF: 1</i>			
<i>Significance level (p-value): P = 0.0020*</i>			

*Abbreviation: DF: Degree of freedom
P<0.05 (Significant value)*

In the group of patients treated with conventional dressing, Wound infection was present in 76% of the patients, while in the group treated with incisional negative pressure wound therapy (iNPWT), wound infec-

tion was present in 32% of the patients. The difference between the two treatment modalities was statistically significant (P=0.0020) in favor of incisional negative pressure wound therapy (iNPWT).

Table 2. Table showing the diagnosis in each modality

Modality	Perforated Appendicitis	Ischemia	Obstruction	Peritonitis	
Conventional Dressing	2	2	7	14	<i>Chi-squared: 4.313</i>
Incisional Negative Pressure Wound Therapy (iNPWT)	5	2	9	9	
					<i>DF: 4</i>
					<i>Significance level: P = 0.3652</i>
Total	7(14%)	4(8%)	16(32%)	23(46%)	

DF: Degree of freedom
P<0.05(Significant value)

Table 2 shows the spectrum of the surgical conditions where most of them have a higher incidence of SSI. Neither of the

groups had greater propensity to develop wound infection (p=0.3652).

Table 3. Risk factors Affecting Dressing Modalities

Modality	Absent	Present
Conventional Dressing	8	17
Incisional Negative Pressure	6	19

Wound Therapy (iNPWT)

Total

14(28%)

36(72%)

Chi-squared: 0.389

DF: 1

*Significance level (P): 0.5329**

DF: Degree of freedom

P<0.05(Significant value)

Table 3 depicts the Risk Factors of the patients in both the groups. The Risk Factors have contributed equally in both groups to the development of the wound infection (p=0.5329).

Thus, iNPWT decreases the incidence of SSI. The p Value is <0.001 which is statistically significant for 95% confidence interval, even by considering the effect of diagnosis and the risk factors affecting equally to both dressing modalities (Figure 1). During the 6-month follow-up, 4 patients in the conventional dressing group and 3 patients in the iNPWT group developed an Incisional hernia. However, the difference between the two groups was not statistically significant, with a p-value of 0.6318 (>0.05). Out of the total number of patients, 15 had a stoma. Among them, 8 patients in the conventional dressing group and 7 patients in the iNPWT group had a stoma.

The Odds Ratio of developing SSI is 8.48 higher with conventional povidone-iodine dressing as compared to iNPWT for 95% confidence interval (2.21-32.45).

Discussion

When negative pressure wound therapy is applied, it effectively creates a barrier between the wound and the hospital environment. This is particularly helpful in cases where there is a stoma, as previous research has shown that stomas are a risk factor for wound infections. Studies have also found that negative pressure wound therapy can improve tissue perfusion and vascularization underneath the dressing, which may increase oxygen delivery and immune cell transportation to the wound [8]. This can ultimately help reduce the incidence of infections. Additionally, negative pressure wound therapy can minimize shear forces that could disrupt the microscopic connections between wound edges during the healing process [9]. In addition to study done by Frazee R et al entitled Open vs Closed Negative Pressure Wound Therapy for Contaminated and Dirty Surgical Wounds found that Wound healing was significantly faster in contaminated and dirty wounds when managed with closed-NPWT [10].



Figure 1. Custom made negative suction wound dressing.

In this study, we conducted a comparative observational cross-sectional prospective trial with a sample size of 50 cases. Of these, 25 subjects were randomly selected for conventional dressing postoperatively, and 25 were randomly allocated for iNPWT postoperatively. We found a statistically significant decrease in the incidence of suture site infection in cases who underwent iNPWT compared to those who underwent conventional

povidone-iodine dressing (p -value < 0.001). Additionally, we observed that the odds ratio of developing surgical site infection (SSI) was 8.48 times higher with conventional povidone-iodine dressing compared to iNPWT, with a 95% confidence interval of 2.21 to 32.45. The results of the study indicated that the incidence of wound infection at 7 days was significantly lower in the iNPWT group (32%) compared to the conventional dressing group (76%) ($p = 0.0020$, Table 1). Furthermore, the analysis of the spectrum showed no significant difference between the two modalities in terms of the propensity to develop wound infection ($p = 0.3652$, Table 2). Regarding the risk factors affecting each modality, the study found that the risk factors contributed equally to the development of wound infection in both groups ($p = 0.5329$, Table 3). This suggests that dressing modality does not influence the impact of risk factors on SSI.

Considering the above findings, iNPWT emerges as a more practical option for reducing the incidence of SSI in emergency non-traumatic laparotomy procedures. The statistically significant difference in wound infection rates and the absence of significant differences in surgical diagnoses and risk factors support the preference for iNPWT over conventional povidone-iodine dressing. A single-center randomized controlled trial performed by Javed AA et al. also showed that SSI occurred in 9.7% of patients in the iNPWT group and 31.1% of patients in the standard closure group (relative risk = 0.31; 95% confidence interval, 0.13–0.73; $P = 0.003$) [11]. They found that iNPWT is associated with a significant reduction in surgical site infection. Another recent study by Piroski V et al. on general surgery patients also noted good results with prophylactic iNPWT [12].

A systematic review and meta-analysis on NPWT in open fractures revealed

that NPWT significantly reduces the risk of infection, wound coverage time, wound healing time, and hospital stay length compared to conventional wound dressings [13,14].

It's worth noting that there is only one Indian study about NPWT in non-traumatic emergency laparotomy wounds performed by Arun Garg et al. The study's results indicated that closed incision NPWT did not provide significant advantages over conventional dressing regarding postoperative complications and hospital stay. However, it significantly reduced the frequency of dressing changes, which reduced the mental stress of the patients and the burden of daily dressing changes [15]. This is the second Indian study about iNPWT in non-traumatic emergency laparotomy wounds, and the findings favors iNPWT compared to the first Indian study. Four patients from the conventional dressing group and three from the iNPWT group developed an Incisional hernia on a six-month follow-up. The difference was not statistically significant with a p-value of 0.6318 (>0.05). No patients developed wound dehiscence. The main strength of the study is: This study revealed that iNPWT exhibited a much better outcome compared to conventional povidone-iodine dressing in decreasing the incidence of surgical site infections (SSI) and despite the equal contribution of the risk factors and the diagnosis to both treatment modalities, the role of iNPWT in decreasing SSI is significant. The limitation of the study is on analysis (logistic regression), the impact of iNPWT is

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18%; hence, there are definitely other factors influencing the outcome that have not been included in this study. However, in this study, their contribution was similar in both modalities.

Conclusion

iNPWT demonstrates clear advantages over conventional povidone-iodine dressing in emergency non-traumatic laparotomy. iNPWT significantly reduces the incidence of surgical site infections and offers potential benefits in terms of improved wound healing. Therefore, considering the observed benefits, iNPWT should be regarded as a preferred wound management modality in non-traumatic emergency laparotomy procedures. Further study in the form of randomized controlled trial may be helpful to identify patient populations who would have the greatest benefit from this technique.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Pramukhswami medical college. Informed consent was taken from all the patients. Data will be available from corresponding author on demand.

Conflicts of interest: Nil

Financial disclosure: Nil

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ORIGINAL ARTICLE

Serum Vitamin B12 in Relation to Anaemia and Neuropathy by MNSI among Type 2 Diabetes

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Abstract

Background: Hematological and neurological symptoms can be signs of B12 inadequacy. This work was intended to evaluate the severity of B12 deficiency and link it to peripheral neuropathy (PN) and anaemia in type 2 diabetes mellitus (T2DM) adults who were using metformin.

Methods: To assess PN, the Michigan Neuropathy Screening Instrument (MNSI) directed a hospital-based cross-sectional investigation of 245 adults with T2DM who were taking metformin. 155 subjects who fulfilled the inclusion and exclusion criteria provided fasting blood samples for measurement of vitamin B12, haemoglobin, HbA1c, and cell morphology using chemiluminescent enzyme immunoassay (C.L.I.A), high performance liquid chromatography (HPLC), and C.B.C respectively.

Results: Among adults with T2DM taking metformin, B12 deficiency (B12 < 200pg/ml) was prevalent in 52% cases. O.R of vegetarian diet and B12 insufficiency was 2.33 (C.I. 1.22-4.47) (p < 0.05). Despite the fact that there were no cases of macrocytic anaemia, 40% of people had anaemia, which was not related to a B12 deficiency. According to ROC analysis, serum B12 has emerged as a fair test to predict PN scores of 2.25 (p < 0.001). 38% of people had PN (PN score ≥ 2.5)

Conclusions: The usage of metformin was linked to biochemical B12 insufficiency. B12 deficiency was likely to result in PN scores ≥ 2.5 on the MNSI. In T2DM individuals using metformin, serum B12 screening and the use of MNSI for PN are suggested.

Keywords: metformin, B12 deficiency, neuropathy, MNSI, anemia, type 2 diabetes mellitus

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Graphical Abstract

Title: Serum Vitamin B12 in Relation to Anemia and Neuropathy by MNSI Among Type 2 Diabetes
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Background
Hematological and neurological symptoms can be signs of B12 inadequacy. This work was intended to evaluate the severity of B12 deficiency and link it to peripheral neuropathy (PN) and anemia in type 2 diabetes mellitus (T2DM) adults who were using metformin.

Methods
To assess PN, the Michigan Neuropathy Instrument (MNSI) directed a hospital-based cross-sectional investigation of 245 adults with T2DM who were taking metformin. 155 subjects who fulfilled the insertion and rejection criteria provided fasting blood samples for measurement of vitamin B12, haemoglobin, HbA1c, and cell morphology using chemiluminescent enzyme immunoassay (C.L.I.A), high performance liquid chromatography (HPLC), and C.B.C respectively.

TABLE 1: COORDINATES OF ROC CURVE ANALYSIS FOR PERIPHERAL NEUROPATHY RELATED TO B12 DEFICIENCY

Test variable: PN score (Positive if greater than or equal to 9)	Sensitivity	1-Specificity
-1.000	1.000	1.000
.250	.826	.554
.750	.826	.541
1.250	.718	.374
1.750	.718	.324
2.250	.605	.257
2.750	.521	.243
3.250	.484	.182
3.750	.481	.149
4.500	.310	.108
5.250	.185	.108
6.750	.116	.081
6.250	0.000	.041
6.750	0.000	.027
7.250	0.000	.014
8.500	0.000	0.000

The test result variable (i) PN Scores has at least one tie between the positive actual state group and the negative actual state group.
* = The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the average of two consecutive ordered observed test values.

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Conclusions: The usage of metformin was linked to biochemical B12 insufficiency. B12 deficiency was likely to result in PN scores ≥ 2.5 on the MNSI. In T2DM individuals using metformin, serum B12 screening and the use of MNSI for PN are suggested.

Introduction

Metformin which forms 1st line therapies in treating type 2 diabetes mellitus (T2DM) across World [1] has been recognized to induce low serum B12 [2,3,4,5,6,7,8]. But there is sparse evidence in this context for Indian population. The symptoms of B12 deficiency are similar to those presented with peripheral neuropathy (PN), a common secondary complication of type 2 diabetes. Assessment of PN has been challenging due to various tools and varying study definitions. The magnitude of PN and its determinants in Indian population has limited evidence. Co-existence of PN along with metformin-induced low B12 levels can be detrimental in T2DM. Thus the present study was formulated with the objectives to map the magnitude of metformin-induced B12 deficiency and PN between T2DM patients in metformin and to study

metformin induced B12 deficiency with connection to neuropathy and anaemia in T2DM.

Materials and Methods

A cross-sectional study of hospitals study on 245 T2DM adults on metformin for minimum of four months duration [3] was done from Medicine O.P.D of Sir Ganga Ram hospital, a tertiary care institute in Delhi, India from December 2013 to February 2019. The study's aim was to calculate the magnitude of serum B12 deficiency among T2DM adults on metformin and study its relation with nutritional anaemia and neuropathy. Those who were diagnosed type 2 diabetes by ADA 2013 [9] [2h plasma glucose ≥ 200 mg/dL during an OGTT or random blood sugar ≥ 200 mg/dL in presence of classical diabetes symptoms or fasting (no

caloric intake for at least 8h) blood sugar ≥ 126 mg/dL or HbA1c $\geq 6.5\%$] from latest blood reports and had been receiving metformin therapy for at least four months [2] were enrolled in the study. The calculated sample size was 245 using the formula $N = \frac{t^2 \chi p (1-p)}{m^2}$ where p is 33%, type 2 diabetes and estimated prevalence of B12 deficiency, t = 95% C.I. and m=margin of error at 5%. After excluding patients with confounders (pregnancy, alcoholism, pernicious anaemia, drugs like P.P.I, H2RAs/Hydrogen blockers, history of CRF, liver disease, CKD, Cardiopulmonary disease, bowel disease/surgery, cancer, acid-base disturbance, those on multivitamin or B12 supplement or B12 injections) that affect B12 absorption, 155 of 245 were screened for serum B12 by Chemiluminescence Immuno assay (C.L.I.A.), anaemia by haemoglobin from C.B.C and cell morphology and HbA1c by high performance liquid chromatography (HPLC) on fasting blood samples (not eating anything for at least 8 hours). The serum from fasting blood samples was kept at a temperature of 20 °C and used to calculate the serum total Vitamin B12 levels by competitive chemiluminescent enzyme immunoassay on Beckman Coulter Access 2 Immuno Assay system using commercial kits.

The study received ethical approval from the Institutional Ethics Committee of Maharaja Sayajirao University of Baroda (No. IECHR/2013/19) and written informed consents were received from each and every participant.

Data Collection and analysis: A total of 245 T2DM adults on metformin was

screened for PN by Michigan Neuropathy Screening Instrument (MNSI) and data was collected on medical history, drug history, diet history, life style factors, socio-demographic characteristics, B.P. and anthropometry by pre designed B12 screening proforma. Individuals consuming non-vegetarian foods like meat/fish/chicken at least once weekly were defined as non-vegetarians, those consuming eggs at least twice weekly but no other non veg foods were defined as ovo vegetarians and those not consuming eggs or non-vegetarian foods but consuming milk were considered vegetarians. Indian diets being rich in phytates provide low calcium for absorption [10] and major absorbable calcium is from milk. Individuals consuming < 200ml milk (~60% RDA for calcium) were defined to have low calcium intake. Body Mass Index (BMI) was calculated as kg/m^2 and to Indian population [11] 18.5–22.9 was normal, 23–24.9 was over weight and ≥ 25 were obese. Waist circumference (W.C.) and hip boundary was weighed and the waist-to-hip ratio (W.H.R.) calculated. Men with W.C. ≥ 90 cm (35in) / W.H.R. ≥ 0.90 cm and women with W.C. ≥ 80 cm (31.5in)/W.H.R ≥ 0.85 were said to have abdominal obesity. JNC VIII cut offs were used for B.P. classification. WHO haemoglobin cut offs were used to define anaemia [12]. Serum B12 ≤ 200 pg/ml was defined as B12 deficient [13]. Subjects with HbA1c $> 7\%$ were said to have poor glycemic control by ADA 2020 criteria [1]. MNSI: is a simple, non invasive valid tool in both hospital and community set up [14,15,16]. The MNSI consists of two parts, first is history related to signs and symptoms of PN and second is

a set of physical examination including: 1) feet appearance, 2) Ulceration, 3) Ankle Reflex, 4) Great toe vibration perception and 5) monofilament test. MNSI history score was computed by a sum of 'yes' responses to 11 questions and a 'no' response on 2 items was scored as 1. Question on weakened circulation and all-around weakness were not included in MNSI history score. MNSI physical assessment score was computed by a sum of score for each foot for physical appearance, ulceration, ankle reflex by hammer, tuning fork by 128 Hz tuning fork, vibration perception at great toe by 128 Hz tuning fork and monofilament test by 10g monofilament and this was called as PN score.

The data was entered into SPSS 16.0 and evaluated in Microsoft Excel 2007 (SPSS, Chicago, IL, USA). Box plot was constructed in Excel 2016. Odds ratio (O.R) was calculated to estimate the strength of a relationship between an exposure and a result.

