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ISSUE HIGHLIGHTS

- A comparative study on clinical features and COVID-19 severity in pediatric patients and adults

- Spectrum of bacterial isolates and their antibiogram in intensive care unit (ICU) of tertiary care hospital as a part of hospital acquired infection (HAI) surveillance

- Serum phosphorus levels as a predictor and severity marker for mechanical ventilation in adults versus elderly patients – A cross-sectional study

- Perspectives of Indian medical students regarding the competency based medical education curriculum – A qualitative, manual, theoretical thematic content analysis

- Vitamin A, E, and C levels in maternal blood of patients with idiopathic preterm premature rupture of membranes, spontaneous preterm birth, and term birth

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Editorial

Heinous crime at healthcare facility: Need for a holistic solution

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A HEINOUS ACT OF VIOLENCE

Nationwide shockwaves have been caused by the unfortunate tragedy that occurred recently at the RG Kar Medical College and Hospital in Kolkata. In addition to bringing attention to the vulnerabilities that women in our society confront, the vicious rape and murder of a young budding lady doctor has also sparked grave concerns about the safety and security protocols that are in place at educational and healthcare facilities. This raises issues regarding the safety of women in our country and in the workplace. Similarly, many incidents of assaults on resident doctors are reported every now and then from various healthcare facilities spread across the country. Two major issues—(1) crime against women and (2) the safety of doctors and healthcare personnel at the workplace—need urgent attention[1].

A CALL FOR JUSTICE

Protests and widespread indignation have been triggered by the horrific incident, with people from all walks of life calling for the victim to receive justice quickly. It's understandable that people are furious. The event has brought to light the obvious flaws in our system that permit such crimes to take place. It is especially concerning since the incident happened in the hospital of a reputable medical college, which emphasizes the pressing need for stronger security measures.

AN APPEAL FOR SYSTEMIC ADJUSTMENT

This is not the first time such an incident has happened and it is high time the government take this unfortunate occurrence for definitive action. Need for deterrent measures are a must and awareness of severe punishment needs to be put in place, which might prevent such crimes from occurring in the first place. We must address the underlying causes of these acts and put in place thorough preventative measures. This entails promoting an egalitarian and respectful culture in addition to enhancing the security infrastructure. To protect the safety of its employees and students, educational institutions must act proactively, and the government must be held responsible for its deeds[2].

STRENGTHENING VOICES

The effectiveness of collective action is demonstrated by the public demonstrations and the participation of numerous groups in the call for justice for deceased young doctors[3]. Seeing people bonding together to demand structural change and to support the victim's family is indeed encouraging. Nevertheless, it is imperative that these voices are heard and that tangible steps are taken to address their needs, both by the central investigating and the central judicial authorities. Similarly, every now and then, we get news of resident doctors being thrashed by unruly attendants of a patient. The frequency of strikes at local, state, and nationwide hospitals is increasing at an alarming rate. Such strikes not only disrupt the training of doctors but more importantly, disrupts patient care. The worst sufferers in these frequent strikes are the patients and their families, who have traveled a long distance to reach medical college/tertiary care hospitals for their appointments, and many lives are lost in emergency situations. Every time a promise is made by the administration, strikes are called off with the hope that such incidents will not occur again.

The current and past episodes raise two issues:

- **Crime against women:** This issue has been long debated and everyone agrees that crime should not happen in the first place. Once it has occurred, the culprit needs to be identified and punished in the shortest possible time.

This can only happen if our system universally shows a commitment to address the issue and act. This crime is most heinous against humanity and should not become a political issue. If one case is unsolved, then it should not become ground for a casual approach in other cases. These cases should not only be investigated promptly but also the guilty should be punished at the shortest possible time.

a. Making a stringent law supported by political system, with no partisan views on this issue.

b. These cases need to be handled with seriousness and all law agencies (local police, CBI, etc.) must act fast.

c. The investigation should be conducted according to the principles of investigation, and anyone found wanting in carrying out police investigation needs also to face displeasure in their service record. If a healthcare worker is found wanting while treating a patient for negligence, then the investigating officer also should be held accountable for his/her lack of initiative and action. There have been innumerable cases in the recent past where no conclusion could be drawn after a botched-up investigation, such as rape and murder, delaying and denying justice. Inadequacy of action in the past is no ground for inaction in the present and future.

d. Such crimes should not occur at first instance. The safety/security and workplace environment need to be surveyed. The resident doctors should be provided with a safe and secure environment to deliver services. This one is the most neglected part in public hospitals. Whenever a healthcare facility is planned, it must have safe and comfortable duty rooms ready for doctors/nurses, which is one of the most neglected areas in government hospitals. If a random survey of all health facilities is conducted on minimum standard criteria, the majority will be found wanting. Since these staff work round the clock and do odd-hour duties, safety should be ensured in their movement to hostels/residences. The hospitals should be well lighted and under cover of CCTV with 24-hour monitoring. This is the responsibility of the facility in-charge (medical superintendents, medical directors, principals of medical colleges), departmental heads, and consultant in-charge in all the hospitals to ensure safety/security of all staff.

- **Attacks/assaults on doctors/nurses in healthcare facilities:** it is now very frequent at the district/primary health center/tertiary healthcare center where the relatives of patients assault/attack the treating doctors and healthcare personnel. It is surprising that relatives of a patient (who is in pain) while getting redressal of his/her problem,

starts taking the law in to their own hands and harm the healer. This problem also needs to be addressed in the right perspective. Why should a person/relative who comes for treatment takes the law into their own hands? Such people should be dealt with stringent actions as the lawbreaker is committing multiple damages:

- Physical assault of doctors/nurses causing injuries and risking their lives.
- Obstructing the treatment of other patients who also are in pain and in need of treatment, thus risking other's lives also.
- The collateral damage caused by frequent strikes by doctor/nurses/healthcare workers in response to such episodes disrupts the normal working in hospitals and causes inconveniences to the millions of patients,
- A negative impact on health economics.

At first instance, such episodes should be prevented and dealt with tough laws and by deploying adequate guards/security staff and having safe healthcare facilities with adequate CCTV cover. In a nutshell, not only adequate law should exists but also its implementation should be ensured on the ground.

Other important aspect is root cause analysis of such instances as to why they have occurred in the first instance and how we can avoid them. The main dissatisfaction and trigger for such incidents is overcrowding and lack of balance between the number of patients and available infrastructure and manpower (doctors and nurses). The counseling of patients takes a back seat in overcrowded hospitals/clinics. The audit of infrastructure and patient load should be carried out periodically so that the infrastructure is augmented for the increased footfall.[4] There should be sufficient waiting areas with properly planned outpatient chambers with adequate manpower so that each patient's medical problems are addressed in a satisfactory manner. The counseling facility for patients in public hospitals also needs to be upscaled. The infrastructure should be organized in such a manner that patients are able to get solutions to their clinical problems on a single visit to the hospital, which will reduce overcrowding in the hospital significantly. The available hospital outputs should be audited to get optimum utilization of facilities.[4] The waiting time for the procedures to be reduce by upscaling operating facilities to fulfill this unmet need.

IN SUMMARY

The rape case involving RG Kar Hospital serves as a sobering reminder of the amount of work that must be done to protect women's safety and dignity in our society. It is a call for action to all of us to take a stance against these crimes and endeavor to make the world a safer, more equitable place. We should

be motivated to work toward a society in which tragedies like this are a thing of the past in the memory of another Nirbhaya. The respect to treating doctors/nurses needs to be restored so that violence in any healthcare facility is prevented.

Jai Hind.

Anil K Jain
Lt Gen (Dr) Velu Nair

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Review Article

A comparative study on clinical features and COVID-19 severity in pediatric patients and adults

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ABSTRACT

Introduction: Coronavirus disease (COVID-19) has emerged as a global threat affecting diverse populations. While the severity of the disease is often associated with comorbidities and inflammation, pediatric patients generally experience a milder course. Limited studies exist regarding the factors influencing acute COVID-19 severity in pediatric patients compared to the elderly. This review aims to bridge this knowledge gap by investigating clinical presentations and potential factors contributing to severity, providing valuable insights into the relationship between age and disease outcomes.

Methods: Our study encompassed diverse settings, including hospitals and communities, with a focus on children and adults. We conducted a comprehensive literature review, analyzing PCR and laboratory-confirmed COVID-19 cases. The primary purpose was to elucidate demographic and clinical features, shedding light on the prevalence of symptoms and signs in pediatric patients.

Results: The results demonstrate a reduced prevalence of COVID-19 in hospitalized children as compared to adults, that are consistent with the generally milder clinical trajectory observed in pediatric cases. The study identifies factors contributing to severity in different age groups, emphasizing the need for a nuanced understanding of COVID-19 manifestations.

Conclusion: This literature review enhances our comprehension of COVID-19 across age groups, emphasizing the milder nature of the disease in pediatric patients. By uncovering factors influencing severity, this work contributes valuable knowledge for effective patient management, especially in older age groups where the risk is higher. The distinctive ability of younger individuals to combat the virus underscores the importance of tailored strategies for diverse age demographics in addressing this global health crisis.

Keywords: COVID-19, Coronavirus, SARS-CoV-2, Pediatric patients, Pediatric, Severity, Age .

INTRODUCTION

Since the onset of 2019, the international community has been contending with the profound ramifications of the COVID-19 pandemic, presenting formidable challenges to healthcare systems worldwide. The causative agent, SARS-CoV-2, responsible for instigating COVID-19, was identified in respiratory specimens procured from individuals diagnosed with pneumonia and subsequently progressing to respiratory failure.[1] The analyzed cases were stratified into symptomatic and asymptomatic categories, wherein the former exhibited clinical manifestations such as fever, rhinorrhea, influenza-like symptoms, and general malaise, necessitating subsequent hospitalization. Conversely, asymptomatic cases were characterized by the absence of discernible clinical signs or symptoms. It is crucial to underscore that the lack of symptomatic presentation did not function as a determinant for assessing the severity of the cases.