The usefulness of the Receiver Operating Characteristic (ROC) curve analysis was used to assess the utility of Serum B12 test in predicting PN. PN scores as assessed by MNSI physical assessment were taken as 'test variable' and B12 deficiency $\leq 200\text{pg/ml}$ was taken as 'state variable'/binary variable. The objective to construct ROC curve was used to calculate the reflection point (cut off) of PN score for

B12 deficiency. Area under the ROC curve (AUC) is a measure of a test's effectiveness (Serum B12) in predicting the desired outcome (PN). A test does not perform any better than chance when the AUC value is equal to 0.5. The fair test performance is indicated by AUC values between 0.70 and 0.79.

Results

Of 245 subjects majority (76.8%) were $\geq 50\text{y}$ and the study subjects had mean age of 58.2y and mean duration of diabetes was 8y. Mean PCI was Rs. 21,700.82 (Rs. 4000 - 1,00,000). 90% did not drink alcohol nor did they consume tobacco/cigarette. 10% were ovo vegetarian, 43% were vegetarian and 47% were non vegetarian while majority (~ 67%) had low dietary calcium (~60% R.D.A) as studied by milk consumption. By BMI, 40.4% were obese, 23% were overweight and 20% were morbid obese. Also 93% had abnormal WHR. 76% had abdominal obesity by WC. More females (83%) than males (64%) had abnormal WC ($p < 0.01$). Majority (62%) were pre hypertensive followed by hypertension stage I (28.2%) and stage II (7.3%). Majority (57.6%) were on 1000mg metformin dosage. Metformin dosage was associated with GI side effects ($p < 0.001$). Three-fourth (70%) reported metallic taste with the metformin dosage upto 2500 pg/ml.

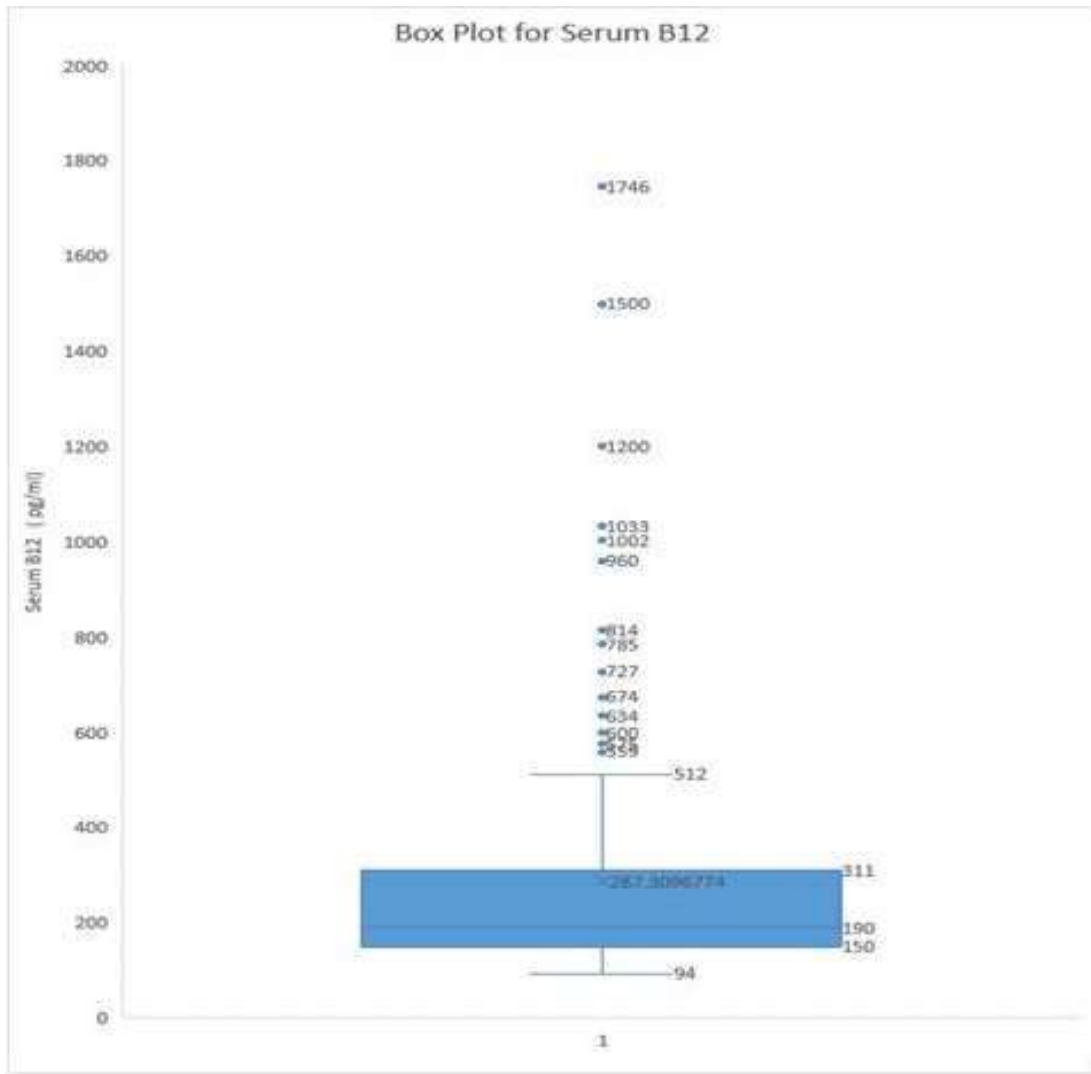


Figure 1. Box plot of Serum B12 distribution for T2DM adults on metformin.

As shown by box plot (Figure 1) the serum B12 of the studied population varied from 94-1746 pg/ml with a median of 190pg/ml and mean of 287.31 pg/ml. 50% of the subjects were in between 150-311pg/ml (Figure 1). Males had higher serum B12 levels than females (363.92±353.88 vs. 250.83±170.62) ($p < 0.05$). More than half (52%, 81 of 245) were B12 deficient, more so in females (58%) than males (40%) ($p < 0.05$). Majority (30.3%) had mild B12 deficiency (150-200pg/ml). There was significantly

higher proportion of vegetarians (54.3%) among those who were B12 deficient in comparison to those who had normal B12 ($p < 0.05$). The odds ratio for vegetarian diets and B12 deficiency was 2.33 (CI. 1.22-4.47) ($p < 0.05$). Low dietary calcium (~60% R.D.A.) as assessed by milk consumption showed no significant association with B12 deficiency.

The mean haemoglobin in this research population was 12.25 ± 1.41 g/dl (7.6-14.6). Majority (60%) had normal haemoglobin and greater males (58%) than females (22.9%) were anemic ($p < 0.001$), due to the custom of recommending iron supplements to women (46) rather than men (29). Subjects given iron supplements had higher haemoglobin than non-supplemented group (12.99 vs. 11.55 g/dl) ($p < 0.001$). Anaemia was more in subjects supplemented with iron than those not on iron supplements (78.7% vs. 21.3%) ($p < 0.001$). Cell morphology and C.B.C showed no positive cases of macrocytic anaemia showing the absence of any clinical vitamin B12 deficiency. There was no significant difference in mean haemoglobin as well as the prevalence of anaemia among B12 deficient and those with normal B12 levels.

HbA1c varied from 6.4-12% and 71% had poor glycemia (HbA1c $> 7\%$). GI side effects of metformin were more in B12 deficient ($p < 0.05$). There was significant difference in the glycemic control of those who were B12 deficient than those who had normal B12 levels ($p < 0.05$). Of those suffering from PN (low or high) majority had B12 deficiency in comparison to those with no PN ($p < 0.001$). Amongst the good glycemic control (HbA1c $\leq 7\%$) majority (53.8%) had no PN ($p < 0.001$). As HbA1c increased the PN score also increased ($r = 0.381$, $p < 0.001$).

ROC curve to define the performance of serum B12 in predicting PN is depicted in Figure 2. Among the several coordinates of the curve (Table 1) the PN cut-off of 1.75 would give a sensitivity ~72% both the specificity of ~67%. The PN

cut-off of 2.25 gives a sensitivity of 60% and specificity of 74%. Ideally, one wants both sensitivity and specificity to be high, but typically for screening, specificity is given more importance, so we select the 2.25 cut-off for PN score to define PN as assessed by MNSI. AUC was calculated as 0.742 (95 C.I. 0.661–0.832, $p < 0.001$) indicating that the serum B12 test performed fairly well in predicting PN in T2DM adults on metformin ($p < 0.001$).

By using the MNSI physical assessment score of 2.5 cut off to define PN the prevalence of PN in T2DM adults on metformin was 38% and the mean PN scores were 2.14 ± 1.98 with no significant gender difference. However as regards various grades of PN it was found that most common grade of PN was low grade PN (39.2%) (*MNSI physical assessment score/PN score $> 0 \geq 2.5$*) followed by high grade PN (34.3%) (*MNSI physical assessment score/PN score $> than 2.5$*).

In addition, MNSI history showed that majority showed numbness (67.8%), burning pain (53.5%) in their legs, feet too sensitive to touch (33%) while few (10%) had an open sore on their foot and amputation cases were very rare (0.4%). Only 6.1% answered 'Yes' for 'if their doctor has ever told you that you have diabetic neuropathy' depicting that PN was under diagnosed.

The PN scores (1.55 ± 2.03 vs 3.1 ± 1.86) calculated from MNSI Physical assessment as well as MNSI history scores (4.9 ± 2.79 vs 2.80 ± 2.48) were higher in those with B12 deficiency than those without B12 deficiency respectively ($p < 0.001$).

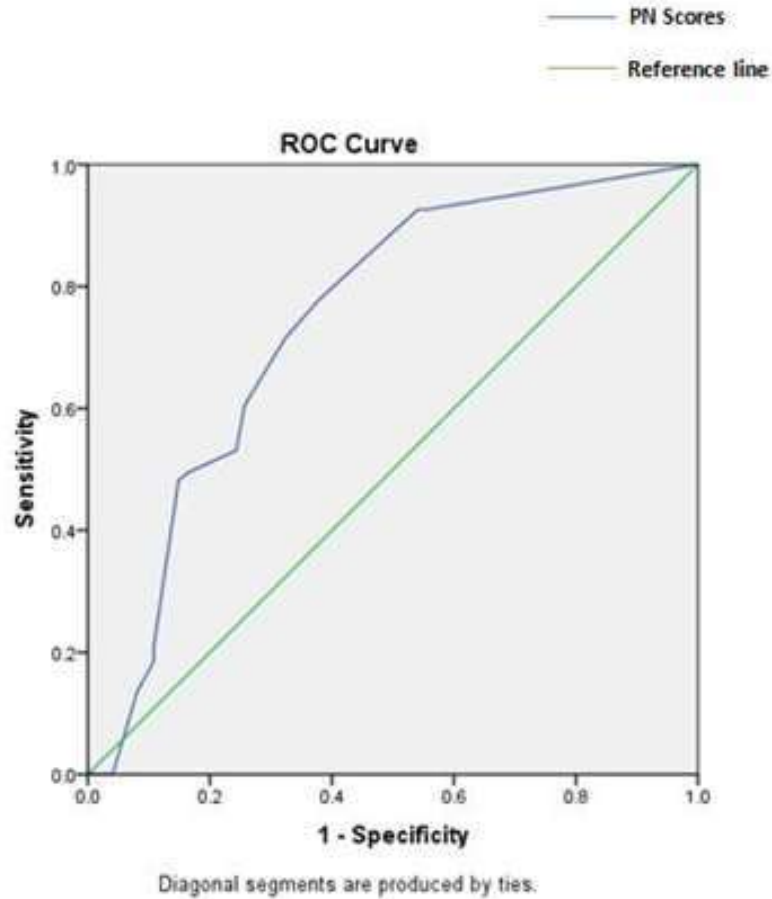


Figure 2. Receiver operating characteristic (ROC) curve for peripheral neuropathy score (PN score) related to vitamin B12 deficiency.

It was seen that of those suffering from PN whether low or high majority had B12 deficiency (58.2% and 70.5% respectively) in comparison to those with no PN where B12 deficient population was only 15.4%. A significant association between PN and B12 deficiency have been found ($p < 0.001$) (Table 2). Odds ratio between B12

deficiency and PN was 10.0 (C.I. 3.89–26) suggesting that those who are B12 deficient are ten times more likely to have PN in comparison to those who are not B12 deficient.

Table 1. Coordinates of ROC curve analysis for peripheral neuropathy related to B12 deficiency

Test variable: PN score (Positive if greater than or equal to *)	Sensitivity	1-Specificity
-1.000	1.000	1.000
.250	.926	.554
.750	.926	.541
1.250	.778	.378
1.750	.716	.324
2.250	.605	.257
2.750	.531	.243
3.250	.494	.162
3.750	.481	.149
4.500	.210	.108
5.250	.185	.108
5.750	.136	.081
6.250	0.000	.041
6.750	0.000	.027
7.250	0.000	.014
8.500	0.000	0.000

The test result variable(s): PN Scores has at least one tie between the positive actual state group and the negative actual state group.

a = The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

Table 2. Association of serum B12 status and PN grades of the T2DM adults on metformin

PN Scores	Total	Serum B12 >200 pg/ml (N=74)		Serum B12 ≤200 pg/ml (N= 81)	
	N	n	%	n	%
No PN (Scores =0)	39	33	84.6	6	15.4
Low grade PN (Score≤2.5)	55	23	41.8	32	58.2
High grade PN (Score>2.5)	61	18	29.5	43	70.5
p value	0.000***				

Table 3. Risk factor association for peripheral neuropathy (PN Scores ≥ 2.5) among T2DM adults of metformin

Factors	Total N	PN Positive (PN score ≥ 2.5)	No PN (PN score < 2.5)	O.R	95% CI	Pvalue
Hypertension Present (Includes Prehypertensives)	240	92	148	2.48	0.27-22.59	0.403
Hypertension Absent	5	1	4			
Sex (F)	162	65	97	0.759	0.437-1.32	0.329
(M)	83	28	55			
Age ≤ 50 (26-50)	65	20	45	1.53	0.83-2.81	0.163
Age > 50 ($> 50-96$)	180	73	107			
BMI ≥ 23	206	71	135	0.406	0.203-0.814	0.009**
BMI < 23	39	22	17			
Glycated Hb > 7	110	59	51	4.62	2.03-10.51	0.000***
Glycated Hb ≤ 7	45	9	36			
B12 deficiency (≤ 200 pg/ml)	81	49	32	4.43	2.23-8.80	0.000***
Normal B12 (> 200 pg/ml)	74	19	55			
Metformin dosage > 1000 mg	50	15	35	0.64	0.32-1.25	0.193
Metformin dosage ≤ 1000 mg	195	78	117			
Duration of DM > 5 yrs	122	52	70	1.48	0.88-2.49	0.134
Duration of DM ≤ 10 yrs	123	41	82			

p < 0.01 , *p < 0.001

Further risk factors of PN (MNSI physical assessment score/PN score ≥ 2.5) were associated by O.R. (Table III). Among the several risk factors of PN, hypertension, age, glycemic control (HbA1c), B12 deficiency and duration of T2DM were associated (O.R. > 1). Nevertheless, glucose regulation (HbA1c ≤ 7) and B12 deficiency were the only significant risk factors for the occurrence of PN among T2DM adults on metformin (p < 0.001). The odds of PN (PN scores ≥ 2.5) was 4.43 times higher (C.I.

2.23-8.80) among T2DM adults on metformin if they were B12 deficient in comparison to those who had normal B12 (p < 0.001). The odds of PN (PN scores ≥ 2.5) was 4.62 times higher (CI-2.03-10.51) among T2DM adults on metformin if they had poor glycemic control (HbA1c > 7) in comparison to those who had good glycemic control (HbA1c ≤ 7) (p < 0.001).

Discussion

The wide range of serum B12 seen here in T2DM adults taking metformin and the presence of outliers can be speculated due to the use of B12 supplements/B12 injections in past as the liver is where vitamin B12 is kept, and it may take years for the stores to run out and cause biochemical B12 deficiency [17]. Although a concerted effort was made to exclude patients who had received vitamin B12-containing supplements for any reason (a review of the available medical prescriptions was made, and patients were questioned about the use of Vitamin B12-containing supplements), it cannot be conclusively said that patients had never taken these preparations before because they are available over the counter.