In light of the official declaration of COVID-19 as a pandemic, a plethora of cases delineating its clinical manifestations has come to the surface, with a substantial number involving pediatric patients necessitating hospitalization. Among individuals succumbing to COVID-19, a considerable proportion exhibited preexisting conditions such as hypertension, diabetes, and, in specific instances, cardiovascular diseases, potentially compromising their immune responses. However, the occurrence of these comorbidities was notably infrequent in the pediatric demographic, indicative of a more resilient immune response to the virus.[2]

Thrombosis and thrombocytopenia, which involve blood clots and low platelet counts, have been reported as rare adverse events following COVID-19 vaccination with COVISHIELD in India.[3] The condition associated with these adverse events is known as vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS). The exact cause of these adverse events is still under investigation, and no predisposing risk factors have been conclusively identified so far. However, it has been observed that antibodies that bind platelet factor 4, similar to those associated with heparin-induced thrombocytopenia, have been identified in some cases.[4]

Research findings consistently highlight a lower susceptibility of children and pediatric patients to severe outcomes from COVID-19. Both medical literature and an expanding repository of cases underscore a comparable infection incidence between adults and children. Nevertheless, the pediatric demographic tends to manifest milder disease forms, as evidenced by a low case fatality rate (CFR) of less than 0.1%. Furthermore, a case series encompassing four infants born to mothers with COVID-19 revealed that none of the three infants subjected to testing exhibited positive results for the virus or displayed clinical symptoms. This observation implies a minimal likelihood of vertical transmission of the virus.[5]

Due to the scarcity of comprehensive investigations into risk factors for COVID-19 in pediatric populations, our objective is to systematically collate and analyze extant data to discern and expound upon these factors. This endeavor seeks to offer invaluable insights to healthcare professionals tasked with mitigating the repercussions of viral infections in this demographic.

METHODS

The methodology for the systematic analysis was meticulously designed to ensure a comprehensive and rigorous review of the literature related to COVID-19 in neonates and children. The identification of relevant references commenced with a thorough search across reputable databases, including PubMed, NCBI, and Lancet's EClinicalMedicine, utilizing specific and pertinent terms associated with 2019-nCoV, COVID-19, and SARS-CoV2 in the pediatric population. Notably, the focus was exclusively on articles published in English to maintain uniformity and accessibility.

The initial screening involved a meticulous review of 76 articles and consultation with 25 databases to ascertain a broad understanding of the existing literature. Subsequently, a judicious removal of duplicates was executed, resulting in 58 review articles and 20 datasets for further scrutiny. This refined dataset underwent a rigorous screening process,

narrowing down to 40 review articles and 14 datasets that met the predefined inclusion criteria.

A stringent approach was adopted to maintain the quality and reliability of the selected studies. One particular study, which investigated infant cases, was excluded due to concerns about the data source's reliability and incomplete parameters, ensuring the integrity of the final dataset. In addressing potential biases and limitations such as repeated calculations and missing data, a judicious decision was made to exclude this study from the pooled data, thereby enhancing the robustness of the systematic analysis.

The quantitative facet of the analysis benefited from the inclusion of seven meticulously selected case series specifically focused on pediatric COVID-19, facilitating a nuanced quantitative examination. Additionally, a qualitative perspective was enriched by the inclusion of 28 review papers, providing a comprehensive and detailed understanding of the subject matter as given in Figure 1.[6-12]
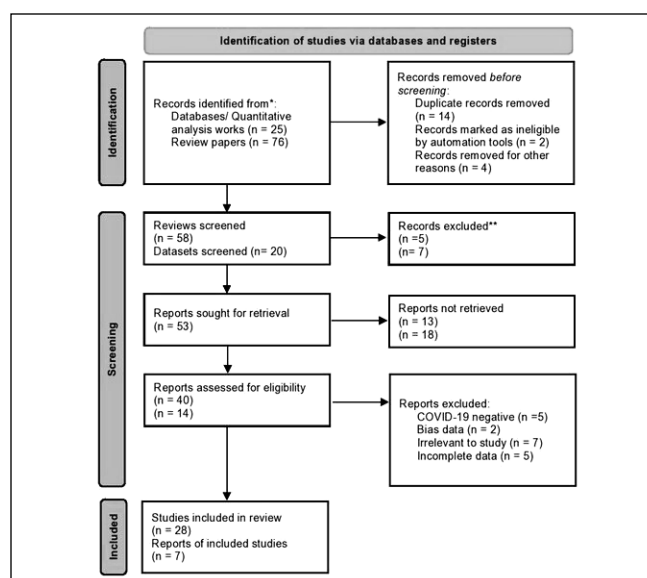
Figure 1: Flowchart depicting the systematic process of study selection in the analysis.

RESULTS

In our examination of epidemiological and clinical features, the targeted population comprises individuals up to the age of 20, with gender deemed irrelevant to our study parameters. Noteworthy is the fact that 75% of the individuals under consideration had a documented history of household contact. Analysis of the provided table reveals that a substantial 98% of the scrutinized patients manifested mild to moderate disease severity, while only 1% encountered severe to critical disease conditions. It is particularly noteworthy that, among the 93 children enrolled in the study, a mere 2 necessitated

Table 1: Characteristics of studies reporting epidemiological and clinical features of COVID-19.

Studies referred to	Study A[6]	Study B[7]	Study C[8]	Study D[9]	Study E[10]	Study F[11]	Study G[12]
Case number (n)	6	15	10	20	31	6	5
n / Total sample size	6/93	15/93	10/93	20/93	31/93	6/93	5/93
Median age (years)	3 y	7 y	6.5 y	2 y	7 y	7 y	3 y
Age range	1–7 y	4–14 y	3 m–10 y	1 d–14 y	6 m–17 y	7 m–14 y	10 m–6 y
Male (%)	2 (33)	5 (33)	4 (40)	13 (65)	15 (48)	5 (83)	4 (86)
Disease severity							
Mild	2	3	6	4	17	3	2
Moderate	3	12	4	15	14	3	3
Severe	1	0	0	0	0	0	0
Critical	0	0	0	1	0	0	0
Clinical features							
Asymptomatic	0	8	0	2	7	3	4
Fever	6	5	8	12	20	3	1
Cough	6	1	6	13	14	2	1
GI symptoms	4	0	0	3	3	1	0
Outcomes							
Intensive care	1	0	0	1	0	0	0
Complication	0	0	0	1	0	0	0

intensive care, and only 1 child experienced complications. This unequivocally points to a diminished incidence of complications within the pediatric demographic, a finding underscored in the results section as given in Table 1.

The manifestations of COVID-19 encompassed a spectrum of presentations, ranging from asymptomatic cases to distinctive symptoms. Around 26% of the patient cohort manifested asymptomatic presentations, while 59% displayed pyrexia, representing a substantial portion of the overall study group. Cough was reported in approximately 46% of patients. However, there was a notable degree of variability in outcomes, with only a minority of patients manifesting gastrointestinal symptoms as given in Figure 2.
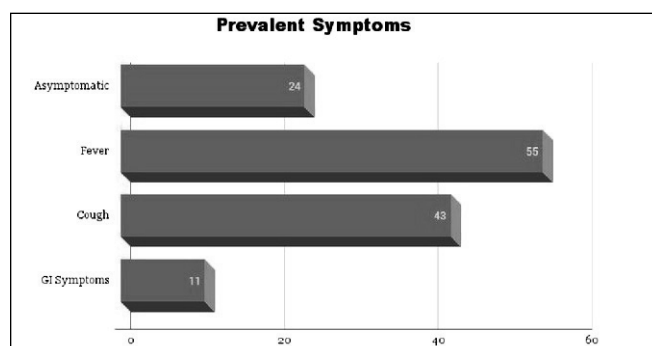
Figure 2: Bar graph depicting the proportional distribution of symptoms associated with COVID-19.

The pathophysiological processes governing viral infection encompass coronaviruses, a class of single-stranded positive-sense ribonucleic acid (RNA) viruses characterized by distinctive spike-like projections on their surface.[13] angiotensin-converting enzyme 2 (ACE2) receptors, distributed widely in various tissues throughout the human body, particularly on the cells of alveolar epithelium II, play a pivotal role in this process. The spike proteins that encapsulate the coronavirus predominantly bind to ACE2 receptors situated on type II alveolar cells, facilitating the introduction of the virus' RNA into these cells. Consequently, this viral RNA takes command of the cell, compelling it to generate and release multiple copies of the virus into the alveoli. This cascade of events culminates in the lysis of the host cell, with progeny coronaviruses subsequently infecting adjacent cells. Significantly, this entire sequence may unfold asymptomatically in the host, underscoring its role as a pivotal factor in the asymptomatic transmission and efficient dissemination of COVID-19. The ascertainment of COVID-19 necessitates a meticulous clinical evaluation aligned with established guidelines, bolstered by supplementary insights gleaned from laboratory tests and radiological observations.[14]

The symptomatic expression of COVID-19 in neonates and children commonly presents as mild, demonstrating consistent patterns across diverse geographical locations.[15,16] Hospitalization for children is predominantly prompted by

symptoms including fever and respiratory complications, encompassing manifestations such as tussis, pharyngitis, facial erythema, rhinorrhea, rapid breathing or respiratory distress, and an elevated heart rate (tachycardia).[17,18] Although infrequent, documented instances highlight the occurrence of neurological manifestations, involuntary muscle contractions, and altered mental status in some cases.[19]

COVID-19 severity classifications, spanning asymptomatic infections, and mild, moderate, severe, and critical cases, have been established through the integration of clinical features, laboratory test results, and X-ray imaging criteria.[20] Notably, lymphocytopenia, a common occurrence in adults with severe COVID-19 and often associated with unfavorable outcomes, does not typically manifest in children, potentially attributed to the naturally higher percentage of lymphocytes in this age group.[21,22] Conversely, adults exhibit significantly heightened levels of D-Dimer, ferritin, and coagulopathy, while these manifestations are infrequently observed in the pediatric population.[23]

Many of the observed laboratory abnormalities in children lack specificity. Notably, 69.2% of children exhibited leukocyte counts within the normal range, and instances of neutrophilia or neutropenia were infrequent, occurring in less than 5% of cases. Platelet counts displayed variability across different studies, generally trending higher than the normal range. Furthermore, elevated levels of C-reactive protein were noted in 13.6% of cases, while increased procalcitonin levels were observed in 10.6% of cases.[24]

Our meticulous review of clinical data on pediatric COVID-19 cases indicates a prevailing trend of mild to moderate disease severity, with varying proportions of asymptomatic patients across studies. While the majority of cases exhibit subtle clinical features, exceptional instances, such as a 1-year-old boy presenting with critical symptoms, underscore the need for heightened vigilance in recognizing atypical manifestations promptly, especially in pediatric cases where challenges in diagnosis may arise as given in Figure 3.
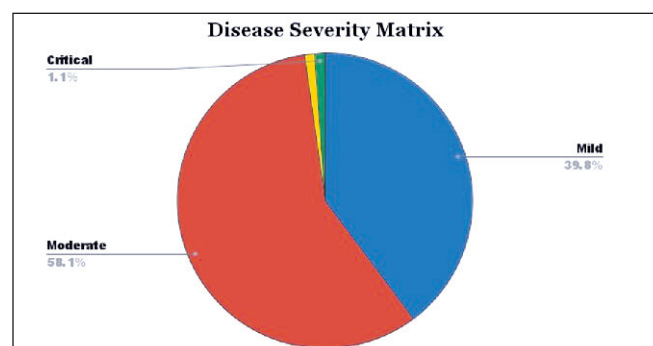
Figure 3: Distribution of severity categories in cases of COVID-19 infection.