Present study exhibited decreased amounts of vitamin B12 after taking metformin which confirms comparable results from other research published earlier [2,3,4,5,6,7,8]. However, our study indicated that vitamin B12 insufficiency was more common among T2DM persons taking metformin than was previously documented in other nations 14%, 22%, 33%, 6.9%, 8.6% and 10.5% of patients with T2DM on metformin [3,6,7,5,8,18]. Due to the increased incidence of vitamin B12 deficiency in India's general population, the higher prevalence of B12 deficiency in our study (52%) is not shocking which is reported to be as high as 33.3%–67% [19,20]. In comparison to earlier Indian research on metformin, our study found a higher rate of B12 insufficiency in T2DM [21,22,23]. It really is likely that the increased frequency of B12 insufficiency in our study is due to significantly higher

proportion of vegetarians (54.3%) among those who were B12 deficient in comparison to those who had normal B12 ($p < 0.05$).

A lack of vitamin B12 caused by metformin as explained by the fact that metformin competes with calcium ions and the ileal uptake of vitamin B12 is dependent on calcium and can therefore be harmed by metformin [24]. Furthermore, it has been noted that Indian diets are low in calcium [10]. The present study, however, found no correlation between B12 deficiency and dietary calcium of less than ~60% R.D.A among Indians was found.

This study demonstrated that despite metformin's ability to diminish serum B12 levels, the haematological parameters (haemoglobin and cell morphology) that were evaluated in our investigation were unaffected and it seems to be iron deficiency anaemia and not the macrocytic anaemia due to B12 deficiency. Similar results depicting that anaemia is associated with studies from various countries and an Indian study [22] have both indicated that metformin use has not been linked to B12 insufficiency in country [25]. One recent study indicates risk of anaemia with metformin use in T2DM but its mechanism is unknown and study is limited to the fact that it has no mention of B12 deficiency with metformin [26].

In our study the vitamin B12 deficiency was associated with peripheral neuropathy (PN score) in T2DM adults on metformin which is similar to the finding of a multi centric study from an Asian country Pakistan [30] and several studies from other countries [7,23]. On the contrary there are some studies which have shown no association of B12 deficiency with

neuropathy in T2DM patients on metformin [22,25]. The studies on association of B12 deficiency and neuropathy has shown conflicting results as there were differences in designs and settings of various studies stated above. Neuropathy was assessed by different tools with various degrees of subjectivity and most of the studies had relatively small sample sizes.

In present study the prevalence of PN by MNSI physical assessment score ≥ 2.5 was 38% which was similar to the prevalence of PN reported in one study from Turkey where neuropathy defined by MNSI physical assessment score ≥ 2.5 was found in 32.1% in type 2 diabetes patients [28]. The prevalence of various grades of PN in our study was higher than that studied by Rani et al. 2010 [29] where diabetic neuropathy was considered as present if the VPT value was >20 V, mild neuropathy (VPT score, 20-24.99 V), moderate neuropathy (VPT score, 25-38.99 V), and severe neuropathy (VPT score, >39 V). The study showed the prevalence of diabetic neuropathy was 18.84% (95% CI: 16.79-20.88); the prevalence of mild diabetic neuropathy was 5.9% (95% CI: 4.68-7.15), moderate diabetic neuropathy was 7.9% (95% CI: 6.50-9.33), and severe diabetic neuropathy was 5% (95% CI: 3.86-6.14). In our study the PN prevalence as defined by MNSI PN scores ≥ 2.5 was 38% which was similar to 39.3% shown by one study in 2019 [30] where PN prevalence was studied by a predesigned semi-structured questionnaire, Semmes Weinstein 10g monofilament test, ankle reflexes, and vibration perception threshold. In our study among the several risk factors for PN studied by O.R the

significant risk factors were B12 deficiency and Glycemic control. However one study in 2019 [30] found significant association between age, sex, BMI, duration of diabetes, and hypertension and the odds of PN. We would like to mention the fact that our population was T2DM patients on metformin while the study population in other studies was T2DM patients.

It can be said from our study that vitamin B12 test has fair chance of predicting PN among T2DM patients on metformin and taking a decision regarding which patients should be referred to a neurologist for electrophysiological studies.

Surrogate biomarkers of vitamin B12 deficiency like serum homocysteine and serum methyl malonic acid levels which are widely utilized in clinical medicine to improve diagnostic sensitivity, despite poor specificity [17] have not been estimated in our study which may seem as limitation to some [22]. However elevated levels of MMA do not necessarily co-relate with clinically evident cobalamin deficiency as evident from published literature [17].

Strength of our study is that the data on serum B12 is without the confounders (pregnancy, alcoholism, pernicious anemia, drugs like P.P.I, H2RAs/Hydrogen blockers, history of CRF, liver disease, CKD, Cardiopulmonary disease, bowel disease/surgery, cancer, acid-base disturbance, those on multivitamin or B12 supplement or B12 injections) which may affect B12 absorption. Secondly the PN has been studied with MNSI: a comprehensive and valid tool for measurement of neuropathy. However, the PN assessment was limited to the MNSI and these results

were not compared by Nerve conduction velocity or Neurothesiometer or Biothesiometer.

Conclusions

The prevalence of B12 deficiency in tertiary care T2DM patients on metformin was estimated at 52%. Metformin use was not associated with clinical B12 deficiency as there were no cases of macrocytic anemia. T2DM patients on metformin with B12 deficiency are probable to have PN scores of 2.25 by physical assessment of feet. To prevent neuropathy in T2DM, MNSI is a useful screening tool in an Indian setting.

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Conflicts of interest

The authors declares that they do not conflict of interest.

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ORIGINAL ARTICLE

The Correlation between Portal Vein Diameter, Splenic Size, platelet count/spleen length ratio, and Gastro-Esophageal Varices in the Liver Cirrhosis

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Abstract:

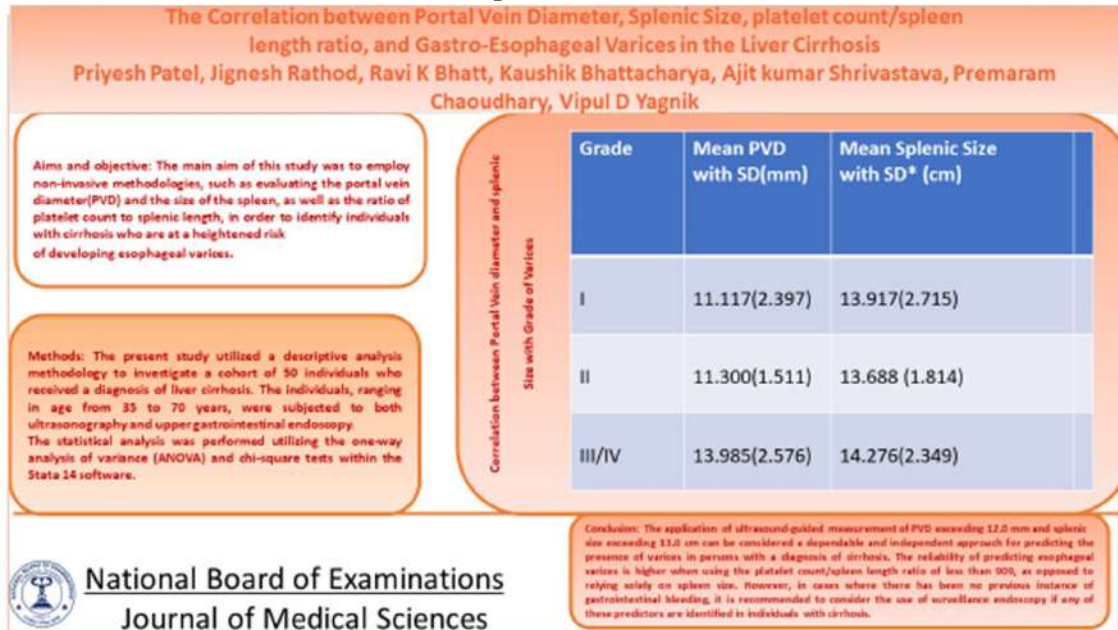
Aims and objective: The main aim of this study was to employ non-invasive methodologies, such as evaluating the portal vein diameter (PVD) and the size of the spleen, as well as the ratio of platelet count to splenic length, in order to identify individuals with cirrhosis who are at a heightened risk of developing esophageal varices. **Materials and Methods:** The present study utilized a descriptive analysis methodology to investigate a cohort of 50 individuals who received a diagnosis of liver cirrhosis. The individuals, ranging in age from 35 to 70 years, were subjected to both ultrasonography and upper gastrointestinal endoscopy. The statistical analysis was performed utilizing the one-way analysis of variance (ANOVA) and chi-square tests within the Stata 14 software. **Results:** In the sample of 50 patients, it was shown that 23 individuals (46%) demonstrated a PVD greater than 12mm. Additionally, a statistically significant correlation was observed between an increase in PVD and a rise in variceal grading. Additionally, it was noted that a total of 31 individuals, including 62% of the sample, displayed a splenic size above 13 cm. Nevertheless, no statistically significant positive connection was observed between the increase in splenic size and the grading of varices. The positive predictive value of a platelet count/spleen length ratio less than 909 is 100%. **Conclusion:** The application of ultrasound-guided measurement of PVD exceeding 12.0 mm and splenic size exceeding 13.0 cm can be considered a dependable and independent approach for predicting the presence of varices in persons with a diagnosis of cirrhosis. The reliability of predicting esophageal varices is higher when using the platelet count/spleen length ratio of less than 909, as opposed to relying solely on spleen size. However, in cases where there has been no previous instance of gastrointestinal bleeding, it is recommended to consider the use of surveillance endoscopy if any of these predictors are identified in individuals with cirrhosis.

Keywords: Cirrhosis, Esophageal varices, Portal vein, Endoscopy, Ultrasonography

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Graphical Abstract



Introduction

Cirrhosis of the liver is a pathological state distinguished by the extensive presence of fibrosis and the transformation of the liver's typical shape into irregular nodules, resulting in the formation of scar tissue and the destruction of the liver's architectural integrity [1]. Alcohol and viral hepatitis (namely types B and C) are widely recognized as the primary etiological factors contributing to the development of cirrhosis. Portal hypertension is a commonly observed outcome and a significant contributor to mortality in persons diagnosed with cirrhosis. The condition is distinguished by an elevation in portal venous pressure over ten mmHg. The hepatic structure experiences modifications that lead to an increased impediment to the passage of portal blood. As a result, this gives rise to the dilatation of the portal vein, enlargement of the spleen, and the formation of varices in the esophagus and stomach. Varices have the potential to induce hemorrhaging, and can give rise to

other issues like ascites, hypersplenism, and encephalopathy.

Upper gastrointestinal bleeding is a commonly seen surgical emergency that requires immediate care to effectively manage hemorrhage and resuscitate the patient [2]. In order to conduct a thorough evaluation of portal hypertension (PHT), it is imperative to ascertain the portosystemic gradient, a method that entails invasiveness and is limited to a few number of specialized facilities. Moreover, the effectiveness of this operation is dependent on the expertise of the physician doing it. In addition, the effective execution of this endeavor requires the allocation of enough logistical assistance and extensive training for the healthcare staff engaged in the effort. Epidemiologic evidence suggests that the occurrence of esophageal varices (EV) is observed in 40% of individuals diagnosed with compensated liver cirrhosis, while the prevalence increases to 60% among patients with decompensated liver cirrhosis. This disparity is attributed to the

presence of a pressure gradient between the portal and caval venous systems [6]. Based on the reference provided, it has been reported that individuals undergoing their first episode of bleeding faced a mortality rate of up to 40% [7]. The esophagogastroduodenoscopy (EGD) is widely regarded as the preferred diagnostic and evaluative approach for esophageal and gastric varices, as well as for predicting the risk of variceal bleeding. However, it is an invasive and potentially uncomfortable procedure that may not be universally available in all healthcare settings. The leading authorities in the field of gastroenterology, such as the Baveno Consensus V, The American Association for the Study of Liver Disease, and The British and French Society of Gastroenterology, endorse the utilization of EGD as the principal diagnostic modality for liver cirrhosis during the initial assessment. Nevertheless, Franchis and colleagues have ascertained that universal endoscopic screening of individuals with liver cirrhosis may result in a substantial number of unnecessary endoscopic procedures. The proposed action could potentially exert more pressure on endoscopic units, leading to increased financial burdens. Furthermore, it may have the unintended consequence of reducing patient compliance with the screening program. Due to these concerns, a considerable body of research has been conducted to investigate noninvasive or minimally invasive methods for identifying individuals with varices, with the goal of avoiding the need for endoscopy in people who have a low likelihood of having varices.

The aim of this study was to examine the possible correlation between the diameter of the portal vein and the size

of the spleen, and platelet count/spleen length ratio in relation to the occurrence of gastroesophageal varices.

Material and Methods

Patient selection: The study comprised a cohort of 50 persons who presented for medical care at Shree Krishna Hospital, Karamsad, and exhibited signs indicative of liver cirrhosis. The participants in this study received upper gastrointestinal endoscopy and abdominal ultrasonography as components of their diagnostic assessment.

Inclusion criteria: pertains to the particular attributes or variables that persons or subjects must possess in order to meet the requirements for participation in a research project.

The study included participants between the ages of 35 and 70 who were diagnosed with liver cirrhosis using ultrasound (USG), laboratory testing, or histopathological examination (HPE). These patients had upper gastrointestinal endoscopy (UGI scopy) and abdominal ultrasound (USG).

Exclusion criteria: The study employed exclusion criteria for individuals who fell outside the age range of 35 to 70 years. Additionally, individuals with liver cirrhosis accompanied by portal vein thrombosis, as well as those with other conditions that induce portal hypertension, such as non-cirrhotic portal fibrosis, Budd-Chiari syndrome, and extrahepatic portal venous blockage, were also excluded from the study.

The analysis was performed using analysis of Variance (ANOVA) and chi square test in Stata 14 software.

The historical and clinical assessment

A thorough patient history was obtained, encompassing relevant factors like occupation, alcohol intake, appetite, jaundice, stomach fullness, disorientation, unconsciousness, presence of hematemesis, and stool color.

The patient underwent a thorough clinical evaluation, with specific attention given to vital signs and various aspects including spleen size, liver span, presence of ascites, detection of fluid thrill, observation of palmar erythema, assessment of axillary hair loss, examination of abdominal venous prominence, and evaluation of the occurrence of gynecomastia and testicular atrophy in males. In order to evaluate the existence of melena, a rectal examination was performed in all cases.

The laboratory conducted a series of conventional hematological examinations, including platelet count, liver function tests (LFTs), Prothrombin Time (PT), International Normalized Ratio (INR), and a standard urine analysis.

Ultrasonography is conducted in all patients with the objective of quantifying the diameter of the Portal vein and evaluating the dimensions of the spleen.

The measurement of spleen size involved assessing the dimensions of the spleen while the patient was in a supine or lateral recumbent position. The imaging treatment was performed during the patient's exhale to enhance visualization of the upper pole of the spleen, which would have been obstructed by lung tissue otherwise. The best placement for the acoustic window for ultrasound transmission is inside the 10th and 11th intercostal gaps. The sonographic evaluation of the spleen was performed in a systematic manner, starting from the

diaphragmatic aspect and progressing towards the lower pole, utilizing the designated imaging window. A curved array transducer with a median frequency ranging from 3 to 5 MHz was utilized. An enlargement is operationally defined as a cephalo-caudal measurement that exceeds 13 cm [9].

The assessment of PVD holds significant importance in clinical evaluation. In individuals without any pathological conditions, the PVD does not exceed 12 mm during quiet respiration. The measurement is frequently obtained at the location where the portal vein meets in front of the inferior vena cava (IVC) [10-12]. The assessment is commonly conducted in the longitudinal orientation of the portal vein. The diagnostic measurements were standardized by the evaluation of individuals in a supine position and during periods of tranquil respiration.

Furthermore, we assessed the ratio of platelet count to spleen length as a prognostic indicator for the development of esophageal varices.

EGD was conducted to examine the presence of gastroesophageal varices and other indications of portal hypertension, such as red wale marks and cherry red patches. The classification of varices was determined using the grading system established by Paquet [13].

The classification system utilized for esophageal varices is structured as follows: Grade I designates the presence of tiny varices that do not extend into the lumen. Grade II refers to varices of moderate size that extend into the lumen, resulting in minor obstruction of the gastroesophageal junction. Grade III: This classification denotes the presence of substantial varices that extend into the

lumen, causing severe obstruction at the gastroesophageal junction. Grade IV denotes the presence of significantly enlarged varices that cause total obstruction at the gastroesophageal junction.

For the sake of evaluation, Grade III and IV varices were categorized as large varices in our study.

Results

We performed an assessment on a cohort of individuals exhibiting varying degrees of variceal grades. Our analysis primarily concentrated on the variceal grade that exhibited the highest magnitude among the observed classifications. Varices of significant size were categorized as Grade III and IV varices.

The results of our study indicated that within the sample of 50 individuals, 80% were male (n=40), while the remaining 20% were female (n=10) (refer to Figure 1a). The age cohort spanning from 51 to 60 years demonstrated the highest incidence of liver cirrhosis, as illustrated in Figure 1b. Among the 50 patients included in the study, it was observed that 52% (26 patients) had a documented medical history indicating alcohol use disorder, whereas 6% (3 patients) were recognized as smokers, as depicted in Figure 1c. Among the entire sample, a subset of 20% (n = 10) of patients were found to have tested positive for Hepatitis B, while a smaller subset of 4% (n = 2) tested positive for Hepatitis C. Within the group of 50 patients, it was observed that 52% (26 patients) had a hemoglobin (Hb) level below 8 gm%, whereas 70% (35 patients) had an international normalized ratio (INR) level exceeding 1.5, as shown in Table 1.

It was noted that 96% (48 individuals) exhibited coarsened echotexture of the liver, 46% (23 individuals) displayed dilated portal veins, and 62% (31 individuals) presented with splenomegaly, as outlined in Table 2.

In relation to varices, the research findings indicated that a subset of the participants, comprising 20% (10 patients), presented with single esophageal varices, whilst a smaller proportion of 2% (1 patient) revealed isolated fundic varices. Furthermore, a total of 4% of the participants (equivalent to 2 patients) exhibited just portal gastropathy, whereas the majority, accounting for 62% (31 patients), displayed esophageal varices in conjunction with portal gastropathy. Moreover, a total of 6 individuals, accounting for 12% of the sample, presented with the coexistence of esophageal varices and fundic varices.

Upon establishing a threshold of 12 mm for the diameter of the portal vein, it was noted that 23 individuals, accounting for 47% of the sample, displayed a portal vein diameter that surpassed this predetermined number. Among the cohort of 21 patients who were diagnosed with extensive varices, a notable proportion of 81% (17 patients) displayed a portal vein width above 12 mm, as illustrated in Figure 2a and b. Upon establishing a threshold of 13 cm for splenic size, it was observed that 62% (31 individuals) exhibited a splenic size above this criterion. Furthermore, within the cohort of 21 patients exhibiting severe varices, it was observed that 68% (15 patients) displayed a splenic size above 13 cm, as depicted in Figure 3a and b.

Table 1. Laboratory parameters

Blood investigations	Number of patients
Hb: > 10 gm%	16
Hb: 8-10 gm%	8
Hb: <8 gm%	26
Raised INR*	35
Hepatitis B positive	2
Hepatitis C positive	2
Platelet Counts <1,50,000 **	32

Hb- Hemoglobin

*INR-International normalized ratio > 1.5 considered as raised INR

** Platelet counts per microliter

Table 2. Ultrasonographic Parameters

Ultrasonographic Findings	Number of patients	Percentage (%)
Coarsened echotexture of liver	48	96.00
Portal vein diameter(>12mm)	23	46.00
Splenic size (>13cm)	31	62.00

Table 3. Correlation between portal vein diameter and splenic size with grade of varices

Grade of Esophageal Varices	Mean Portal Vein Diameter with SD* (mm)	Mean Splenic Size with SD* (cm)
Grade I	11.117(2.397)	13.917(2.715)
Grade II	11.300(1.511)	13.688 (1.814)
Grade III/IV	13.985(2.576)	14.276(2.349)

*SD- Standard deviation

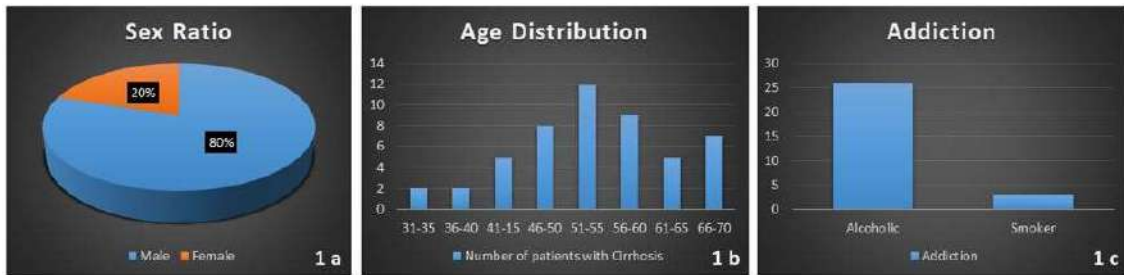


Figure 1a. Sex Distribution of Patients: 1b. Distribution of Liver Cirrhosis in various age groups. 1c. Addiction in patients with Cirrhosis

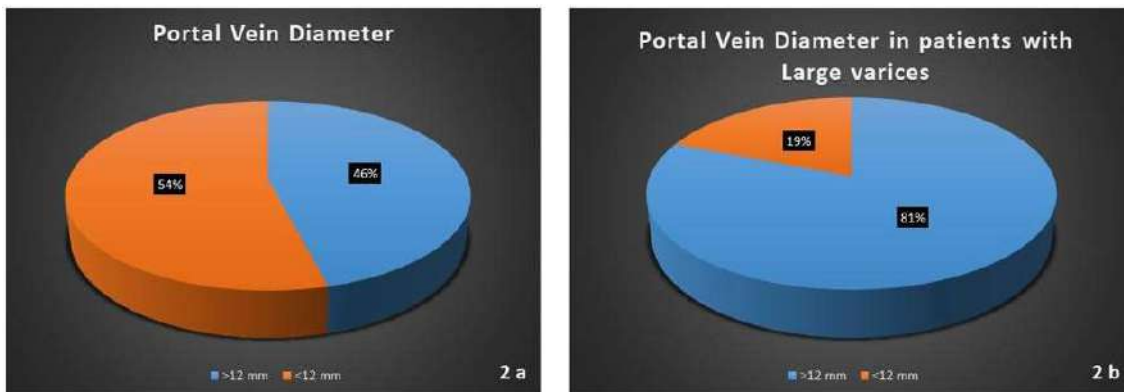


Figure 2a. Percentage of patients having Portal vein diameter >12mm and <12mm. 2b. Percentage of patients with large varices (Grade III/IV) having Portal vein diameter >12mm and <12mm

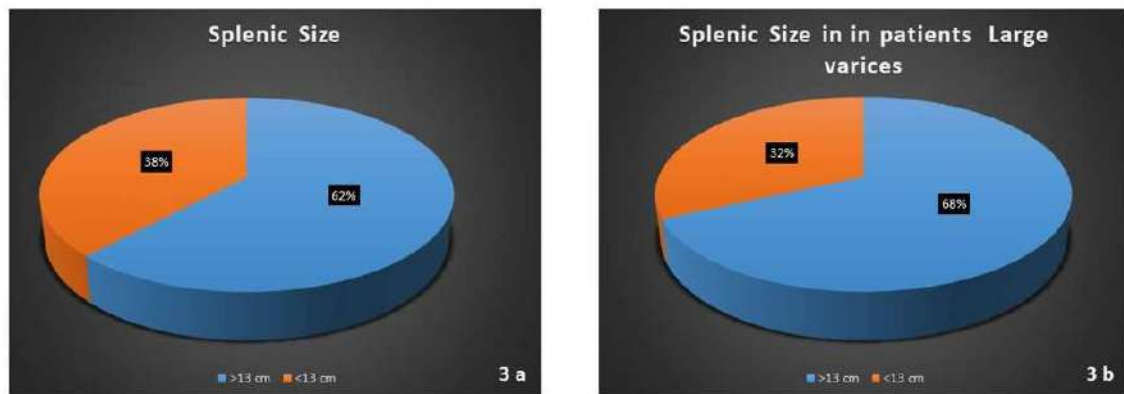


Figure 3a. Percentage of patients having Splenic size >13cm and <13cm; 3b. Percentage of patients with large varices (Grade III/IV) having Splenic size >13cm and <13cm

According to the study, the mean PVD in Grade I esophageal varices was determined to be 11.117 ± 2.397 millimeters. The recorded number in the second grade was 11.300 ± 1.511 , whereas in the subsequent grades of third and fourth, it was measured as 13.985 ± 2.576 . Table 3 demonstrates a statistically significant positive correlation ($p=0.0019$) between the augmentation in portal vein width and the elevation in variceal size (grade).

The average size of the spleen (measured in centimeters) in cases of Grade I esophageal varices was found to be 13.917 ± 2.715 . In the second grade, the average score was 13.688 with a standard deviation of 1.814, while in the third and fourth combined grade, the average value was 14.276 with a standard deviation of 2.349. However, no significant association was seen between spleen enlargement and variceal size (grade). The statistical analysis yielded a p-value of 0.3157, suggesting a lack of statistical significance (Table 3).

Within our sample of 50 individuals, the analysis of variance (ANOVA) test revealed that there was no statistically significant variation in the platelet count to spleen size ratio among different grades of esophageal varices ($p > 0.05$). When employing a threshold of 909 for the ratio of platelet count to spleen size in order to anticipate the occurrence of esophageal varices, our findings revealed a Positive Predictive Value (PPV) of 100% and a Negative Predictive Value (NPV) of 8.1%.

Discussion

The study population comprised 50 persons who had been diagnosed with liver

cirrhosis. Among them, 40 (80%) were male, while the remaining 10 (20%) were female. The study group demonstrated a median age of 53.8 years, encompassing an age range of 35 to 70 years. A study conducted in India by Sharma and Aggarwal [14] revealed that the proportion of male patients (87 out of 101) was similar to that observed in our study. The aforementioned observations align with the results given by Tharwa et al. [15], which indicated that 59.4% of the participants were male. Similarly, Hekmatnia et al. [16] found that the average age of the participants was 52.1 years, with a range spanning from 28 to 83 years. Among the 50 persons included in the study, it was noted that 26 patients displayed symptoms of alcohol use disorder. This condition has been well recognized as a substantial and noteworthy risk factor linked to the development and advancement of cirrhosis, as supported by prior research [17-18]. In the current study, it was noted that a subset of patients, comprising 20%, displayed exclusively esophageal varices, whereas 2% presented with fundic varices. Furthermore, it was observed that 4% of the patients presented with portal gastropathy, while a majority of 62% had a coexistence of esophageal varices and portal gastropathy. Finally, a small proportion of 12% had concurrent esophageal varices and fundic varices. Upon establishing a criterion of 12 mm for the diameter of the portal vein, it was observed that 23 patients, accounting for 47% of the overall sample, had a portal vein diameter beyond this specified threshold. Among the entire cohort consisting of 21 patients who were diagnosed with large varices, it was noted that 17 individuals exhibited a PVD

greater than 12 mm, representing roughly 81% of the sample. The study revealed that the average PVD in individuals diagnosed with gastro-esophageal varices was determined to be 12.372 ± 2.701 mm. Several studies have indicated that the presence of increased peripheral venous distension (PVD), splenomegaly, and splenic collaterals as observed through ultrasound can serve as predictors of esophageal varices [19-20]. In a recent study conducted by Nouh et al., it was demonstrated that the measurement of portal vein diameter and portal hemodynamic indices can assist clinicians in noninvasively predicting the occurrence of esophageal varices in patients with cirrhosis [21-22]. The researchers determined that a portal diameter cutoff of 10.4 mm can accurately predict the presence of esophageal varices with a sensitivity of 94.03%. The specificity of this cutoff was found to be 75.76%, with a positive predictive value of 88.73% and a negative predictive value of 86.21%. The overall accuracy of this prediction model was 88%, and the area under the curve (AUC) was calculated to be 0.877, particularly for large varices. In a study conducted by Nouhn in 2019, it was concluded that the optimal cutoff value for portal vein diameter was 11.5 mm, while another author suggested a cutoff value of 10.5 mm [23]. Additionally, Schepis et al. [12] found that an increased portal vein diameter of 13 mm was associated with the presence of higher-grade varices. A statistically significant positive correlation was seen between the the grade of esophageal varices and the PVD ($p=0.0019$). When the criterion for determining splenic size was set at 13 cm, it was observed that 31 people (62%) had a splenic size that above this barrier. Among

the cohort of 21 patients who presented with large varices, it was noted that 15 people, constituting roughly 68% of the sample, demonstrated a splenic size above 13 cm. The average size of the spleen observed in people with varices was measured to be 14.034 cm. According to a study conducted by Esmat et al. [10], there was a significant association between the presence of esophageal varices in individuals with cirrhosis and a splenic size above 13.1 cm. Thomopoulos et al. conducted a study which revealed that a significant proportion of persons diagnosed with gastro-esophageal varices had spleen sizes greater than 13.5 cm [24]. This observation is consistent with the findings of our own research. However, the data analysis reveals that there is no statistically significant positive association between the enlargement of the spleen and the size (grade) of the varices. This is supported by a p-value of 0.3157, indicating that the observed relationship is not statistically significant. The correlation between platelet count and spleen diameter with portal hypertension and varices is significantly stronger than the correlation with lower platelet count alone [7]. In clinical practice, the platelet count to spleen longest diameter ratio (PSDR) is frequently utilized due to its potential for predicting the presence of esophageal varices. Upon application of the platelet count/spleen size ratio to our dataset, a robust positive predictive capacity was observed in relation to the emergence of esophageal varices. A ratio below 909 accurately indicated patients who were likely to develop the varices. Nevertheless, the effectiveness of its application as a negative predictor is constrained, as indicated by the relatively low negative predictive value (NPV). This underscores

the necessity of adopting a comprehensive methodology that takes into account additional clinical indicators in order to evaluate the risk associated with esophageal varices. This analysis offers an examination of the prognostic capability of the ratio between platelet count and spleen size within the confines of this particular dataset. The observed variation could perhaps be attributed to inherent genetic traits present in the western and Asian source groups under investigation. In a study conducted by Yu Sihao et al., it was demonstrated that the platelet count/spleen volume ratio exhibits superior predictive capabilities for Esophageal varices when compared to the platelet count/spleen longest diameter ratio [25]. The ratio of platelet count to spleen thickness, when ≤ 1.36 , has been identified as an independent risk factor for variceal bleeding in patients diagnosed with cirrhosis [26]. In our study, we assessed the platelet count to spleen length ratio as a potential indicator for the emergence of esophageal varices in individuals with cirrhosis. Multiple studies, including our own, have demonstrated that the predictive value of complications related to portal hypertension, specifically esophageal varices, is better determined by the ratio of platelet count to spleen length, diameter, or thickness, rather than spleen size alone.

Conclusion

Ultrasound-guided measurement of PVD (>12.0 mm) and splenic size (>13.0 cm), and platelet count/spleen length ratio <909 can function as an independent and

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non-invasive predictive tool for identifying gastro-esophageal varices in patients with cirrhosis. A significant correlation was identified between an increase in the diameter of the portal vein and a higher grade of esophageal varices. Nevertheless, a notable association between an increase in splenic size and the size (grade) of esophageal varices was not found. The ratio of platelet count to spleen size, when it is less than 909, can be used as a predictor for the development of esophageal varices. This prediction has a Positive Predictive Value (PPV) of 100. The inclusion of surveillance endoscopy should be given due attention in cases where persons with cirrhosis, who lack a previous record of gastrointestinal bleeding, exhibit any of these criteria. However, it is crucial to carry out multicentre randomized double blind controlled trial in order corroborate the findings of the study.