DISCUSSION

This systematic investigation meticulously collected and amalgamated prevailing observational studies concerning COVID-19 in the pediatric cohort. The surge in global COVID-19 cases is evident, with the most extensive epidemiological survey revealing a predominant demographic impact within the age range of 30–79 years, encompassing 87% of reported cases. It is crucial to highlight that advanced age and the presence of pre-existing medical conditions correlate with an elevated susceptibility to the deleterious effects of the virus. Conversely, the prevalence among the pediatric population remains considerably modest, constituting a mere 2.2% of the 44,672 confirmed cases, thereby yielding a conspicuously low crude mortality rate of 0.1%. This stands in sharp contradistinction to the elevated mortality rates documented in contemporary published data for the adult demographic, ranging from 2.3% to 14.6%.[25,26]

The study maintains adherence to standardized categorization, harmonizing pooled data accordingly. The results reveal a tendency towards mild to moderate disease severity among children, with mild cases often characterized by subtle and transient clinical features, contributing to varying proportions of asymptomatic patients across distinct studies. It's worth noting that these outcomes may, in part, reflect the early stages of the COVID-19 outbreak, akin to observations in adults, where more symptomatic or severe cases were prevalent. This variability introduces a moderate level of heterogeneity in the pooled data concerning clinical features.

A male infant, aged one year, was categorized as critically ill. His presentation initially involved vomiting and diarrhea over a 6-days period, devoid of apparent cough or respiratory symptoms. However, his condition swiftly deteriorated post-admission, leading to shock and subsequent progression to acute respiratory distress syndrome (ARDS), necessitating mechanical ventilation.[27] Furthermore, the patient exhibited nephropathy necessitating hemodialysis during the course of hospitalization. Recognizing such atypical presentations promptly poses heightened challenges in pediatric cases.

In comparison to a closely related virus, SARS-CoV, it's evident that SARS-CoV-2 leads to milder disease. While the precise factors contributing to this phenomenon are still being investigated, some of these parameters are widely acknowledged. Numerous factors may underlie this phenomenon, with a crucial determinant in the attenuated course of COVID-19 in children being the lack of baseline inflammation. In contradistinction to adults, pediatric individuals exhibit a more robust immune response and demonstrate diminished vulnerability to pre-existing medical conditions.[28] Severe respiratory complications requiring intensive care are infrequent among children in comparison

to adults.[29] Notably, children with pneumonia often encounter coinfections involving both viruses and bacteria, potentially enhancing their immune memory against a broader spectrum of pathogens. However, the applicability of this observation to pneumonia related to SARS-CoV-2 remains uncertain.

Another significant aspect is the emergence of multisystem inflammatory syndrome in children (MIS-C), temporally associated with COVID-19. MIS-C represents a recently recognized, infrequent, and potentially life-threatening hyperinflammatory condition characterized by features that overlap with both typical and incomplete presentations of Kawasaki disease and toxic shock syndrome.[30-32] Moreover, comprehending the diverse risks associated with children can be intricate. Those in whom coronaviruses are identified in the respiratory tract may encounter viral coinfections in as much as two-thirds of the cases.[33]

An additional hypothesis warranting investigation regarding the reduced severity risk of COVID-19 in children compared to adults revolves around the attenuated expression of ACE2 in the nasal epithelia of children.[34,35] The binding affinity of SARS-CoV-2 to ACE2 provides partial insight into why it induces less severe disease than SARS-CoV while retaining a high level of infectiousness. However, it is crucial to acknowledge that this explanation does not comprehensively address why children exhibit lower susceptibility to severe COVID-19. Previous studies have indicated that SARS-CoV induces higher ACE2 shedding than human coronavirus NL63.

The divergent regulation of ACE2 receptors holds close relevance to lung injury.[36] Research indicates that aging induces changes in the pulmonary renin-angiotensin system, correlating with heightened inflammation and more pronounced lung injury in a rat model.[37] Notably, smoking is a predominant factor among adults as opposed to children. An underlying hypothesis posits that smoking may elevate ACE2 expression, potentially augmenting the entry of coronaviruses into pulmonary epithelial cells.[38]

CONCLUSION

In our systematic analysis, several inherent limitations merit consideration. The COVID-19 outbreak occurred over two years ago, leading to a substantial accumulation of detailed descriptions, posing challenges in data relevance and reliability due to potential variations in employed assessment tools. Continuous follow-up studies are imperative for assessing long-term outcomes and potential sequelae, while the prevalence of multiple viral infections akin to COVID-19 in the same environment adds complexity to diagnosis. Additionally, the treatment strategy for children warrants further examination. In conclusion, the pediatric population tends to exhibit a less severe response to viral infections, with

explanations subject to evolution as new patient cohorts are examined. The increased prevalence of asymptomatic and mild cases adds complexity to the diagnostic process and infection management.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

An insight into the heatstroke in Northern India: Clinico-pathological observation and outcomes from a tertiary care center

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ABSTRACT

Objectives: To observe the clinical presentation, pathological changes, and outcomes of heatstroke at a tertiary care center.

Material and Methods: Patients presented with an axillary temperature above 104°F to the casualty during summers in the months of April and May 2022 were screened. After excluding the other causes of fever and based on history, patients were diagnosed as suffering from heatstroke. After taking valid consent, treatment was initiated, and all observations were taken. Clinical presentation, demographic data, vitals, and investigations (hemogram, renal function, liver function, CPK, IL6, CRP, and random glucose levels) were recorded, diagnosed, and enrolled for observation. Chi-Square test for 2 x 2 contingency table used to identify the association between CPK and muscle cramps. The T-test for 2 Independent Means and the Pearson Correlation Coefficient test were used for analyzing other data.

Results: For the study, 112 patients were enrolled and classified as per severity: 80 were pre heatstroke, 22 were mild heatstroke, and 10 were severe heatstroke. Age above 50 years is associated with severe forms of disease and poor outcomes. Out of 112, 28 (25%) participants were 50 years or above age. Nine (32.1%) out of these 28 developed pre-heatstroke, and 19 (67.8%) developed mild to severe heatstroke. Creatinine kinase was raised in 17 out of 112 (15.1%) participants, but the proportion of participants having raised CPK does not differ by the presence of myalgia. IL6 was also found to be elevated and related directly to the severity of the disease in this study.

Conclusion: Heatstroke is a common disease that occurs due to working on farms during the summer. Old age is more prone to severe disease and poor outcomes. Raised IL6 also correlates directly with disease severity.

Keywords: Heat cramps, Heat exhaustion, Heat injury, Heat stress, Heatstroke, Summer sickness

INTRODUCTION

Heatstroke is a condition of abnormal thermoregulation characterized by a fatal rise in core body temperature of more than 40°C or 104°F in addition to central nervous system abnormalities like altered consciousness, seizures, and sometimes coma along with ,heatstroke can also cause multi-organ failure and death. It is a common disease that usually occurs in states with tropical climate conditions. Bundelkhand region of central India is geographically located at a place where most landscapes consist of irregular uplands with outcrops of rocks intermingling with lowlands rocky hills, and the climate is semi-arid during summers. Every year since 2010, more than 1000 deaths have been reported from various parts of India, with a maximum of 2040 deaths in 2015 and 1111 in 2016. Most of these are from Uttar Pradesh, Bihar, Maharashtra, Orissa, and Andhra Pradesh. From 2006 to 2010, more than 3332 deaths were attributed to heat-related illness.[1] Death records due to heatstroke from South Asian countries in April 2023 were 179 (India), 22 (Pakistan), 2 (Malaysia), and 2 (Thailand).

Several other infectious diseases prevalent in tropical areas of India often share common symptoms like high-grade fever, altered sensorium, and seizures. The presence of acute renal failure, rhabdomyolysis, cardiac arrhythmias, and seizures determines the high mortality rate and fatal outcomes. Effective cooling of the body and reducing core body temperature to normal without landing to hypothermia is the gold standard for the management of heatstroke. Management of hyperpyrexia or hyperthermia in the initial 24 hours of presentation to the hospital is often rewarding in cases of heatstroke. That's why an early diagnosis and management are very important to prevent mortality and

morbidities. Management of comorbidities like shock, acute renal failure, rhabdomyolysis, seizures, and multi-organ dysfunction (MODS) is done on the usual lines of treatment.

The rapid increase in the environmental temperature in the months of April and May has increased the number of cases of casualty in our Institute. In this study, we hereby present the clinical, biochemical, and treatment outcomes of the cases presented.

Significance

Bundelkhand is one of the hottest regions in India and is primarily composed of farmlands. This study contributes clinical and pathological data among field workers. Thus, results from this study help further derive better treatment guidelines for the management of heatstroke among this group of patients.