Conflicts of interest: Nil

Financial disclosure: Nil

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Human Research Ethics Committee of the Pramukhswami medical college granted approval for the study. The patients were informed about the purpose of the study, written informed consent was taken and the study was conducted in accordance with the Declaration of Helsinki.

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REVIEW ARTICLE

A Comprehensive Primer on Transgender Health in India

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Abstract

Background: Transgender health care deals with the prevention, diagnosis, and treatment of physical and mental health conditions along with sex reassignment surgeries and hormonal therapies pertaining to transgender population. Despite the numerous positive developments and efforts made for the welfare of transgender individuals, the plight of these people is yet very dire across the globe. The limited access to specialized healthcare services further exacerbates their predicament due to associated social stigma.

Objectives: This mini-review delves into several crucial aspects concerning transgender healthcare in India. It focuses on the evolution of intersex states at birth and during development in general, the sociocultural challenges faced by transgender people within healthcare institutions, the ethical dilemmas entwined in their care and the need for more gender inclusive medical curriculum.

Results: The current state of knowledge on transgender health among healthcare providers is inadequate and there is a strong need for revision of medical curriculum to suit the needs of transgenders. Matters such as the prevalence of transgender identity, gender dysphoria, sociocultural aspects of disorders in sexual development (DSD), and hormonal and surgical therapies for sex reassignment are explored, emphasizing the importance of gender-affirming surgeries in supporting gender identity. However, concerns regarding coerced surgeries, quack interventions, and lack of specialized medical expertise in treating transgenders are raised. **Conclusions:** Establishing specialized transgender clinics and revising medical curricula, while addressing ethical, legal, and sociocultural challenges of transgender individuals, is vital for improving transgender healthcare in India.

Keywords: Transgender, Transsexualism, Gender Dysphoria, Disorders of Sexual Development (DSD), Mental Health, Sex Reassignment Surgery, Health Services-Needs and Demand, Health Status Disparities.

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Introduction

A four-year-old child was brought to the urology consultant with complaints of ambiguous external genitalia, i.e., a 'penis-like organ', absent testis, under-developed scrotum, and delayed speech development. Upon examination, it was observed that the child had an underdeveloped uterus and ovaries, along with a blind-ending vagina. The caregivers chose to bring up the child as a male.

A fourteen-year-old boy with a 'girlish voice' was accompanied by his parents for medical evaluation with complaints of gynecomastia, girlish voice, and absent testis. Upon examination, the uterus was found on radiological examination and further tests revealed the presence of elevated female sex hormones in his body. The parents wanted to bring up the child as a male.

A 12-year-old girl presented with hoarseness of voice, abnormal external genitalia, and minimal secondary sexual characteristics. Upon evaluation, the uterus and ovaries were absent on radiological examination, and undescended testes were discovered. The parents chose to bring up the child as a female.

A transgender individual who, being biologically male, wanted to remove their testicles to continue their life as a transgender individual in alignment with their sexual orientation. However, due to the insensitivity of healthcare professionals to their needs, they could not undergo the procedure at any healthcare institution and resorted to an unscientific surgery carried out by a quack, which resulted in their death. (It is worth mentioning that the Supreme Court and the Government of India have made it legal to undergo a sex reassignment surgery).

A group of cis-males pretending as transgenders tried to extort money from several shopkeepers in a busy business area of a metropolitan city. These people were apprehended and subjected to a medico-legal examination which revealed that they are cis males and were doing such acts in the guise of transgenders because they believed nobody would apprehend or punish a transgender.

All these instances bring forward the crucial questions of ethical dilemmas faced by medical practitioners in treating transgender patients, sociocultural influences on the decisions of parents of transgender individuals jeopardizing their future sexual role, stigma and fear among doctors associated with providing gender reassignment and other health care services to transgender individuals, the societal ostracization of these individuals, exploitation of transgender identity by others and difficulties faced by these individuals in availing professional health care services. This review focuses on how and why individuals become transgender and includes the socio-cultural aspects related to disorders of sexual development, health concerns of transgender individuals, the stigma associated with seeking healthcare, and the overall welfare of transgender individuals in India.

Literature Review

According to the world population review [2], about 3% of India's population can be labeled as transgender, and this number may not represent actual figures, as many do not disclose their identity. It is essential to understand that gender identity is very different from sexual orientation where gender identity refers to the way people portray their gender on the outside, and sexual orientation refers to the gender

to which they are naturally attracted to. Having said that transgender people may identify themselves as heterosexual, homosexual, bisexual, or none of the above. It is also worth a mention that a few transgender people may experience "gender dysphoria" which can be defined as an acute psychological discomfort or stress caused by a mismatch between their assumed sex at birth and their gender identity.

According to the DSM-5-TR [3], gender dysphoria in adolescents and adults is defined as a significant incongruence between one's experienced or expressed gender and their assigned gender, lasting for a minimum of six months. This incongruence is characterized by at least two of the following:

- There is a clear mismatch between an individual's experienced or expressed gender and their physical sex features, whether primary or secondary (or predicted secondary sexual characteristics for early adolescents).
- The individual seeks to change or eliminate their main and/or secondary sex traits because they significantly clash with their experienced or expressed gender (or, in early teenagers, they wish to avoid the natural development of predicted secondary sex characteristics).
- There is a powerful yearning to have the primary and/or secondary sex characteristics typical of the gender, opposite to their assigned gender.
- There is an intense desire to identify as a gender other than their assigned gender, or a different alternative gender.

- The individual wants to be treated and recognized as a gender other than their assigned gender, or as a distinct alternative gender.
- There is a firm belief that the individual experiences the typical emotions and responses associated with the gender they identify with, or a different alternative gender than their assigned gender.

The Transgender Persons (Protection of Rights) Act 2019 [1] defines a transgender person as someone whose gender does not match the gender assigned at birth. The group encompasses transmen, transwomen, individuals with intersex traits, gender queers, and those with socio-cultural identities like kinnar and hijra (Indian terms for transgender individuals). Intersex features can be attributed to deviations in primary sexual characteristics, external genitalia, chromosomes, or hormones at birth from the conventional male or female standards.

Disorders of Sexual Development (DSD)

Disorders of sexual development are categorized into numerous categories and are associated with abnormal chromosomal, gonadal, or anatomic sex development. Patients with DSDs may present as infants with ambiguous genitalia or as adults with abnormal pubertal development. Numerous pathological conditions, spanning from genetic factors to mullerian anomalies and enzyme deficiencies, can lead to the development of Disorders of Sexual Development (DSD). In another condition involving 46XX infants with congenital adrenal hyperplasia(CAH), excessive androgen synthesis by the adrenal glands results in

the development of virilized genitalia (similar to males) with a variety of morphologies.

In the following paragraphs, our focus will be on exploring the psychosocio-cultural implications faced by individuals with DSD.

Meyer-Bahlburg et al.'s [4] pioneering study looked at the outcomes of chromosomally XY people who were reared as females due to significant nonhormonal anatomic sex development abnormalities. Their study provided compelling evidence supporting the notion of a fixed gender identity. The congenital abnormalities studied included conditions like penile agenesis, cloacal exstrophy of the bladder, and penile ablation. For a significant period, the prevailing approach for these patients involved assigning them a female gender and undergoing surgical feminization. The results unambiguously demonstrated a higher likelihood of patients opting for gender reassignment to male later in life after being assigned female during infancy or early childhood. However, these findings contradict the idea that core gender identity is entirely determined by prenatal androgens. Furthermore, the researchers investigated the level of satisfaction with surgical intervention expressed by persons with 46 XY genotype and discovered that those raised as boys exhibited a significantly higher level of comfort with their gender identity [5].

In a study conducted by Dessens et al. [6], the primary focus was on individuals with 46 XX chromosomes who were raised as females and had Congenital Adrenal Hyperplasia (CAH). The findings revealed a higher incidence of male gender identity compared to the general population of individuals with female chromosomal makeup. While the majority of patients

brought up as females consistently identified themselves as women in the long term, a small subset, approximately 5% in total, encountered notable difficulties concerning their gender identity.

In another study on the same subject, the research included 16 genetic males with cloacal exstrophy ranging in age from 5 to 16 years. Fourteen of the sixteen were designated female at birth, but two were not. Eight of the assigned females later identified as males, and two raised as males remained male. Subjects displayed diverse sexual identities, with some reassigning themselves to male sex. All exhibited male-typical interests and attitudes. The study calls for a reconsideration of clinical interventions for such cases due to the unpredictability of sexual identification. This study provides strong evidence for the biological basis of gender identity, even in cases where genetically and hormonally male individuals were raised as females and underwent feminizing surgery at birth [7].

Another DSD related to 5 alpha-reductase-2 and 17-beta-hydroxy-steroid dehydrogenase-3 deficiencies alter testosterone production and conversion to dihydrotestosterone, resulting in impaired male genital development and possible genital ambiguity. While researching DSDs, we must evaluate the role of aberrant hormone exposure in the development of transgender identity in some people. It is important to note, however, that the majority of transgender people acquire their gender identification independently of abnormal sexual development. Additionally, even those with typical sexual differentiation can experience the development of a transgender identity later in life [8].

Several current hypotheses suggest that the biological basis of transgender

identity lies in the sexual differentiation and maturation of the brain. Gender perception seems to be linked to brain sexual differentiation, which might differ from the physical characteristics of transgender individuals [8]. Swaab et al. propose that this distinction could be due to the timing of brain sexual differentiation, which takes place after the sexual differentiation of gonads during early fetal development [8]. As a result, the amount of genital masculinization may not immediately match the extent of cerebral masculinization.

Transgender neuroscience is a field of study that investigates brain differences between conventional cisgender people and transgender individuals, providing insights into gender identity. Certain brain structures, such as the bed nucleus of the stria terminalis (BSTc) [9] and the third interstitial nucleus of the anterior hypothalamus (INAH 3) [10], have been shown in studies to exhibit patterns more consistent with transgender individuals gender identity. Moreover, MRI studies have identified variations in brain volume and activation patterns among transgender individuals, suggesting unique cerebral characteristics. This notion of transgender-specific cerebral phenotypes finds further support through postmortem brain studies that explore the neuroanatomical aspects of gender identity. These studies, predominantly focusing on male-to-female (MTF) transgender individuals, provide evidence suggesting that atypical cerebral networks in transgender individuals have a neuroanatomical basis [8,11].

Research on white matter properties has also provided evidence for the neuroanatomical basis of transgender identity. According to several studies [8, 12, 13], the corpus callosum shape in transgender people resembles that of people

with shared gender identities rather than those with the same natal sex. Furthermore, white matter fasciculi linked with higher cognitive abilities in female-to-male (FTM) transgender persons who had not received hormone therapy revealed patterns comparable to those seen in normal males. Male-to-female (MTF) transgender people who had not had therapy, on the other hand, showed an intermediate pattern between male and female controls for the same white matter fasciculi.

Health concerns of transgenders in India

The plight of transgender individuals in various parts of the world, particularly in India, has long been overlooked and poorly addressed. Their concerns, often considered insignificant, have shattered their aspirations and left their dreams in ruins. Healthcare issues are among the most critical challenges they face, demanding urgent attention. Despite some improvements in the health system, a significant knowledge gap persists among doctors regarding the specific needs of transgender individuals. Medical education in India falls short of sensitizing future doctors to this aspect, potentially impacting future generations' understanding of the gravity of this problem.

A literature review by Hana et al. [14] in the Western world states that, for many years, mental health clinicians classified transgender and gender-diverse identities as psychiatric disorders. However, the 11th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) brought about a change by replacing this contested categorization with the term "gender incongruence." This word refers to the idea that one's gender differs

from the gender assigned at birth. Gender incongruence was transferred from the Mental and Behavioural Disorders chapter to the new Sexual Health Conditions chapter in 2018. People, regardless of their gender, should have the right to live in the best possible health and without prejudice. This is their paramount human right.

Ensuring the highest attainable standard of health and protecting individuals from discrimination are fundamental rights that must be universally accessible, regardless of gender. However, a significant knowledge gap and lack of attention in conducting surveys have hindered the accurate recognition of transgender individuals in our part of the world. In the 2011 population census in India, approximately 4.88 lakh individuals identified as "other" for their gender, encompassing not just transgender individuals but also those who chose not to identify within the binary gender system [15].

According to a study conducted by Blondeel et al. in 2016 [16], transgender individuals have health needs similar to the general population, but they may also require specialized healthcare services such as gender-affirming hormone therapy and surgery. However, evidence suggests that transgender people often experience a disproportionately higher burden of diseases, particularly concerning mental, sexual, and reproductive health matters. The physical anomalies or malformations that lead to being classified as the third gender outside the binary system can be associated with certain mental health risks.

Moreover, they encounter elevated levels of violence, victimization, stigma, and discrimination. Additionally, they encounter obstacles in accessing healthcare and other essential resources, such as education, employment, and housing.

A study in the Indian subcontinent region [17] reported Transgender individuals, officially recognized as a third gender in Nepal, Pakistan, India, and Bangladesh since 2010, face difficulty in accessing health care services. Referred to as hijras (hijra) locally, this civil recognition has significant implications for their social rights, as it ensures their inclusion as beneficiaries in government schemes, claim reservation in educational institutions, and state employment. However, despite this legal recognition, their access to quality healthcare is remarkably limited compared to their cisgender counterparts. It's worth noting that 14.5% of India's total HIV population identified themselves as transgender, indicating a serious lack of adequate knowledge and health promotion for this community. Further KAP (Knowledge, Attitude, Practices) studies pertaining to transgenders are a need of the hour.

A Study by Wanta et al. [18] studied all the published data regarding the specific medical/health concerns posed to transgender individuals, which include the risk of cancer, endocrine-related disorders, surgeries, diabetes, osteoporosis, HIV, etc. The major areas of research are gender reassignment surgeries (both male-to-female and female-to-male), hormone therapy, metabolic syndrome, and the risk of cancer. Very few studies have concentrated on the reproductive health issues of transgender individuals and further studies are needed in this arena as well.

Transgender surgery, also known as gender reassignment surgery (GRS) or sex reassignment surgery (SRS), is a technique used to assist people whose gender identification varies from the gender assigned to them at birth. These procedures are designed to match the physical

attributes of the body to the person's gender identification. In 2019, the demand for sex reassignment surgery surpassed 316 million USD, with Asian countries, notably India, becoming attractive destinations for people seeking these treatments. Male-to-female (MTF) operations, on the other hand, are less common than female-to-male (FTM) procedures. This is one potential area for medical tourism in our country if the state facilitates them in a legal and ethical framework [19].

A self-help and information website [20] emphasizes hormone therapy as the preferred treatment for transgender youth experiencing gender dysphoria, which has also shown success in preventing substance misuse. Despite its benefits, only 415 out of a significant number of 21,000 transgender adults suffering from depression could afford hormone therapy. Early intervention with hormone therapy has been proven to significantly reduce depression. However, the limitation lies in the availability and affordability of such therapy for these individuals.

A study conducted by Dos Ramos Farías et al. [21] on 111 transgender sex workers in Argentina found that 97% of anal mucosa samples contained HPV DNA. Additionally, 83% of the participants had high-risk carcinogenic genotypes, and 71% were co-infected with two or more HPV genotypes. Another study by Poteat et al. [22] reported that transgender people, particularly transwomen, have one of the highest laboratory-confirmed prevalence estimates for Human Immunodeficiency Virus (HIV) infections worldwide.

Given these challenges and health risks faced by transgender and gender-diverse individuals, establishments and health programs must emerge and offer easily accessible support and services tailored to meet their specific needs. A

special attention is needed with respect to sexually transmitted diseases in these individuals.

Various government initiatives and programs have been established to promote the welfare of transgender people in India. In August 2022, the Ministry of Social Justice and Social Empowerment signed an MOU with the National Health Authority to provide a Comprehensive Medical Package, including free cosmetic surgery, under Ayushman Bharat-PMJAY [23]. The Government of India has also launched a separate online portal for the comprehensive welfare of transgender persons which includes providing scholarships for education, and identification documents to claim health and welfare benefits.

South Indian states have demonstrated impeccable records in integrating the transgender community into the mainstream. In Hyderabad, a Government general hospital has taken a significant step by setting up an exclusive clinic for transgender persons, offering a range of medical services, such as psychiatric, endocrinological, surgical, and gynecological care, all under the supervision of a transgender doctor [24]. Tamil Nadu demonstrated commendable inclusivity by establishing the Transgender Welfare Board in 2022 to promote the development of transgender individuals, particularly in education and employment [25].

The Transgender Protection Act of 2019 places a strong emphasis on offering healthcare services to transgender individuals. It includes provisions for separate HIV surveillance centers and sex reassignment surgeries. Additionally, the act advocates for the revision of medical curricula to address the unique health needs of transgender individuals and the

establishment of comprehensive medical insurance schemes to support their healthcare requirements [1].

One impactful program, “Pehchan,” launched in 2008, managed to reach a significant population of transgender community members, many of whom had never accessed HIV prevention services before. This program was developed through consultation involving various stakeholders, government agencies, and NGOs like the India HIV/AIDS Alliance [26].

Additionally, several non-governmental organizations (NGOs) such as the Sahodari Foundation, Udaan Trust, Gay Bombay, Sappho for Equality, and The Humsafar Trust actively work towards empowering the transgender community, advocating for equality, education, healthcare, and spreading awareness about HIV [27]. These efforts collectively aim to improve the lives and well-being of transgender individuals in India.

Certain transgender-specific health complications of hormonal therapy like increased breast cancer incidence and metastatic prostate cancer incidence were also studied by a few researchers and are areas worth exploring [28-32].

The Stigma Associated With Seeking Healthcare

Transgender populations worldwide face significant unmet health needs, resulting in worse health outcomes compared to their non-transgender peers of the same age. Furthermore, comorbid psychiatric problems and drug misuse/abuse are major concerns in the transgender population. Individuals with gender identity disorders are vulnerable to

physical harassment from family, friends, schoolmates, and strangers. Abuse can be physical or psychological, and it is frequently linked to depression over time. Poverty, dependency on illicit methods of income, and a lack of family or social support all contribute to this susceptible population's vicious cycle of abuse and depression, deeply impacting their mental well-being. A study conducted on the US population revealed that major depression tends to increase with age. However, in contrast to this finding, the onset of many psychiatric illnesses is related to the beginning of the gender identity transition, especially in trans people [18]. Tragically, transgender populations experience significantly higher rates of suicidal deaths, which can be attributed to the risks of physical and sexual violence they often face [28-30].

Social stigma emerges as a major obstacle for transgender individuals seeking healthcare and medical advice [30]. The behavior of healthcare professionals toward transgenders requires a significant change, and government hospitals should strive to have sensitized and trained staff to ensure the comfort and privacy of transgender patients. Several doctors who identify themselves as trans woman/man, emphasize on the need for more manpower and sensitivity in government hospitals to cater to the specific needs of the transgender community.

Language also plays a crucial role in the healthcare experience of queer patients. A psychiatrist who identifies as queer and non-binary points out that healthcare workers must be sensitive about the language they use when caring for transgender and non-binary individuals, as medical vocabulary often lacks inclusivity and understanding. An empathetic and non-judgemental approach toward LGBTQ

communities is necessary to improve health-seeking behavior in them.

Several distressing stories highlight the stigma and mistreatment faced by transgender people while accessing healthcare, leading many to avoid seeking medical attention altogether. This fear and mistreatment contribute to the negative impact on the quality of life for transgender individuals [28-30].

Family-based treatment has proven beneficial for transgender and gender-expansive youth, reducing depression and suicidal tendencies [30]. Family acceptance plays a pivotal role in the mental health and overall well-being of transgender individuals, significantly reducing the risk of self-harm. Creating awareness and sensitizing the general public about their behavior towards transgender individuals is crucial for fostering an inclusive and supportive environment.

Hormonal and surgical therapies for sex reassignment

The Transgender Persons Bill passed in August 2019 faced severe criticism as it does not allow transgender individuals the right to self-identify their gender without undergoing sex reassignment surgery. According to the legislation, only those who have undergone such surgery will receive a gender certificate assigned by the district magistrate and screening committee at the district level. Those who haven't undergone the surgery could not be identified as transgender, not as male or female in spite of their non binary nature. This has led to concerns that transgender individuals are being coerced into surgery, while the demand for free or low-cost sex reassignment surgeries remains unmet [36].

Gender-affirming surgeries are not widely available in public hospitals in India. These meticulous procedures are not frequently performed, and not many plastic surgeons have specialized in this field. Private options are costly, with vaginoplasty or phalloplasty costing at least Rs 3-4 lakhs. The lack of guaranteed good-quality service has led to unfortunate instances where some transgender individuals have experienced pain or even lost their lives due to botched surgeries [37]. It was also stated that gender affirmation surgeries are not essential for individuals with gender dysphoria. Many patients opt for top surgery, with only 1 to 4 percent choosing bottom surgery. The success rate for genital reconstructive surgeries is not very high, and complications may arise, necessitating corrective surgeries [38].

The lack of specialized doctors and sensitivity among surgeons has resulted in many botched surgeries for transgender individuals, causing both aesthetic and functional issues. Corrective surgeries are often needed to rectify the damage caused by these procedures [39].

Hormonal therapy has been used since the introduction of testosterone in 1935 and diethylstilbestrol in 1938. It has been shown to reduce depression and improve the quality of life in transgender individuals [38-39].

Gender-affirming surgeries are available for transgender individuals to support their desired gender identity. The WPATH (World Professional Association for Transgender Health) standards of care provide guidelines for surgical approaches, requiring psychiatric and gender specialist/endocrinologist recommendations for those seeking gender reassignment surgery [40]. Surgical options include facial masculinization surgery, mastectomy,

hysterectomy, phalloplasty, testicular prostheses, voice surgery, chondrolaryngoplasty for AFAB (Assigned Female at Birth) individuals, and facial feminization surgery, orchidectomy, vaginoplasty, and breast augmentation for AMAB (Assigned Male at Birth) individuals. The gold standard in gender reassignment surgery developed 70 years ago, involves creating a neovagina through the penile inversion method. Complications related to the rectum and urethra, such as strictures and injuries, are the most commonly encountered post-surgical issues. [41-46].

Discussion

Intersexuality primarily involves issues related to stigma and trauma rather than being solely a gender issue. Surgical procedures should not be performed on intersex children solely to alleviate parents' distress. Seeking professional mental health care for the child and the parents is crucial in such cases.

Families faced with ambiguous genitalia in their children may struggle in deciding how to raise them, considering the assigned gender. Healthcare workers also encounter difficulties in delivering and explaining such news to families. The health care provider has an ethical responsibility to try to make child-centric plans as part of the goals of care. Providing detailed medical information appropriate for the child's age, developmental stage, and cognitive abilities is essential as they grow from childhood to adulthood.

In the context of transgender individuals, various concerns arise regarding medical and surgical therapies, such as ethical considerations, potential loss of future natural fertility, family dynamics, potential health issues, and their

impact on marital and sexual lives. These complex questions underscore the multidisciplinary nature of the challenges faced by individuals with DSD (Disorders of Sex Development) and the importance of a holistic approach in dealing with these scenarios.

The Transgender Health Awareness Initiative aims to combat limited awareness in regions like tribal areas of Bihar, Tamil Nadu, Madhya Pradesh, and Andhra Pradesh. The overarching goal is to create a society free from discrimination against the Trans community and other gender-diverse individuals. Ensuring accessible healthcare services, including cancer screenings, HIV/AIDS counseling, specialized gender-affirming surgeries, affordable hormone therapy, psychiatric treatments, and counseling facilities, is crucial for their well-being and overall national health.

The lack of essential healthcare services has led to increased mortality rates due to cancer, AIDS, complications from unregulated gender-affirming surgeries, and depression among the transgender community. To address these issues, medical education must incorporate gender diversity awareness and educate students about the health risks faced by the Trans community. Implementing such curriculum changes, as suggested by the National Medical Commission (NMC), is vital to bridge the gaps in healthcare and promote inclusivity for all.

Implications for International Audience

While this study does not include religion as a sociocultural aspect to remain open to the Asian audience, it acknowledges that religious beliefs can significantly influence societal attitudes toward transgender individuals. In some regions, transgender individuals are

regarded as sacred, and various religious texts and mythology recognize diverse gender identities. It is essential to consider and respect these cultural traditions. Instead of suppressing the transgender community's culture, we must contemplate and take action to promote understanding and inclusivity, fostering a positive environment for all.

The perspective towards the transgender community varies significantly between different nations, particularly between the Western and Eastern parts of the world. In the West, there is a growing movement towards transgender empowerment and recognition, allowing the community to be more vocal about their issues. However, in the Eastern part, sociocultural situations, stigmas, and taboos still prevail, hindering their progress.

Despite these differences, one common challenge across regions is the persistent gaps in healthcare for transgender individuals. To address this issue effectively, it is essential not only to integrate transgender healthcare into curriculums but also to bring about transformation at the grassroots level of society. This transformation is of paramount significance, not just in India but also in other southern nations collectively known as "The Global South." Legislation is very important, but it should be complemented by philosophical and ideological principles to foster a harmonious societal change.

Health clinics - a one-stop solution [47-49]

Living with a stigmatized identity takes a toll on the mental health of LGBT individuals, and finding understanding medical practitioners can be a challenge.

Dr. Prasad Raj Dandekar initiated HPQI (Healthcare Professionals for Queer Indians) to sensitize professionals to the healthcare needs of the LGBT community. Training and workshops by such organizations aim to create a network of LGBT-friendly doctors and increase awareness.

To promote inclusivity, medical curricula should include transgender competencies, and public hospitals should provide special health services, including sex reassignment surgery and hormonal therapy, as mandated by the Transgender Persons Act, 2019. However, few hospitals offer such services, and private options are financially demanding and beyond reach for these marginalized people.

Establishing transgender clinics with a queer-friendly environment, along with a team of Gynecologists, Urologists, Endocrinologists, and Psychiatrists, would better cater to the needs of transgender individuals. Screening tests for common diseases like HIV and cancers should be provided in these clinics.

Medical professionals can promote inclusivity by using inclusive language and avoiding assumptions about their patient's sexual orientation or gender identity. A little effort in communication and motivation can make a significant difference in the well-being of the transgender community.

Displaying a rainbow flag in the clinic can signal openness and acceptance for transgender individuals seeking medical care, fostering a more comfortable and supportive environment for them.

When one of the authors questioned the National Medical Commission (NMC) about its efforts in bringing changes to the medical curriculum in accordance with the transgenders act, they openly admitted that

except for a few changes made to the Post Graduate (PG) curriculum of the Doctor of Medicine course in Psychiatry by introducing a module on gender dysphoric disorder they haven't done anything substantial. It is very unfortunate that the Under Graduate (UG) curriculum has not been revised at all and no national wide workshops or trainings were organized for medical teachers and doctors to sensitize them to the needs of transgenders.

Conclusion

The recent changes brought by the Government of India (GOI) led to improvements in the area of transgender health care. There are a considerable number of NGOs in India that religiously work for the empowerment of the community and towards non-discrimination in the areas of education and employment.

However, an alarming knowledge gap still exists, and further research is certainly needed to understand the specific diseases and health needs of transgender individuals in our country. The medical curriculum at all levels (including UG and PG) should be adequately revised to include all the aspects related to transgender health. There is also a strong necessity for introduction of more Attitude Ethics and Communication (AETCOM) modules in transgender health, where workshops that simulate the hospital environment should be conducted to sensitize students for future interactions with transgender patients. Such efforts will lead a long way in promoting integrated and holistic health care services to transgender individuals.

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A copy of the RTI communication mentioned in the text may be obtained for perusal by contacting the authors.

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REVIEW ARTICLE

Impact of Space Environment on Human Body From an Otorhinolaryngologist Perspective: A Brief Review and Future Initiatives for Development of Healthcare, Education and Research Facility in India

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Abstract

Background: Microgravity in space causes changes in the physiology of human body and as a result makes them susceptible to various pathology. As a result astronauts suffer from health disorders which includes otorhinolaryngological disorders

Aim: To gather information about the various otorhinolaryngological manifestations occurring in microgravity by compiling the available scattered data existing in literature

Methods: This is a narrative review article. Using keywords a search was made on the internet, various databases such as googlescholar, pubmed to find out the description of various otorhinolaryngological manifestation in microgravity environment of space. A few proposals or initiatives are given at the end of the discussion so that more research can be conducted on this aspect of otorhinolaryngology

Results: Studies have revealed that the microgravity environment leads to mastoid effusion, predisposes to sinusitis, causes cytoskeletal changes and altered gene expression in thyroid cancer cells, decreases salivary secretion, causes difficulty in airway management, affects temporomandibular joint function, causes impairment of balance. Regarding sleep some studies revealed that microgravity improves sleep while other studies revealed that microgravity causes increase in sleep disturbances. Important future initiatives include establishment of world class health and research facility, National Health Programme for astronauts, Fellowship courses by NBEMS etc.

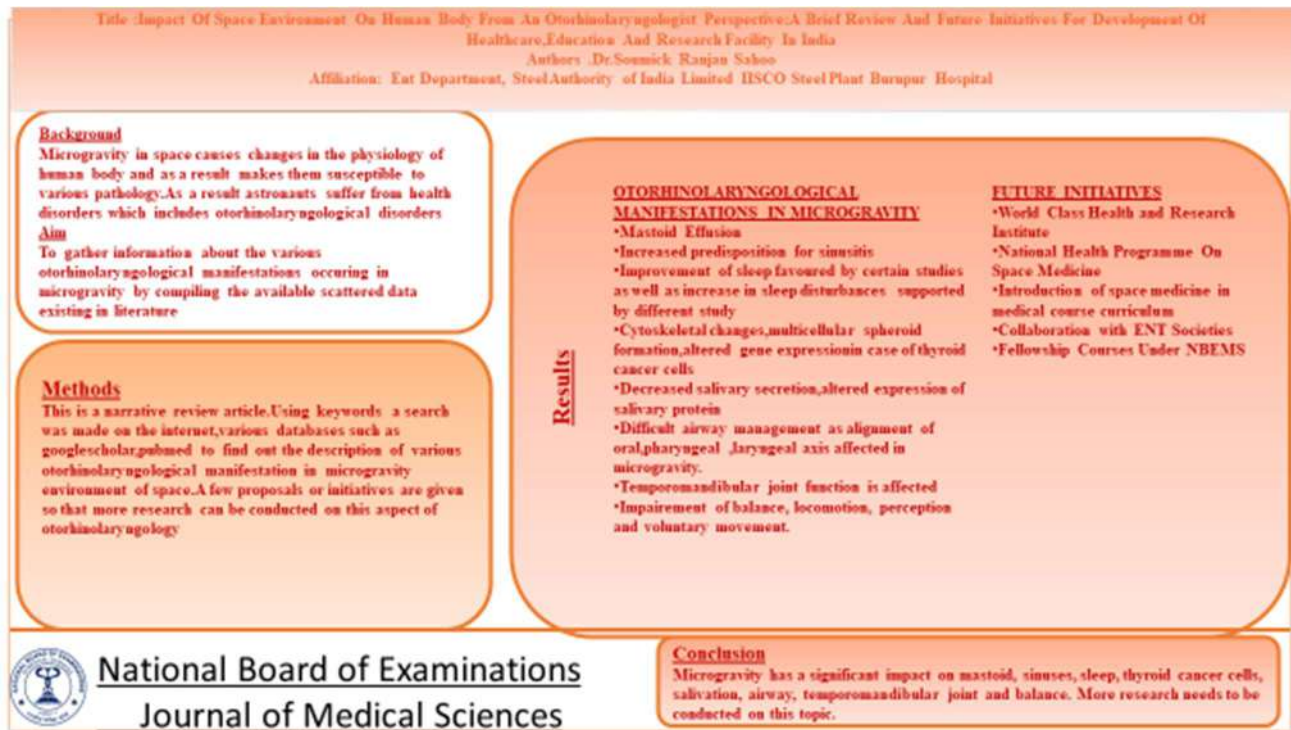
Conclusion: Microgravity has a significant impact on mastoid, sinuses, sleep, thyroid cancer cells, salivation, airway, temporomandibular joint and balance. More research needs to be conducted on this topic.