MATERIAL AND METHODS

Study design and settings

The study was conducted in the Department of Medicine at Rani Durgawati Government Medical College, district Banda, Uttar Pradesh, India and S N Medical College, district Agra, Uttar Pradesh, India. The study was conducted during the months of April and May 2022. Participants enrolled were those presented to the casualty department seeking treatment. Participants presented to casualty with fever having an axillary temperature of ≥104°F, signs of dehydration, hypotension or low pulse pressure, muscle cramps and tenderness, altered behavior, and classical clinical background were screened for inclusion. The diagnosis was made after the exclusion of all other infectious causes of presenting clinical features by sepsis screening.

Data collection and classification

Enrolled participants were interviewed for onset, duration and progression of symptoms, duration and type of exposure to heat, any aggravating factor for present symptoms, and treatment taken before presentation to casualty. Every possible symptom pertaining to heat-related illness described in the literature search was enlisted in the data record sheet. Vitals, including BP, pulse, respiration and temperature, and random blood glucose, were recorded. Systemic examination with special details of the neurological system was done and recorded. Based on presenting symptoms and vitals, participants were graded for severity and grouped into (1) pre heatstroke, (2) mild heatstroke, and (3) severe heatstroke. Severe heatstroke is further graded to heat cramps, heat exhaustion, and classical heatstroke.

Ethical approval

Ethical clearance of this observational study was received from Ethical committee of S N Medical College, Agra (Letter No: SNMC/ IEC/2021/52, Dated: 05-Apr-2022). Written informed consent was obtained from all enrolled subjects.

Methodology

Participants diagnosed with heatstroke were investigated, including complete blood picture, renal, liver, thyroid functions tests, arterial blood gas analysis, random blood glucose, creatinine phosphokinase, C reactive protein, and complete urinalysis. Treatment to reduce core temperature included ice sponging, chilled saline infusions, and oral rehydration solutions. Treatment guidelines for complications were adopted from updated standard evidence-based recommendations. Death due to heatstroke is defined as any mortality during treatment in hospitalization duration or one week after the discharge due to any complication arising out of the primary condition, including deep vein thrombosis (DVT), acute renal failure (ARF), liver failure, brain death, any cardiac problem, etc.

Statistical analysis

The website https://www.socscistatistics.com was used to do all statistical calculations. Various statistical tools like the Chi-Square test for a 2 x 2 Contingency Table, T-test for 2 Independent Means, and Pearson Correlation Coefficient test were used for analyzing the data. The one-way, or one-factor Analysis of Variance (ANOVA) test for independent measures is used to compare the means of all investigations in three groups.

RESULTS

Demography

A total of 267 patients admitted with axillary temperature ≥104°F were screened for heatstroke. After exclusion and removing who lost follow up, a total of 112 patients were enrolled for the study. Two participants with severe grades expired due to multi-organ failure. The remaining r 110 participants completed the study with no long-term morbidity.

Age is an important factor in disease severity. Figure 1 illustrates the age distribution in different severity groups. Older age is often associated with poor outcomes of acute diseases. Eighty-four (75%) participants were less than 50 years of age, out of which 71 (84.5%) developed preheatstroke, whereas 13 (15.5%) had mild to severe heatstroke. On the
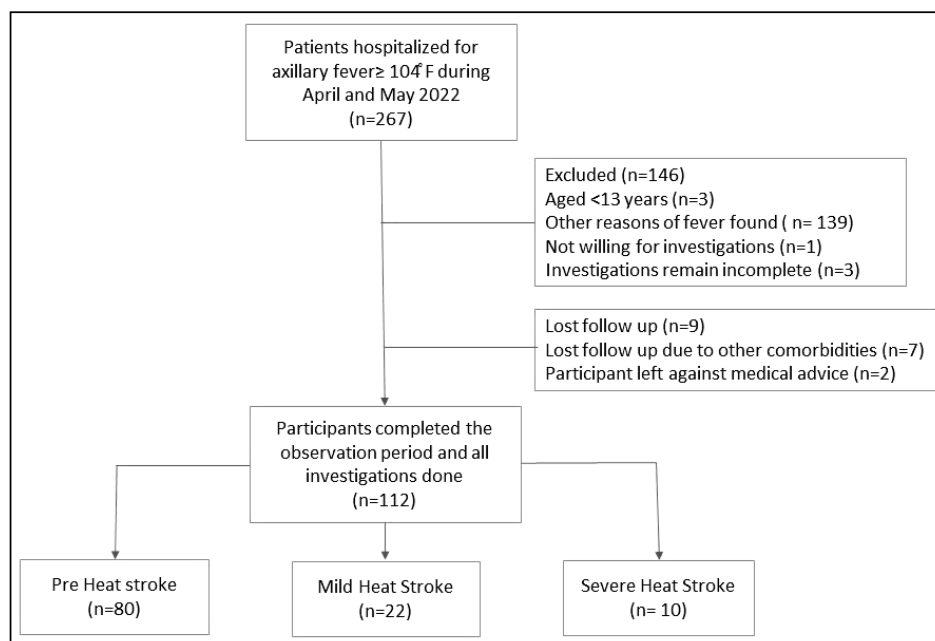
Figure 1: Flow chart of the case selection process.

other hand, 28 (25%) participants were 50 years or above age, out of which nine (32.1%) developed preheatstroke and 19 (67.8%) developed mild to severe heatstroke. A chi-square test of independence showed that there was a significant association between age above 50 years and disease severity, X^2 (1, N = 112) = 28.2, p = 0.00001.

Clinical presentation

Oliguria due to dehydration was the first symptom complained by 30.5% of participants. Three participants were also presented with anuria. Myalgia, which occurs due to intermittent contraction of muscles due to electrolyte imbalance, was the second most prominent symptom present in 25% of participants. Creatinine kinase (CK) is raised (normal value 10 to 120 mcg/L) in 17 out of 112 (15.1%) participants. The proportion of participants having raised CK did not differ by the presence of myalgia, X^2 (1, N = 112) = 1.8, p > 0.17. The result is not significant at p < 0.05. Myalgia and CK are not associated with heatstroke.

Pathological findings

All demographic, clinical, and pathological characteristics and outcomes are summarized in Table 1. A significant difference is found in three groups at the parameters of hematocrit, serum creatinine, and Blood urea Nitrogen (BUN). Figure 2 illustrates all the pathological findings among different severity groups and their frequencies.
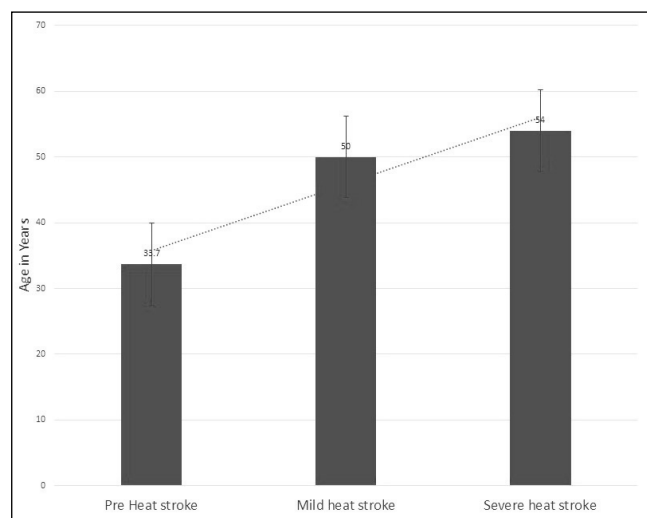
Figure 2: Age distribution and disease severity.

DISCUSSION

Heatstroke remains one of the leading causes of morbidity and mortality in summers in tropical regions in India. This study contributes several important inputs for various clinical and pathological characteristics of heatstrokes. Patients' age always remains the most important factor for disease occurrence and disease outcomes.[2] In our study, out of 112 participants, 28 (25%) were ≥50 years of age. 61 ± 13.5 years was the mean age of 27 study participants in a study by Ninan *et al.*[3] Old age is associated with less adaptive mechanisms towards heatstroke. Classical heatstroke occurs in young and

Table 1: Clinical and pathological characteristics of participants.

Sl. No.	Characteristics	n	SD
1	Age	38.7 years	14.2
2	Sex		
	Male	72	
	Female	40	
3	Duration of symptoms onset	23.2 hours	14.1
4	Received first aid		
	Yes	91	
	No	21	
5	Disease severity		
	Pre heatstroke	80	
	Mild heatstroke	22	
	Severe heatstroke	10	
	• *Subtype heat cramps*	*2*	
	• *Subtype heat exhaustion*	*4*	
	• *Subtype classical heatstroke*	*4*	
6	Axillary temperature °F (Avg.)	103	1.5
7	Pulse rate per min	139	15.9
8	Systolic BP mmHg	118	25.8
9	Diastolic BP mmHg	73.3	15.7
10	Respiratory rate per min	24	11.3
11	Clinical features n (%)		
	Myalgia	28 (25.0)	
	Diarrhea	13 (11.6)	
	Oliguria	34 (30.5)	
	Respiratory distress	9 (8.0)	
	Confusion	20 (17.8)	
	Delirium	3 (2.6)	
	Hallucination	1 (0.8)	
	Decerebrate	1 (0.8)	
	Seizures	1 (0.8)	
	Coma	1(0.8)	
12	Pathological findings		
	Hemoglobin g/dL (12–18 g%)	11.3	2.1
	Hematocrit % (36%–50%)	48.9	3.1
	Platelets count in lakh (1.5-4.5 lakh/µL)	1.3	0.4
	CRP mg/L (<0.3 mg/dL)	6.5	2.1
	IL6 pg/mL (<7 pg/mL)	24	8.6
	Creatinine mg/dL (0.7–1.3 mg/dL)	0.8	0.5
	BUN mg/dL (7–20 mg/dL)	24.7	20.4
	SGPT IL/L (19–33 IU/L)	37.9	22.6
	CPK mcg/L (10–120 mcg/L)	86.1	32.7
	RBG mg/dL (<140 mg/dl)	102.2	51.8
13	Outcome		
	Survived	110	
	Expired	2	

CRP: C reactive protein, IL6: Interleukin 6, BUN: Blood urea nitrogen, SGPT: Serum glutamic pyruvic transaminase, CPK: Creatine phosphokinase, RBG: Random blood glucose, SD: Standard deviation.

old age people due to extreme heat waves during summers without preceding exertion, whereas exertional heatstroke occurs due to athletic activity or strenuous exertion during variably warm or hot weather or while wearing heat-retaining clothing.[4] Poor sudomotor, cardiovascular, and immune function, along with defective behavioral thermoregulation, are the important factors why geriatric age is at high risk for heatstroke.[5]

Measuring rectal temperature is the best way to access the exact core body temperature during heatstroke. We lacked this in our study as we measured the axillary temperature. Axillary temperature was 103 ± 1.5°F in this study. In a study by Deshwal *et al.* among paratroopers suffering from exertional heat exhaustion in the Agra district of India, the average rectal temperature was 104.74°F.[6] This is equivalent to our study considering the difference between rectal and axillary temperature, where the former remains 0.5 to 1.0°F higher than the latter.[7] Oliguria, followed by myalgia, was the most frequent manifestation in our study. Dehydration and oliguria are present in 29% of sufferers of heatstroke.[8] Inability to maintain hydration due to lack of water and unawareness towards heat while engaged in farm work were the common reasons due to which our study participants land up into heat-related illnesses, especially dehydration and oliguria.

Myalgia was the prominent manifestation of heatstroke presented in 28 (25%) participants. Hyponatremia and dehydration, hypokalemia, increased lactic acid levels, and exertional muscle injuries are the prominent causes of myalgia and fatigue among patients.[9] Judicious selection of fluids, correction of electrolytes, and cold sponging are effective methods to reduce myalgia.[10] The presence of confusion, mental obtundation, and restlessness are prominent features of mild and severe heatstroke.[6] Hyponatremia, hypercalcemia, cortical vein thrombosis, lactic acidosis, and metabolic alkalosis are defined as etiological factors behind CNS manifestations of heatstroke. Further, sepsis and MODS could lead to metabolic encephalopathy and seizure.[11] Symptomatic management, effective cooling, and rehydration during golden hours in critical care units are always rewarding, with minimal residual CNS deformities.[12] Delirium, hallucinations, and decerebrate rigidity are also rarely reported CNS manifestations of heatstroke.[13–15] Renal dysfunction like pre-renal ARF secondary to dehydration or intrinsic renal failure due to prolonged dehydration, myoglobinuria, or sepsis syndrome is also recognized complications of heatstroke.[16,17] The average S creatinine levels in our study in the severe heatstroke group was 1.8 mg% whereas it was 0.8 mg% in pre heatstroke group. In 13 out of 112 (11.6%), S creatinine and 34 out of 112 (30.3%), BUN were more than 13 mg% and 24 mg%, respectively. The raised values of S creatinine and BUN responded to rehydration in all participants. All participants
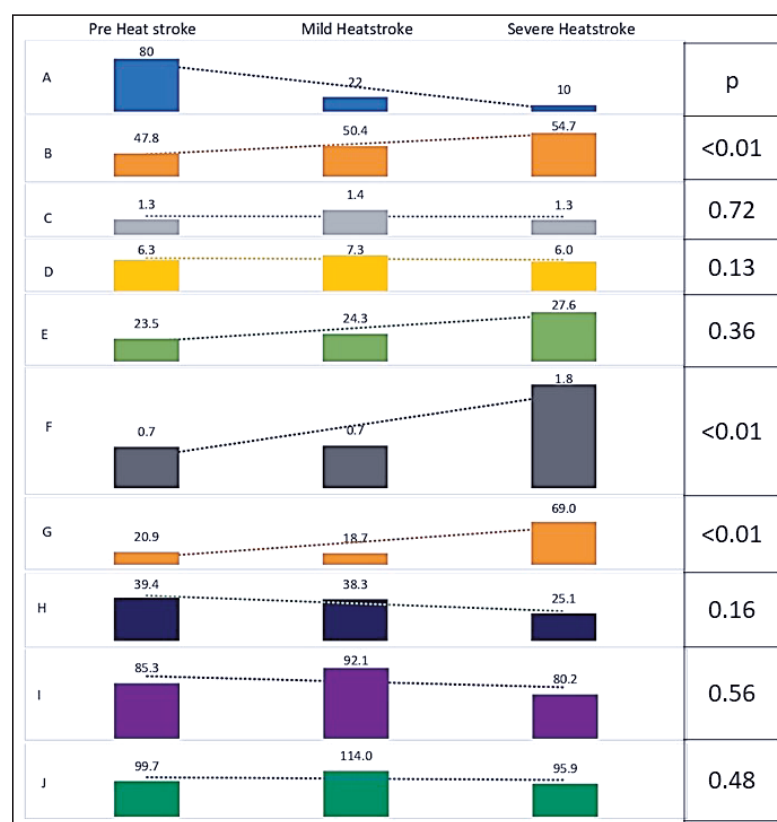
Figure 3: Changes in pathological findings in different stages of heatstroke. (A) subject count; (B) Hematocrit; (C) Platelet count in lakh; (D) CRP; (E) IL6; (F) S. Creatinine; (G) BUN; (H) SGPT; (I) CPK; (J) RBG. Trendline denotes changes as per severity. CRP: C reactive Protein, IL6: Interleukin 6, BUN: Blood Urea Nitrogen, SGPT: Serum Glutamic Pyruvic transaminase, CPK: Creatine Phosphokinase, RBG: Random Blood Glucose.

who received institutional first aid elsewhere before visiting our institute had normal renal functions clearly explains its importance. Values of other relevant investigation like Hematocrit, Platelet count, C Reactive protein, Interleukin 6, Blood urea Nitrogen, serum glutamic pyruvic transaminase (SGPT), Creatine phosphokinase and Random Blood Glucose in different severity groups are illustrated in Figure 3. Management and outcomes of participants requiring dialysis for ARF due to heatstroke are not different than the cases with other causes.[18] Severe acute liver injury has also been reported due to heatstroke.[19] Recognition of common pathological changes and their clinical correlation helps in management. In a study by Gharibi *et al.*, hematocrit is raised in 87.1% of participants admitted for heatstroke.[20] In another study by Deshwal *et al.*, no changes in hematocrit levels were observed during heatstroke.[6] In our study, the significant difference in hematocrit between pre heatstroke group and the combined mild and severe group was found (t-value is –6.97367; p-value is <0.00001. The result is significant at p < 0.05). This suggests that raised hematocrit could be a predictor of poor prognosis

and outcomes in heatstroke. Elevated CRP levels (152±40 mg/L) were reported by Bouchama *et al.* in 72% out of 28 hajj pilgrims who suffered heatstroke.[21] IL6 was also found to be elevated and related directly to the severity of the disease in this study. In another study by Kuo-Cheng Lu *et al.*, among participants with exertional heatstroke, proinflammatory cytokines IL-1beta, tumor necrosis factor-alpha, IL-6; T helper 1 cytokines INF-gamma and IL-2 receptor; and chemokines IL-8, monocyte chemoattractant protein 1, and Regulated upon Activation, normal T cell Expressed and Secreted (RANTES) were found to be elevated.[22] CRP and IL6 levels were also elevated in this study and correlated directly with the disease severity.

The biggest strength of this study is that it is the first- study done in the Bundelkhand region of India, which experiences extremes of temperature during summers and winters. The study incorporated participants suffering due to their working conditions, thus may help to add data for developing basic and advanced treatment lines for them. After searching all databases, we found that this study contributes all relevant

information from the maximum number of participants ever reported from Indian studies. There are certain limitations of this study that need to be considered. First, measuring axillary temperature is not a standard method as done in this study. However, measuring oral or rectal temperature in an agitated and altered patient was not feasible. Second, a few subjects were referred to our institute after getting basic treatment. Thus, the exact clinical presentation and investigation may differ from the actual. Finally, as most of the participants were laborers working in farms and fields, thus, exactly defining the type of stroke as classical or exertional among participants was not possible.

CONCLUSION

Exposure to hot environmental temperatures can cause heatstroke with variable presentations. The outcome of heatstroke could be benign or fatal. Results from this study suggest an early and basic treatment can improve the prognosis and outcome of heatstroke. Raised hematocrit, S creatinine, and BUN suggest poor prognosis and should be managed intensively. Besides other pathological investigations, inflammatory markers like IL6 and CRP could determine prognosis in case of heatstroke. Further detailed investigatory studies are needed in critical heatstroke subjects to substantiate the observations found so far.

Ethical approval

The research/study approved by the Ethical committee at S N Medical College, Agra , number SNMC/ IEC/2021/52, dated 05th April 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

Six-minute walk test among silicosis patients: Its correlation with abnormal radiographic findings on chest radiograph and high resolution computed tomography scan

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ABSTRACT

Objectives: Silicosis is one of the oldest chronic lung diseases that leads to relentless fibrotic changes in the lungs with a resultant fall in lung functions. This study was conducted to assess exercise capacity utilizing a six-minute walk test (6-MWT) among patients detected to have "simple" and "complicated" forms of silicosis. A further correlation between 6-MWT parameters and abnormal chest imaging findings was also done.

Material and Methods: Silicosis diagnosis among study subjects was based on the history of exposure to occupational silica dust along with suggestive radiological findings of pneumoconiosis assessed by the trained experts. Study subjects performed the 6-MWT as per standard protocol. Chest radiological and "high resolution computed tomographic" (HRCT) abnormalities were also analyzed in each subject and compared with their 6-MWT components (distance walked in meters and oxygen desaturation occurrence, if any).

Results: One hundred twelve study subjects (males 106 and females 6; mean age 44.05 ± 10.84 years) constituted the final study population. The six-minute walk distance (6-MWD), fall in SpO_2 and BORG dyspnea scale in patients with grade "0" on chest X-ray was 362.79 ± 34.2 meter, $1.28 \pm 0.91\%$ and 0.96 ± 0.59, respectively and these parameters gradually converted with increasing International Labour Organization silicosis grading with 94.21 ± 29.4 meter, $7.11 \pm 1.61\%$ and 4.50 ± 0.93, respectively in grade "C." A gradual change in 6-MWT parameters was also evident when compared with HRCT scan grading abnormalities.