Keywords: Microgravity, Space Medicine, Mastoid, Sinuses, Sleep, Thyroid, Salivation, Airway, Temporomandibular Joint, Vestibular

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Graphical Abstract



Introduction

Astronauts working in various space missions are faced with various challenges. They are exposed to a microgravity environment which makes them susceptible to various changes in body. After sometime the body gets acclimatized to the space environment. Once the scientists return back to earth body must again learn to adapt to the change from microgravity to normal gravity. Similarly when the astronauts land in moon from space they are exposed to a completely different environment. Till now only a limited number of astronauts have been trained to venture into space and most of the space missions in the past have been unmanned space missions, so the lacunae is that the existing knowledge available till now is still very less. The main objectives of

this review article are to find answers about the various bodily changes from the perspective of an otorhinolaryngologist by compiling the available scattered data in literature. Effect of microgravity on middle ear and mastoid, sinus, sleep, thyroid cancer cells, swallowing and salivation, airway, temporomandibular joint and balance is going to be covered in this review article. Keeping in mind the future plans of Government of India and ISRO to send civilian population in human space flight missions and establishment of Bharatiya Antariksha Station (Indian Space Station), a list of recommendations/proposals are given through which the existing knowledge from the literature review can be implemented on the astronauts. It is hoped that such initiative will encourage academic research and

collaboration on this aspect of otorhinolaryngology and will be a boon in the context of providing health care to the astronauts involved in Human spaceflight program of India (GAGANYAAN) and boosting medical and space tourism in India. The initiatives will also help in establishing India as a pioneer in the field of space medicine in the world.

Methods

This review article is a narrative review. A search was made on various databases such as PUBMED, GOOGLE SCHOLAR and on internet on the effect of microgravity environment on the various bodily systems from an otorhinolaryngologist point of view. Using keywords/research titles such as microgravity and mastoid, microgravity and sinuses, microgravity and sleep, microgravity and thyroid, microgravity and salivation, microgravity and airway, microgravity and temporomandibular joint, microgravity and vestibular, etc an online search was conducted. The articles included those which were free open access articles.

Discussion

Now a brief discussion will be done on the effect of microgravity on ear, nose, sleep, thyroid cancer cells, swallowing and salivation, airway management, Temporomandibular Joint, balance.

Mastoid Effusion

Astronauts in space are at significant risk of developing mastoid effusion [1]. The three important causes of mastoid effusion on earth are eustachian tube dysfunction,

eustachian tube obstruction and venous congestion. We will briefly discuss about each of these three causes in earth as well as in space.

Eustachian tube dysfunction is a very common cause of mastoid effusion [2]. In earth function of eustachian tube dependent on gravity. When the body is in a horizontal position there is increase in venous tissue pressure around the eustachian tube. This in turn decrease the airflow from the middle ear as compared to upright position [3].

In space flight because of head ward shift of fluids leads to venous congestion which in turn leads to eustachian tube dysfunction [4].

In both these cases the drainage of fluid from the mastoid mucosa is hampered.

Middle Ear Barotrauma occurs in divers and pilots due to failure of a dysfunctional eustachian tube to equalize the ambient pressure with the pressure in mastoid air cells [5,6]. On doing MRI on such subjects we get the findings of mastoid effusion.

In space a recent study was conducted by using two groups ISS (International Space Station) and the space shuttle group. Astronauts in ISS group engaged in extravehicular activities experience changes in barometric pressure [1], in presence of eustachian tube dysfunction they may show features of middle ear barotrauma [1]. In space shuttle group crew members not participating in extra vehicular activities also experienced changes in cabin pressure [1,7]. Now coming to eustachian tube obstruction, sinusitis and middle and upper respiratory inflammation, hypertrophic adenoids are the

common causes [2,8]. There are many risk factors in the space environment which predispose to inflammation of upper respiratory tract hence leading to eustachian tube obstruction [1].

Lastly let us discuss venous congestion. In the earth stagnancy of the venous flow lead to increased upstream hydrostatic pressure and in turn lead to mastoid effusion [9]. Pathological conditions such as lateral venous sinus thrombosis where there is stagnancy of venous flow cause increase in upstream hydrostatic pressure and leads to transudative mastoid effusion [10]. In microgravity there is loss of gravity dependant hydrostatic pressure gradient which leads to head ward fluid shift and venous congestion in head and neck [11]. A lack of gravity leading to impaired venous drainage in head and neck could possibly lead to increased backward pressure and transudative mastoid effusion with a similar mechanism as lateral venous sinus thrombosis. Internal jugular vein thrombosis has been found in 2 ISS astronauts in ultrasonography by Marshall-Gobel et al and the mechanism is similar to lateral venous sinus thrombosis [12].

Sinusitis

Various studies from literature give us an idea about the risk factors, clinical presentation, investigation and the diagnostic workup of sinusitis in space environment.

There are many risk factors present in a microgravity environment which predispose to sinusitis. Gravity dependent drainage of the sinuses is absent leading to

impaired clearance of the mucus from the sinuses. Also closed environment in space leads to impaired mucociliary clearance. These factors lead to blockage of the sinus passages and increased chances of upper respiratory infection [13].

In the earth in upright posture a normal head to toe hydrostatic pressure gradient is exerted. This gradient is lost in microgravity which leads to headward shift of fluids [14, 15]. This manifests clinically as facial puffiness and subjective symptoms of nasal stuffiness.

Studies conducted by researchers have also concluded that there is altered presentation of rhinosinusitis in microgravity conditions [16].

It is important to make a prompt early diagnosis and start early treatment to prevent complications [17].

The problems encountered in space is remote location and minimal diagnostic equipment.

Various investigations have been proposed for sinusitis patient which are briefly discussed. The current diagnostic reference standard for Acute Bacterial Rhinosinusitis is needle puncture and bacterial culture of the sinus contents through the canine fossa or the inferior turbinate [18]. The limitations of this investigation is that it is a complicated, traumatic and painful procedure which must be performed by a expert sinus specialist/rhinologist because of requirement of technical expertise [19].

Another important investigation is middle meatal cultures which requires a lot of technical expertise and must be performed in controlled environment [20].

Ultrasonography (US) is a very good technique for detection of maxillary sinusitis in space environment [21-24]. Minimally trained, non physician operators can perform diagnostic US for medical diagnosis of sinusitis [25,26]. The advantages of US it is a painless and noninvasive technique for diagnosis of sinusitis.

Important findings of US done on a animal swine model (anesthetized swine) is disassociation of air fluid interface and uniform dissolution of the fluid to the walls of the sinus with the introduction of microgravity [16].

A very recent study was conducted by Ingles et al using two groups [Space shuttle group And ISS group] in space environment to know whether MRI PNS opacification Lund Mackway scores increased post flight compared to preflight. They have concluded that there was no association between exposure to space flight conditions and changes in PNS opacification [1].

Sleep Disturbances

In the study done by researchers to know the effect of space environment on the sleep pattern various parameters such as number of sleep-related breathing disturbances, number of arousals, the amount of time spent in snoring etc have been studied. All these parameters were reduced in the microgravity environment and it has been concluded that sleep quality improves in such a environment, especially for those human beings with positional sleep disorders, obstructive sleep apnea, upper airway resistance syndrome [27].

However certain physiological changes occur in microgravity which leads to increased sleep disturbances. Microgravity causes a cephalad shift of blood and body fluids [28], which leads to altered respiratory mechanics and chemoreceptor function.

The increased volume of fluids in the head and neck passively reduces the caliber of upper airway and increased chances of obstructive sleep breathing disorder. Altered chemoreceptor function leads to both obstructive and central periodic breathing [29]. Blood gas derangement during apneas also occurs due to altered chemoreceptor function leading to arousal from sleep. [30,31].

Head and Neck Cancer

The effects of the space environment on the cancer cells have been studied by the researchers. Of notable interest from an otorhinolaryngologist perspective are the various studies and review articles demonstrating cytoskeletal changes and gene expression changes in the thyroid cancer cells exposed to both real and simulated microgravity situations [32].

The examples of real microgravity short time exposure study are 31 parabolas of a parabolic flight and TX53 sounding rocket mission [32].

There was observation of upregulation in the ACTB and KRT80 mRNAs in ML-1 cells after 31 parabolas of a parabolic flight [33].

In TX53 sounding rocket mission molecular biological analyses of the FTC-133 cell material were done after the flight. [34,35]. The analyses showed elevation in

them RNAs of the ECM genes FN1, SPP1, TGFB1, TIMP1, MMP1, MMP3, and MMP14 [35]. It was also observed that there was upregulation in the cell adhesion genes ICAM1 and VCAM1, the focal adhesion factors CFL1 and CDH1, as well as cytokines IL6 and CXCL8 in $r\text{-}\mu\text{g}$ samples. All these alterations observed in the molecular biological analysis have demonstrated their sensitivity to gravity [35] and involvement in MCS (multicellular spheroids) formation.

The Shenzhou-8/SimBox experiment is an important study done by researchers in which thyroid cancer cells are exposed for a long time in space [32]. The significant findings are the formation of large 3D aggregates by the thyroid cancer cells, together with an altered expression of the EGF and CTGF genes [36]. These changes in the gene expression pattern have been observed in parallel to spheroid formation [37].

In case of exposure to a simulated microgravity environment such as Random Positioning Machines (RPMs), thyroid cancer cells showed early cytoskeleton changes and changes in ECM, focal adhesion molecules, proliferation, the rate of apoptosis, migration, and growth [32,38-46]. A very important finding was the formation of MCS.

All these studies give the scientific community knowledge about process of cancer progression and potential development of therapeutic drugs.

Swallowing and Salivation

Various experiments have been carried out under laboratory conditions

which resemble environment of space to understand the effects of microgravity on swallowing and salivation. The examples of various devices used in laboratory conditions include random positioning machines (RPMs), clinostats, and levitating magnets at the cellular level whereas at the subject level examples include a -6° head-down bed rest in humans and tail suspension (TS) or hind limb unloading (HU) in rodents [47].

The oral phase of swallowing involves chewing of food which is accomplished by the activity of muscles of mastication causing movement of mandible, shearing action of teeth. During chewing food is lubricated by the saliva and the digestive juices present in saliva play a role in digestion.

However many things change in microgravity. It has been observed that there is reduction of bone density of the mandible, alveolar bone and also bone mineral content in microgravity [47,48].

It has also been observed in rats exposed to simulated microgravity conditions that the masseter muscle fibres were partially dissolved after 1 week. There was further reduction in second week and complete alleviation in fourth week [47,49].

Changes have also been noted in the salivary proteins and salivary flow in microgravity.

The levels of salivary amylase and proline rich protein reduced which may be related to cAMP signaling pathways [47,50].

Immunoglobulin A in saliva showed increased concentration and secretion rates

which might be related to immune stress experienced under microgravity [47,51].

The level of matrix metalloproteinases MMP-8 and MMP-9 are elevated which might be related to immune response to bacterial virulence due to microgravity [47,48].

There is reduction in salivary flow which occurs as a result of changes in fluid distribution and fluid imbalance in microgravity. This further leads to xerostomia [52].

Difficult Airway Management

In earth due to presence of gravity patient can be properly positioned by the doctor so as to achieve proper alignment of laryngeal, pharyngeal and oral axis and hence visualize the glottis and supraglottic structure for introduction of endotracheal tube [53].

In direct laryngoscopy the elevation of the epiglottis occurs because of the pressure exerted by the laryngoscope blade tip against the vallecula. This elevation of epiglottis is gravity dependent.

However in microgravity the scenario is little different. Lejune has proposed a hypothesis in 1978 which explains difficult endotracheal intubation in microgravity. In microgravity head and neck moves out of the field of vision as a result of force exerted by the laryngoscope because of the lever effect exerted on the head which is generated through the laryngoscope blade. This in turn leads to difficult endotracheal intubation [54].

In such circumstances video laryngoscopy is a good alternative which is associated with higher intubation success

rate and can be used for airway management in long duration flight.

Supraglottic airway devices can also be used as an alternative to endotracheal intubation using direct laryngoscopy in microgravity. In a study by Hinkelbein et al in a microgravity simulated environment they have achieved 90 % success rate with these devices and also time required to ventilate is also reduced [55].

Temporomandibular Joint Disorder

In a microgravity environment the temporomandibular joint is significantly affected. The possible etiologies are the disfigurement of circadian rhythm, physiological and psychological stress. Stress causes a decrease of bone mineral density of the temporomandibular region. [56, 57] Additionally there is decrease in overall muscle mass, thereby causing an insufficient increase in muscle tonicity during stressful period. On exposure to longer duration space visits, circulating parathormone concentration also decreases leading to reduced Vitamin D metabolism and ultimately Vitamin D deficiency. The effect on disorientation of complete body homeostasis affects combined toward disarrangement of TMJ function [58].

Balance Disorder

Astronauts experience balance disturbances on entering a microgravity environment which is similar to vestibular pathology.

There are 2 situations in which astronauts experience impairment of balance and poor gaze control, one during the initial few days after entering into space

environment and secondly while returning back to earth [59,60,61].

In normal situation an internal model is built by the brain of the expected sensory input from active movement [59,62,63]. This model is important for maintaining postural stability, spatial orientation and precise voluntary movement [59,64].

The brain compares the expected sensory input of its model with the actual sensory input it receives from the visual, vestibular, proprioceptive and somatosensory system and thus validates the consequences of forces of gravity [59,65,66]. On earth expectation from gravity is an important component of this model of the brain. In space the force of gravity becomes negligible which causes a mismatch between expected and actual sensory input from the unloading of otolith [59]. Microgravity causing an alteration in the sensory input from the vestibular system, which in turn generates a persistent conflict (i.e., mismatch) between expected and actual sensory vestibular inputs during active movements [59,67].

Let us first discuss about posture in microgravity. In microgravity the body acquires a neutral posture characterized by a semicrouched torso, flexed arms and legs and forward bent neck and head [59,68,69]. It is postulated that neural mechanism stabilizing posture in normal gravity persist on entry to microgravity [59,70-74] plays a role in posture maintenance. Hoffman reflex (otolith spinal reflex) [59,75] also play a role in posture. However still it is debatable among many researchers about the role of neural mechanisms in long space missions.

Once the astronauts return back to earth, there is disruption of the neural mechanism leading to transient postural instability [59,76,77]. Gradually there is improvement in postural stability [59,78,79].

Oscillopsia is also experienced by the astronauts suggestive of head trunk in coordination [80]. To be more precise, oscillopsia occurs because the coherence between pitch head and vertical trunk movement is decreased after spaceflight. [59,80,81]. In earth patients with peripheral vestibular loss [81] and on galvanic vestibular stimulation [82] also have a reduction in coherence between pitch head and vertical trunk movement.

In the micro gravity environment astronauts experience spatial disorientation and destabilizing sensation and perception is affected [59]. This impaired perception compromises the astronauts ability to control the spacecraft [59,83]. On earth the brain computes the head and body orientation relative to gravity using inputs from the vestibular and sensory system. This is violated in space environment [59,84]. For instance, loss of otolith input that normally orients relative to gravity, there is loss of spatial anchoring to the surroundings in space when the eyes are closed [59,85]. If the eyes are open astronauts may intellectually know their position but normal sense of orientation with respect to surroundings is not experienced. They experience sensations of inversion and tilt which tend to abate as astronauts adapt to the new environment. This perceptual adaptation to altered gravity has been studied using centrifugation on the ground as well as in space [59,86].

Lastly accurate control of voluntary movements such as reaching is affected in a space environment [59,87–90]. In earth on instruction to reach up or down, there is demonstration of asymmetric arm kinematic in humans. This suggests that the brain has an internal model to predict and take advantage of its mechanical properties to optimize efforts [59, 89].

In microgravity this asymmetry disappears [59,87,89,91]. Possible causes are reduction of arm weight in microgravity [59, 92] or increased vestibular activity as suggested by EEG findings in a comparable visuo motor task [59,93]. Similar effects were observed in a ground model when vestibular input was abated via labyrinthectomy [59, 94].