Conclusion: Results of this study shows abnormally reduced lung function parameters among subjects with silicosis and it also correlates with degree of the profusion of nodules seen radiologically both on chest radiograph and HRCT.

Keywords: Silicosis, 6-minute walk test, Chest radiology, HRCT scan

INTRODUCTION

Silicosis is an age-old pneumoconiosis that occurs following inhalation, retention, and subsequent pulmonary reaction to crystalline form of silica.[1] The "Chronic silicosis" is the most common type of silicosis that occurs following low silica dust exposure for more than 10 years. The "acute silicosis" develops following high silica concentrations exposure, usually over a period of weeks or months; on the other hand, the "accelerated silicosis" mostly develops about 5 to 10 years of high dust exposure to silica.[2] As per the recent International Labour Organization (ILO), guidelines, the standard method of silicosis diagnosis is X-ray chest studies and occupational history of exposure to the crystalline form of silica.[3]

Pulmonary function tests are not considered the standard diagnosis modality for this disease, however, these are commonly utilized for longitudinal studies among workers having silicosis.[4,5] The lung volumes measured on spirometry and "diffusing capacity for carbon monoxide" (DLCO) values are reduced among silicosis patients according to the extent of underlying pulmonary fibrosis.[6] Six-minute walk test (6-MWT) is a commonly utilized tool to assess exercise capacity that essentially measures the distance walked by an individual over 6 minutes.[7] This is cost-effective, easy to be performed by subjects, and indicates the functional assessment of patients therefore accepted as a useful and reproducible test specially for the "chronic respiratory disorders."[8,9] This test helps to determine supplemental oxygen requirements among

chronic pulmonary illnesses such as "chronic obstructive airway disease," "idiopathic pulmonary fibrosis," etc. It also serves as an important prognostic tool to predict morbidity and mortality in such conditions. This is now an important assessment parameter for lung transplantation too.[10,11]

This study was an attempt to analyze the 6-MWT performance among subjects with silicosis and further to explore the correlation if any, between its parameters with radiologic and computed tomographic examination abnormalities.

MATERIAL AND METHODS

Study population

The study subjects were patients with radiologically proven silicosis attending the occupational health clinic of our institution over the last three years. Those having occupational exposure to silica dust in various forms were included in this study. Those with other comorbidity contraindicating 6-MWT and those with associated active pulmonary tuberculosis were ruled out by appropriate investigations and excluded from the study. All patients were evaluated by in-depth clinical history with a specific focus on occupational exposure to silica dust in detail. This study was conducted following due approval by the institutional ethical committee.

Six-minute walk test (6-MWT) and chest imaging

The diagnosis of silicosis constituted a true occupation history of silica dust exposure along with suggestive chest radiographic findings. The trained pulmonologist and experienced radiologist separately examined the chest radiographs of the study participant. The radiological assessment essentially included a standard chest roentgenogram and a high-resolution computed tomographic (HRCT) scan of the thorax. The pulmonary function tests performed by these patients were spirometry and 6-MWT.

In 6-MWT, the distance walked by a patient in meters on a flat surface over a period of 6 minutes time was recorded. This test is commonly used these days to assess medical intervention response in cardiac as well as pulmonary diseases. The most important measurement in the 6-MWT is the number of meters that the patient walks, however, modification in oxygen saturation provides additional information regarding disease progression and treatment response more precisely.[7]

The test was conducted on a long, evenly flat, and straight hard surface corridor in an indoor setup. The walking course length was 30 meters and the corridor was marked at every 3 meters length distance. The pre- as well as post-walk "Borg dyspnea and fatigue levels" were recorded. SpO_2 and pulse rate were measured by a digital oximeter. The distance walked by the subjects was measured and recorded separately for each

individual. Patients with baseline SpO_2 below 88%, those with an inability to perform the test, and requiring supplemental oxygen during the test were excluded from the final analysis.

Using standard radiographs, differing types ("shape and size") and severity ("profusion") of abnormalities were identified and recorded in individual patient record sheets. The study subjects were classified into four categories (0, 1, 2, 3) on the basis of small opacities and three categories (A, B, C) of large opacities as per standard criteria.[12] All eligible patients were subjected to an HRCT scan thorax to assess the nature, extent and details of radiographic abnormalities. The standard criteria were used to describe radiographic lesions and recorded separately for each patient.

Statistical analysis

SPSS software, version 20 (Chicago IL, USA) was utilized to analyze the study data. The quantitative data were presented by mean and standard deviation while qualitative data were presented in the percentage. Kruskal Wallis "H" test, followed by post hoc if required, was utilized to test the difference of the mean between more than two groups. A p-value of <0.05 was considered to be statistically significant.

RESULTS

One hundred twelve patients were found eligible as per the protocol and constituted the final study population. They were mainly between the third and fifth decades, with males constituting the most (male 94.6%, female 5.4%). More than one-third of subjects (37.5%; n = 42) were non-smokers, whereas 32.1% (n = 36) were ex-smokers, and 30.4% (n = 34) were current smokers. Most of these patients were engaged with stone cutting work (35.71%) followed by stone grinding (16.1%), well digging (15.17%), stone drilling (14.28%), stone slabs breaking (8.9%), stone fine cutting with chisel & hammer (0.89%), supervisory work at stone powder factory (0.89%) and stone powder packaging (0.89%).

The mean values among 6-MWT indicators, such as 6-Minute Walk Distance (6-MWD), fall in SpO_2 and Borg Rating of Perceived Exertion (BORG) rating changes, were 243.89 ± 108.94 (range 60–410) meter; 3.67 ± 2.64% (range 0%–10%) and 2.28 ± 1.57 (range 0.5–5.5) respectively [Table 1].

Chest X-ray grading was according to ILO categories in which distribution of study participants for small opacities was as follows: 28 (25%) in category "0"; 22 (19.69%) in category "1"; 22 (19.64%) category "2," and 28 (25%) in category "3." Large opacities were seen only in 28 patients; of them, type "A" opacity was seen in 10 (8.9%) patients, while type "B" and type "C" opacities were seen in 6 (5.3%) and 12 (10.7%) patients, respectively. As per the abnormal HRCT findings, the computed tomography (CT) grading pattern among the

Table 1: 6-Minute Walk Test (6-MWT) findings in patients with silicosis

Variable	Range	Mean value	SD
Distance covered (meter)	60–410	243.89	108.94
BORG rating before test (0–10)	0.0–2.0	0.32	0.48
BORG rating after test (0–10)	0.5–7.0	2.72	2.03
Change in BORG rating	0.5–5.5	2.28	1.57
SpO_2 before test (%)	89–99.0	95.37	9.42
SpO_2 after test (%)	81–96	91.49	8.34
Degree of O_2 desaturation (%)	0.0–10.0	3.67	2.64
BORG: Borg rating of perceived exertion, SD: Standard deviation.			

Table 2: Chest X-ray finding in study subjects

Chest X-ray finding	Grade	No.	%
Small opacities	0	28	28%
	1	22	22%
	2	22	22%
	3	28	28%
	Total	100	100%
Large opacities	A	10	35.71
	B	6.	21.42
	C	12	42.85
	Total	28	100%
Pleural thickening		21	18.75%

Table 3: HRCT finding in study subjects

HRCT finding	Grade	No.	%
HRCT grading	0	12	10.71%
	1	16	14.28%
	2	28	25%
	3	24	21.42%
	4	32	28.57%
	Total	112	100%
Emphysematous changes	1	14	43.75%
	2	7	21.87%
	3	6	18.75%
	4	5	15.62%
	Total	32	100%
HRCT: High resolution computed tomographic.			

study subjects was as follows: 12 (10.71%) in category "0"; 16 (14.28%) in category "I"; 28 (25%) in category "II"; 24 (21.42%) in category "III," and 32 (28.57%) in category "IV." The emphysema findings were also notable in 32 (28.57%) individuals with different gradings on HRCT [Tables 2 and 3].

The 6-MWD, fall in SpO_2 and BORG dyspnea scale while performing 6-MWT in patients having grade "0" on chest X-ray was 362.79 ± 34.2 meters, 1.28 ± 0.91% and 0.96 ± 0.59 respectively and these values changed a lot with increasing ILO silicosis grading to an extent of 94.21 ± 29.4 meter, 7.11 ± 1.61% and 4.50 ± 0.93 in those individuals having ILO grading "C" with a clear difference in 6-MWD by 268 m, fall in SpO_2 by 5.83% and BORG dyspnea scale by 3.54; statistically these changes were highly significant (p < 0.01) [Table 4].

The 6-MWD, fall in SpO_2, and BORG dyspnea scale while performing 6-MWT in patients having grade "0" on HRCT

Table 4: 6-Minute Walk Test (6-MWT) parameters in relation to the radiographic profusion in patients with silicosis

Parameters	Chest X-ray ILO grading					p value
	0	1	2	3	C	
Distance covered (meter)	362.79 ± 34.21	297.0 ± 90.84	216.64 ± 69.13	165.86 ± 69.47	94.21 ± 29.45	<0.01
O_2 desaturation (%)	1.28 ± 0.91	2.01 ± 1.61	4.18 ± 2.31	5.50 ± 2.02	7.11 ± 1.61	<0.01
Change in BORG rating (0–10)	0.96 ± 0.59	1.31 ± 1.10	2.86 ± 1.53	3.01 ± 1.27	4.50 ± 0.93	<0.01
BORG: Borg rating of perceived exertion, ILO: International labour organization.						

Table 5: 6-MWT parameters in relation to the tomographic categories

6-MWT parameters	HRCT grading					p value
	0	I	II	III	IV	
Distance covered (meter)	370.33 ± 32.94	367.63 ± 38.0	293.8 ± 60.39	182.0 ± 66.55	131.20 ± 65.51	<0.01
O_2 desaturation (%)	1.01 ± 1.09	1.37 ± 0.74	2.07 ± 1.32	4.45 ± 2.29	6.60 ± 1.56	<0.01
Change in BORG rating (0-10)	0.75 ± 0.61	1.06 ± 0.62	1.46 ± 1.08	2.63 ± 1.16	3.97 ± 1.27	<0.01
BORG: Borg rating of perceived exertion, HRCT: High resolution computed tomographic.						