There are changes in the peripheral vestibular system in a microgravity environment which is briefly discussed.

In the earth the otoliths are stimulated by changes in the spatial orientation of the head. However in space environment they are not stimulated because of unloading of otoliths.

Experiments carried out on rats and dogs suggest that the mass of the otoconia increase following short exposure to microgravity due to unloading of otoliths [59,95-98]. Similar experiments carried out in model systems have concluded that opposite changes in mass of otoconia occurs in hyper gravity [59,99-102].

Recent studies using electron microscopy have found out that mass of otoconia outer shell increase in long duration space flight as compared to short duration spaceflight or hindlimb unloading [59,103]. Additional finding are thinning of

the inner shell and cavitation of otoconia following centrifugation. Structural changes following hindlimb unloading have been reported following long but not short duration hindlimb unloading [103,104].

Recent studies point out about various structural changes in type II hair cells following long exposure to microgravity [59,105-107]. Such changes include increase in number of type II utricular hair cells synapses [106]. In addition to that there is increase in the mean number of presynaptic processes of type I cells [108]. However another study has found out a reduction of synapse densities in hair cells in the utricle of mouse following exposure to microgravity [109].

Studies also point out that on entry to a microgravity environment there is increase in the baseline activity and sensitivity of the otolith afferents [110]. This finding was common in all the nonmammalian animal models used for testing [59,111-115]. These baseline activities and sensitivities return back to control levels after 5 days exposure to microgravity [114] and 24 hour after return to ground [111]. It has been proposed that the presynaptic adjustment of synaptic strength in the hair cells contributes to the initial hypersensitivity of otolith afferents on entry into microgravity conditions [107].

The above discussion has been summarized in Table 1.

Limitations

This review article has scarcity of data in otorhinolaryngological manifestations in human beings who have actually ventured into space. Many of the studies mentioned in this article involve

simulation experiments or animals. Also the information available from the review article are only preliminary findings and cannot be generalized or confirmed unless and until original studies of civilian missions involving the common man are conducted by the space agencies. The various academic

societies of otorhinolaryngology also need to be involved to reach at a consensus and frame guidelines on various aspects of otorhinolaryngology in relation to space.

A lot of initiatives need to be undertaken to make our understanding of the concepts more clear in this topic.

Table 1. Different Aspects of Otorhinolaryngology in Microgravity

MASTOID	<p>MASTOIDEFFUSION</p> <ul style="list-style-type: none"> • EUSTACHIAN TUBE DYSFUNCTION • EUSTACHIAN TUBE OBSTRUCTION • VENOUS CONGESTION
SINUS	<p>SINUSITIS</p> <ul style="list-style-type: none"> • GRAVITY DEPENDANT SINUS DRAINAGE ABSENT • CLOSED ENVIRONMENT LEADING TO IMPAIRED MUCOCILIARY CLEARANCE
SLEEP	<p>IMPROVED SLEEP</p> <ul style="list-style-type: none"> • DECREASE IN NUMBER OF AROUSAL • DECREASE IN TIME SPENT IN SNORING <p>DISTURBED SLEEP</p> <ul style="list-style-type: none"> • CEPHALAD SHIFT OF BLOOD AND BODY FLUIDS LEADING TO ALTERED RESPIRATORY MECHANICS AND CHEMORECEPTOR FUNCTION
HEAD AND NECK [THYROID] CANCER	<ul style="list-style-type: none"> • CYTOSKELETAL CHANGES • GENE EXPRESSION CHANGES • MULTICELLULAR SPHEROIDS FORMATION
SALIVATION AND SWALLOWING	<ul style="list-style-type: none"> • DECREASED SALIVARY FLOW • LEVELS OF SALIVARY AMYLASE AND PROLINE RICH PROTEIN REDUCED • MASSETER MUSCLE FIBRES WERE PARTIALLY DISSOLVED
AIRWAY	<ul style="list-style-type: none"> • DIFFICULT AIRWAY MANAGEMENT • ALIGNMENT OF LARYNGEAL, PHARYNGEAL AND ORAL AXIS AFFECTED
TEMPOROMANDIBULAR JOINT	TEMPOROMANDIBULAR JOINT IS AFFECTED

	<ul style="list-style-type: none"> • DISFIGUREMENT OF CIRCADIAN RHYTHM • PHYSIOLOGICAL AND PSYCHOLOGICAL STRESS
BALANCE	<ul style="list-style-type: none"> • OSCILLOPSIA • SPATIAL DISORIENTATION • DESTABILIZING SENSATION • PERCEPTION IS AFFECTED • ACCURATE CONTROL OF VOLUNTARY MOVEMENTS AFFECTED • UNLOADING OF OTOLITHS • STRUCTURALCHANGES IN TYPEII HAIR CELLS

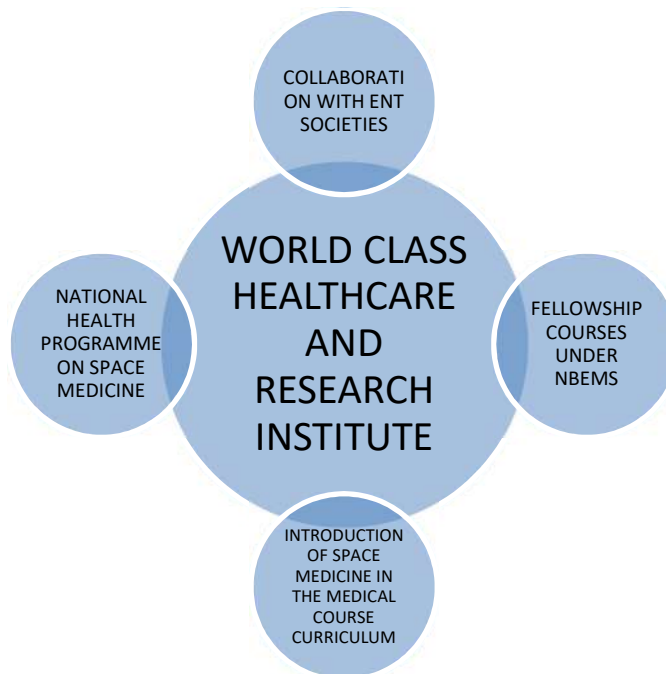


Figure 1. Future Initiatives for Development of Space Medicine and its Otorhinolaryngological Aspects in India

Future Initiatives/Proposals

1. There is a need to have a tertiary referral center for the astronauts of India and other countries having space missions and facing ENT and other health

disorders. This center will have world class health and research facilities.

2. National Health Programme On Space Medicine Disease. Such a programme will be definitely be needed as more

manned space missions are being planned and the health of the astronauts should be prioritized. The main objectives are to determine the burden of diseases among the astronauts, to prevent and treat diseases among the astronauts, rehabilitate the astronauts suffering from diseases. In addition the programme will aim to promote education and research. This can be achieved through training of doctors and paramedical staff, building simulation laboratory, starting orientation program in various medical colleges.

3. To start various fellowship courses accredited by the National Board Of Examinations In Medical Sciences (NBEMS) on the topic of space medicine.
4. To add various aspects of space medicine Otorhinolaryngology in the undergraduate [MBBS] and postgraduate Otorhinolaryngology [M.S ENT, DNB ENT] curriculum in consultation with National Medical Commission (NMC) and National Board of Examinations in Medical Sciences (NBEMS).
5. To include these topics as a panel discussion in national conference of Association Of Otolaryngologists Of India [AOICON], other prominent ENT conferences in India, Indian Medical Association Conference.
6. To collaborate with International Federation Of Otorhinolaryngological Societies for more research on this aspect of otorhinolaryngology .
7. To collaborate with prominent vestibular societies such as Barany Society and

undertake research studies on balance disorders

8. To appoint visiting faculty/doctors from prominent medical institutes from all over the world who have done research in space medicine and have treated astronauts suffering from various health disorders.
9. Expert opinion and advise can be taken from scientists and researchers working in ISRO, ICMR, Indian Institute Of Science, IIT, National Academy Of Medical Sciences, A.I.I.M.S, Institute Of Aerospace Medicine, Medical Colleges, NBEMS, members of Indian Medical Association and policy makers in NITI AAYOG.
10. To host International Space Medicine Conference where doctors and researchers can share their ideas on this topic.
11. To start short term internships for doctors working in medical colleges and NBEMS accredited DNB training institutes.
12. To develop International exchange scholar programmes for Indian doctors .

The important future initiatives proposed have been diagrammatically represented in Figure 1.

Conclusion

Microgravity has a significant impact on mastoid, sinuses, sleep, thyroid cancer cells, salivation, airway, temporomandibular joint and balance. More research needs to be conducted on this topic.

The list of recommendations which are proposed will help in applying the

existing knowledge in this subject practically in the future and lead to development of world class health and research facility In India.

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Conflict of interest

The author declares that they do not have conflict of interest

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CASE REPORT

Rare Retroperitoneal Cystic Lesions Causing Diagnostic Dilemma – A Case Series

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Abstract

Retroperitoneal cystic tumours often cause a diagnostic dilemma and present several clinical challenges because of their rarity, relative late presentation, anatomical location, close relationship with several vital structures in the retroperitoneal space and the surgical expertise required for the management. We present three challenging retroperitoneal cystic space occupying lesions – hydatid cyst, dermoid cyst, and cystic lymphangioma. All 3 cases underwent surgery after initial diagnostic difficulty and had smooth postoperative recovery. Retroperitoneal cyst needs surgical expertise for complete excision which is often difficult due to neighbouring important vital anatomical structures.

Key words: Hydatid cyst, Dermoid cyst, Mesothelial cyst, Retroperitoneum

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Introduction

Retroperitoneal cystic lesions are a rare occurrence and often causes a diagnostic challenge for the clinicians. Since its usually not seen often in the clinical medicine, Cystic lesions of the retroperitoneum donot have any fixed classification. They are classified as either neoplastic or nonneoplastic. The most common neoplastic space occupying retroperitoneal cystic masses are cystic lymphangioma and cystic mesothelioma [1]. Other malignant cystic tumours are mucinous cystadenoma, cystic teratoma, Müllerian cyst, epidermoid cyst, tailgut cyst, bronchogenic cyst, cystic change in solid neoplasms, pseudomyxoma retroperitonei, and perianal mucinous carcinoma. Nonneoplastic lesions include primarily retroperitoneal fibrosis, non-Langerhans histiocytosis (Erdheim-Chester disease), extramedullary haematopoiesis, pancreatic pseudocyst, nonpancreatic pseudocyst, lymphocele, mesenteric cyst, urinoma, and hematoma [2].

We present 3 cases of retroperitoneal cystic lesions which underwent surgery after a lot of diagnostic dilemmas.

Case 1

40-year-old male patient presented with left low back ache of 6 months duration. Ultrasound abdomen revealed a space occupying hypoechoic lesion of 6cmX6cm with internal hyperechoic undulating membrane with close proximity to the left psoas muscle in the retroperitoneum. CT scan of the lower abdomen was inconclusive, and a

provisional diagnosis of hydatid cyst was made, and the patient was posted for surgery (Figure 1). On performing a laparotomy through a left lumbar extraperitoneal approach, a 6cmX8cm dermoid cyst seen attached with the L3 and L4 vertebra. The cyst contained cheesy material with hairs. Excision of the entire cyst done, and the cyst wall was sent for histopathology (Figure 2).



Figure 1. CT scan showing suspected dermoid cyst attached to the left psoas muscle.

Case 2

36-year-old male patient presented with occasional back pain with a vague swelling in the right lower back. Both ultrasound and the CT scan of lumbar region revealed hydatid cyst with thick encasing wall within the substance of the

right erector spinae muscle in the retroperitoneum (Figure 3). The patient underwent excision of the hydatid cyst with the extraperitoneal approach with a smooth postoperative recovery.

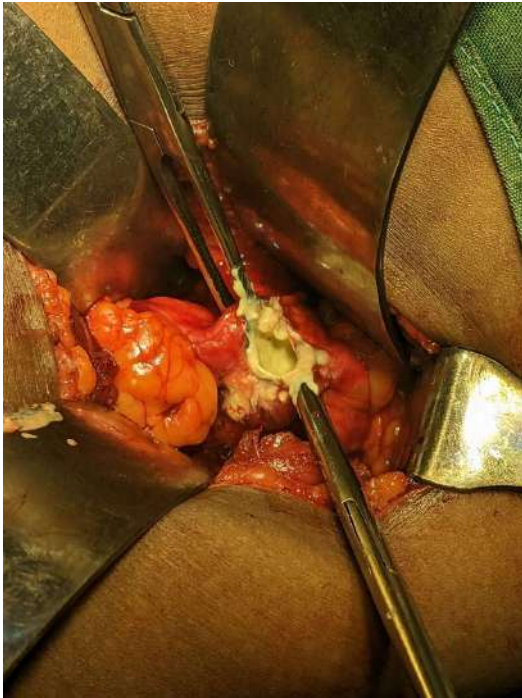


Figure 2- Intraoperative finding of dermoid cyst retroperitoneum

Case 3

A 62-year-old lady patient presented with pain in the lumbar region. Ultrasound diagnosis revealed a space occupying lesion of 3cmX3cm with provisional diagnosis of a cystic neoplasm. CT scan abdomen revealed a cystic lymphangioma with multilocular cystic mass with enhancing septations and lobulations in the psoas muscle (Figure 4). The patient underwent surgery with complete excision of the lymphangioma with a smooth postoperative recovery.

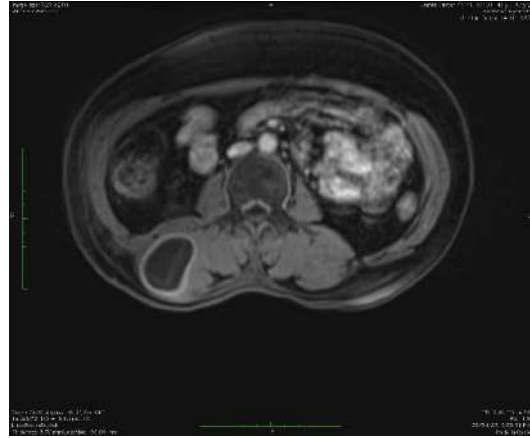


Figure 3. CT scan showing hydatid cyst of retroperitoneum.



Figure 4. CT scan showing cystic lymphangioma retroperitoneum

Discussion

The reason for making this case series is to highlight the fact that usually the retroperitoneal cystic lesions are rare clinical entity and differentiating cystic retroperitoneal space occupying lesions from other cystic growths by imaging studies alone is often inconclusive and confusing and surgery is most frequently required for definitive diagnosis and to ameliorate the symptoms. A completely curative excision the retroperitoneal lesion even if it is seen to encase major vessels is possible with surgical expertise [3]. The differential diagnosis that these retroperitoneal cystic tumors often give rise to is being reported as ovarian tumours in radiology and ovarian cyst has the almost

similar ultrasound findings and clinical symptoms [4]. These tumours are also reported late or in the advance stages due to late clinical presentation and inaccessible clinical position. The surgical management should aim for complete excision in most of the retroperitoneal tumors. Few of the malignant retroperitoneal tumors like the liposarcomas, leiomyosarcomas, or Malignant Fibrous Histiocytomas require wide clear resection margins to allow local control of the disease. The factors affecting complete margin-negative surgical resection include tumor biology, invasion of adjacent structures, surgical management in high-volume centers and last but not the least is the expertise of the surgeon. The surgical skill is of paramount importance in the management of retroperitoneal lesions as surgeons should have a sound knowledge of the anatomy of the retroperitoneal space to avoid injury to the adjacent visceral, vascular, and nervous structures, resulting in intraoperative or postoperative

complications like haemorrhage and neurological complications. If a case is confirmed as benign retroperitoneal tumor, it can be treated conservatively with frequent radiological surveillance if the patient is asymptomatic.

In conclusion, every retroperitoneal cystic lesion of abdomen should be treated with utmost care with a high level of clinical suspicion. Every case of retroperitoneal cystic lesion invariably poses a diagnostic challenge and the clinical decision-making is of paramount importance for the management.

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