Table 6: Spearson's correlation coefficients for the correlations between 6-minute walk test and results of the scores obtained with high-resolution computed tomography and chest X-ray.

		HRCT grading	Chest X-ray grading
Change in BORG rating	r value	.783	.745
	p value	.000	.000
O^2 desaturation	r value	.843	.793
	p value	.000	.000
Distance	r value	−.841	−.840
	p value	.000	.000

BORG: Borg rating of perceived exertion, HRCT: High resolution computed tomographic.

chest was 370.33 ± 32.91 m, 1 ± 1.09% and 0.75 ± 0.61, respectively and this also drastically fall with increasing HRCT silicosis grading to 131.00 ± 65.51 m, 6.60 ± 1.56% and 3.97 ± 1.27 in those with grade IV of HRCT abnormality with a change in 6-MWD to 239.33 m, fall in SpO_2 to 5.60% and BORG dyspnea scale to 3.22. Changes in these parameters were statistically significant ($p < 0.01$). Parameters of 6-MWT significantly changed from patients having "progressive massive fibrosis" (PMF) to those with "simple silicosis" as per the ILO from grade 0 to III and IV (p value < 0.01) [Table 5].

This study also analyzed correlations between 6-MWT and different scores observed with abnormal findings on high-resolution computed tomography and chest skiagram. Distance covered during 6-MWT by patient was found to be inversely proportionate to the chest X-ray grading (r = −0.82) ($p < 0.000$) as well as HRCT chest grading (r = −0.87) ($p < 0.001$) while O_2 desaturation and change in BORG rating were directly proportionate to chest X-ray (r = 0.78; $p < 0.000$ and r = 0.71; $p < 0.000$, respectively) as well as HRCT chest grading abnormality according to the profusion (r = 0.93; $p < 0.000$ and r = 0.7; $p < 0.000$) [Table 6].

DISCUSSION

The "simple silicosis" (category 0, 1, 2) was not observed to produce significant impairment in pulmonary functions in this study; however, this was evident among those having advanced simple silicosis (category 3). At the end of 6-MWT, Izabela Cozza *et al.*[13] noticed a significant rise in "BORG rating perceived exertion scale" (Borg scale) as well as a drop in SpO_2 by 5% (n = 18, 28%; $p < 0.01$), however, 6-MWT was not correlated with larger opacities in radiological images. In a series of 83 coal workers' pneumoconiosis, a good correlation of the 6-MWT to lung function was found by Noh,[14] but its significant correlation with abnormal radiological grading in silicosis was lacking (p-value = 0.706). These observations are

different from our study and may be explained by the variable selection criteria of study subjects. Deepak *et al.*[15] observed a gradual decrease in distance walked with increased dyspnea rating and fall in SpO_2 when compared to abnormal radiographic grading on ILO classification. A mean difference of 188 meters in 6-MWD was seen among patients with grade "C" i.e., "pulmonary massive fibrosis." Blanco Pérez *et al.*[16] also observed abnormal 6-MWT in patients having complicated silicosis with grade "B" or "C" abnormality, and this was also associated with an increase in desaturation and a decrease in distance of walking during the test. Karhate Andaloussi *et al.*[17] also observed abnormal 6-MWT among 147 patients with silicosis with a statistically significant correlation between dyspnea, quality of life, anxiety level, and distance walked. The overall observations in most studies are similar to those with the present study and reflects compromised lung functions and poor functional reserve in patients having extensive radiological lesions.

There is scantly literature addressing the relationship between the profusion of parenchymal opacities detected on "HRCT" and 6-MWT. While correlating the HRCT abnormalities of silicosis patients with 6-MWT, we observed significant changes in 6-MWT parameters among patients having "pulmonary massive fibrosis" (PMF) to "simple silicosis" with HRCT grade 0, I, II, and III. Further, increased profusion on HRCT was significantly associated with increased dyspnea rating with a fall in SpO_2 that reflects the increased degree of parenchymal destruction to be associated with increased grading on HRCT.

There is a paucity of data in radiology on a description of the computed tomography abnormalities in silicosis patients.[18] Computed tomography is definitely superior to standard chest radiographs as far as early detection of pulmonary nodules and interstitial changes in silicosis patients is concerned. Thin CT slices in the "trans-axial plane" decrease the superimposition of parenchymal structures and permits more clearer visualization of the distribution and severity of parenchymal abnormalities.[19]

The main strength of this study lies in conducting 6-MWT among fairly good number of silicosis patients and correlating 6-MWT parameters with various grades of HRCT abnormality first time in literature. However, there were a few limitations also that include a lack of inclusion of patients with baseline $SpO_2 < 88\%$ with supplement oxygen to perform 6-MWT, which could have further increased the sample size. We also could not compare 6-MWT parameters among smokers versus nonsmokers.

This is to be noted that restriction in 6-MWT may also occur due to other co-founding factors like muscular strength, nutritional status of a patient, and ability to comprehend

instructions etc. and this part was also not addressed in this study. But despite such limitations, this study suggests that compromised lung function in the form of decreased exercise capacity, decreased oxygen saturation, and increased BORG rating, dyspnea score, etc. correlates well with the extent of radiological abnormalities.

CONCLUSION

6-MWT is a simple and non- invasive investigation, this can be used as a complementary test to evaluate disease severity and monitor disease progression in patients having silicosis at frequent intervals during follow-up visits. It could also be utilized as a prognostic factor to predict functional status, quality of life and need for hospitalization and rehabilitation among such patients.

Ethical approval

The research/study is approved by the Institutional Ethics Committee at Jawahar Lal Nehru Medical College, Ajmer, number S.No. 268/education III/MCA/2018/ columm no. 70, dated 06th February 2018.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

Spectrum of bacterial isolates and their antibiogram in intensive care unit (ICU) of tertiary care hospital as a part of hospital acquired infection (HAI) surveillance

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ABSTRACT

Objectives: The introduction of the study discusses the prevalence of Urinary Tract Infections (UTIs) as a common hospital-acquired infection worldwide. The specific goals of the study were to isolate and identify the organisms causing UTIs, and determine their antimicrobial sensitivity patterns.

Material and Methods: A total of 150 consecutive urine samples were collected over a 24 month period from selected surveillance units Medical-Surgical ICU (MICU) Respiratory ICU (RICU) Pediatric ICU (PICU). Microbiological culture, subsequent bacterial identification and antimicrobial susceptibility test were performed for the positive samples. The prevalence of the causative agents was analyzed according to the patient's gender and age group.

Results: A total of 45 uropathogens were isolated, with *Enterococcus* spp. being the most common at 33.3%. The study found that Nitrofurantoin antibiotic had the highest sensitivity at 77% against *Enterococcus* spp. The study also found that nosocomial infections lengthened hospital and intensive care unit stays, and during the surveillance period eight patients expired, who were infected by *Enterococcus* spp., *Klebsiella pneumoniae*, *Enterobacter* spp. and *Klebsiella* spp.

Conclusion: The conclusion section of the study highlights that the study documented the pathogenic effect of *Enterococcus* spp., which was responsible for the majority of infections. This study may be useful for future studies to assess the genetic profile of the MDR gene of isolated microorganisms and to early assess the methods for detecting pathogenic organisms in clinical samples in order to save lives in critical care units. The study also suggests that Nitrofurantoin antibiotic was found to be the most effective against urinary tract isolates of *Enterococcus* spp.

Keywords: UTIs; CAUTI and Non- CAUTI; Antibiotics; MDR; Nosocomial infection, HAI

INTRODUCTION

A nosocomial-acquired sickness called a hospital-acquired infection (HAI) is typically dormant or developing when the patient is admitted. These infections typically start to appear >2 calendar days after being admitted to the hospital, and Centers for Disease Control and Prevention organizations like the National Healthcare Safety Network continuously monitor the infection rate.[1] Infections acquired in a hospital or nosocomial settings are estimated to affect more than 1.4 million people worldwide and it is estimated that 2 million cases of HAI occur each year, and 80,000 people die from this type of infection.[2] In the United States and Europe, the most prevalent urinary tract infection caused by a catheter affects more than 1 million people each year.[3] One of the most frequent device-associated infections that patients admitted to the ICU

get is catheter-associated urinary tract infection (CAUTI). One of the most often reports revealed that device-associated infections among patients admitted to the ICU with urinary tract infection brought on by a catheter and around 75% of hospitalized patients have a urinary catheter inserted, which creates challenges for CAUTI management and prevention. They continue to rank second in importance among health care associated infections (HCAIs) in the intensive care unit (ICU), where 95 percent of urinary infections are catheter-associated. When CAUTI is not recognized and is handled incorrectly, there is an increased risk of complications, which lowers the effectiveness of healthcare delivery and to avoid complications such as nephritis, acute urethritis, septicemia, and urosepsis, prompt action is required.[4] The signs and symptoms exist as frequent urination, burning, or pain while urinating or lower abdomen pain, among signs of kidney

infection are fever, chills, backache on one side or in the lower back, and nausea.[4] Other elements, such as previous urinary tract infections (UTIs), sexual behavior, and modifications to the vaginal flora or bacteria, might also raise UTI risk. For instance, these bacterial alterations can be brought about by periods or urinary tract structural problems, for example, enlargement of the prostate and children who are potty training may exhibit poor cleanliness.[5] According to reports by Rezai *et al.*[6] this amount is too high and double what it is in other nations. An extended hospital stay and overall hospital costs are increased brought on by this infection and antibiotic-resistant pathogen infections typically have greater fatality rates.[6] Aman *et al.*[7] reported that the risk of contracting device-associated nosocomial infections are highest in an intensive care environment. The frequent use of medical equipment, increasing device days, length of hospital stays, and severity of patient disease are all contributing factors to the high infection prevalence in ICUs. Our study found a startling rise in multi-drug resistance (MDR) among device associated nosocomial infections (DANI) patients, indicating the urgent need to manage this MDR. This study's updated guideline aims to address Urinary tract infection prevention for patients receiving short or long-term urinary catheterization in any setting and catheterization, external catheters, and suprapubic catheters are examined for their efficacy.[7]

Therefore, the specific goals of this present research work were; i) To study the isolate organisms in selected surveillance unit according to the age group of the patients, ii) To determine the antimicrobial sensitivity pattern of the isolate organisms, iii) To determine the relation between the hospital stay and the type of bacteria causing nosocomial infection.

MATERIAL AND METHODS

The CAUTI and Non-CAUTI infection surveillance were conducted in the Medical-Surgical ICU (MICU), Respiratory ICU (RICU), Pediatric ICU (PICU), in the Agartala Government Medical College and Hospital (AGMC and GBP Hospital, Agartala, Tripura, India) from July 2020 to June 2022. The institutional ethical committee granted approval for the surveillance to continue in those ICUs (IEC Ref. No. 3935). In accordance with the CDC's (Center for Disease Control) guidelines, the surveillance was carried out.

Patient selection

Patients who had completed >2 days of with or without urine catheterization following ICU admission, and provided written informed consent were included in the study. Patients who had positive urine cultures before catheterization and had been catheterized for less than two calendar days were not included in the study.[8]

Sample collection

The CDC recommended that the microbiological samples were taken from patients who had UTIs and had at least one of the following signs or symptoms: fever (>38.0°C) in the event of catheter-associated urinary tract infection (CAUTI) at any age. Urinary urgency, frequency, suprapubic tenderness, and dysuria are all symptoms of a urinary tract infection. Additionally, Non-Catheter-associated Urinary Tract Infection (Non-CAUTI) in patients of any age who have a fever (higher than 38°C), Urinary frequency, urgency, or dysuria, suprapubic soreness, cerebral vascular accident (CVA), or tenderness.[9]

Sample collection from CAUTI patients

Get the necessary supplies and wear personal protective equipment when collecting samples from catheterized patients. Make sure the catheter tubing does not contain urine before collecting a sample from a sampling port. Apply the clamp 3 inches below the level of the sampling port and clean the sample port with a prep wipe allowed to dry it properly. Aspirate at least 10 ml of urine and disconnect the syringe put the specimen into a sterile container and, properly label it and released the clamp from the catheter tube.[10]

Sample collection from non-CAUTI patients

Prior to performing Midstream urine, make sure your hands and genitalia must be clean. The vaginal entrance should be held open by women. It is recommended for males to retract their foreskin. After that, discard a few drops of urine and the rest were collected and placed in a sterile container. Samples were collected in a screw cap sterile container. The infection will increase if any contact with the container while touching the patient's genitalia and reattach the container's lid.[11]

Identification of microbes

For the semi quantitative approach, routine urine cultures were plated using calibrated loops and this approach has been benefited of providing information on the CFU/ml count as well as isolated colonies for susceptibility testing and identification.[12] For normal urine culture, a mixture of blood agar (BA) and MacConkey agar, cystine lactose electrolyte deficient (CLED) was applied because it promotes the growth of all potentially harmful urinary pathogens as well as a number of contaminants such diphtherias, lactobacilli, and micrococcus. Additionally, it distinguishes between colonies that ferment lactose and those that do not, and it prevents the growth of Proteus species from swarming. With all of these advantages, CLED agar may be utilized as the only medium, lowering costs without sacrificing quality.[13]

Bacterial identification

Pure culture isolates of the bacterial pathogen were preliminarily characterized by colony morphology and Gram staining technique along with some standard biochemical tests through which bacterial isolates were identified up to the species level.

Antimicrobial susceptibility testing

Antimicrobial susceptibility test was carried out by standardized Kirby Bauer disc diffusion method as per the Clinical Laboratory Standards Institute (CLSI) guidelines on Muller Hinton agar medium. The bacterial suspension of each isolate was prepared in 0.5 ml of nutrient broth medium and the turbidity was adjusted to match that of 0.5 McFarland standards. A sterile swab was dipped into the suspension and then the swab was applied to the center of the Muller Hinton agar plate and evenly spread on the medium. Antibiotic discs were placed onto Muller Hinton agar seeded with each isolate and were incubated for 24 hours at 35–37˚C. Inhibition zone (IZ) diameter was measured using a caliper and interpreted according to the CLSI guideline as susceptible (S), intermediate (I), or resistant (R).

Antibiotics used

In this study different antibiotic disc were used at various concentrations namely, Gentamicin 10 μg, Amikacin 10 μg, Cefotaxime 30 μg, Ceftazidime 30 μg Ceftriaxone 30 μg, tetracyclines 30 μg, trimethoprim- sulfamethoxazole 25 μg, oxacillin 30 μg, penicillin10μg, Ampicillin 10 μg, vancomycin 30 μg, Imipenem 10μg, Meropenem 10 μg and ciprofloxacin 5 μg for the determination of antibiotic property.[4]

Statistical analysis

All the calculations were done with the help of PAST (Alaeontological STatistics) software version 2.17c. The experimental results were analyzed using Two-Way ANOVA (analysis of variance) following Tukey's honestly significant difference (*HSD)* test were conducted to find out the significance among the different parameters of studied patients at *p*<0.05.

RESULTS

The prevention of ICU-acquired infections requires a thorough understanding of infection rates, sources, pathogens, and the risk factors. The incidence of nosocomial infections varies according to the setting, i.e., the type of hospital or ICU, the patient population, the precise definition and surveillance techniques. This study revealed that the main causative

organism for CAUTI and non-CAUTI infections varied by age group and gender.

During the study period from July 2020 to June 2022, 150 patients with hospital-acquired urinary tract infections were identified in the surveillance critical care unit. Of these, 82.2% (n = 37 out of 45) were identified as Catheter-Associated Urinary Tract Infections (CAUTIs) and 17.8% (n = 8 out of 45) as non-CAUTIs. Of the 150 samples tested and 45 tested samples isolated as positive infection. Among the 45 positive isolates, 35 were from the Medical-Surgical ICU (MICU), 5 were from the Pediatric ICU (PICU), and the remaining 5 were from the Respiratory ICU (RICU).

Outcomes of this study revealed that the most affected infection caused by CAUTI which was highly observed in the male age group it ranges from 20 years to 40 years, whereas in females it ranges from 41 years to 60 years [Figure 1]. It was also observed that males over 60 years of age becoming mostly affected age group. In the case of the RICU, the age group between 18 years to 40 years and over 60 years of age was mainly affected by CAUTI. On the other hand, infection caused by Non-CAUTI was highest at the age range of 18 years to 40 years in females and males over 60 years were mostly affected. The age ranges and relative rates of CAUTI and Non-CAUTI across patients' sexes indicated a significant influence across age ranges and sexes (F = 3.91, *p*<0.0002 and F = 13.41, *p*<0.006).

Isolation of bacteria

As a result of the processed samples 45 microbial pathogens were identified out of 150 suspected UTI infections. Among the bacteria isolated, *Enterococcus* spp. was found. To determine the significant effect of the isolated organisms on patients, a two-way analysis of variance (ANOVA) was applied. If a significant effect was found in at least one sample at a 5% level of significance (i.e., *p*<0.05), a Tukey HSD test was then conducted to identify the most significant effects of the isolated organisms in relation to the number of patients.

Among the total bacterial isolates, *Enterococcus spp*. accounted for the highest percentage at 33.3%, followed by *Escherichia coli* (29%), *Staphylococcus aureus* (11.1%), *Klebsiella pneumoniae* (8.89%), *Acinetobacter* spp. (2.22%), *Citrobacter freundii* (2.22%), and *Enterococcus faecalis* (2.22%). In case of CAUTI, *Enterococcus spp*. was the most common microbial pathogen, accounting for 32.4% of the total isolates, followed by *Escherichia coli* at 29.7%, *Staphylococcus aureus*, and *Enterobacter spp. Klebsiella pneumoniae* was 8.11%, *Klebsiella spp*. 5.41%, *Acinetobacter spp*, *Citrobacter freundii* and *Enterococcus faecalis* were 2.7% of total isolates. For Non-CAUTI infections, *Enterococcus spp*. was isolated at 37.5%
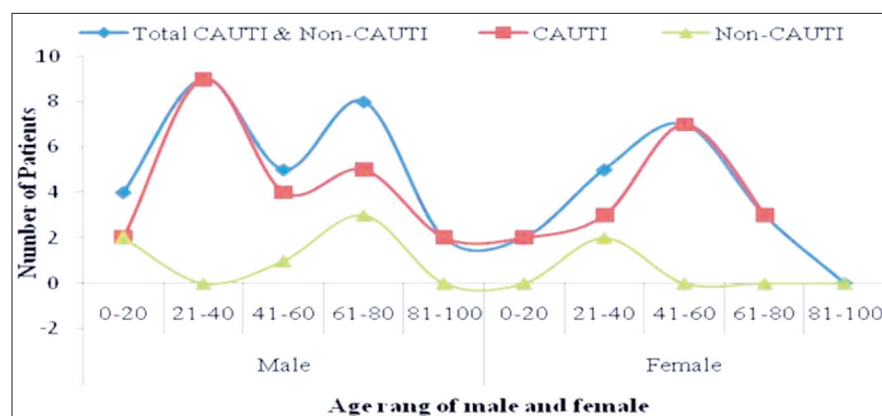
Figure 1: Shown the different age group of people with and without catheter device. CAUTI: Catheter-associated urinary tract infection.
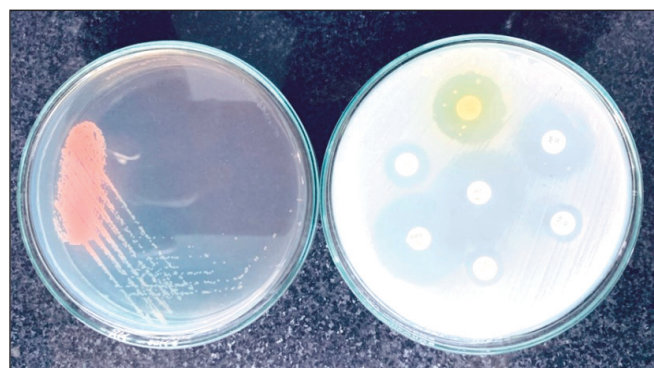
Figure 2: Urine culture and sensitivity test.

from total isolates, followed by *Staphylococcus aureus* and *Escherichia coli* at 25%, and *Klebsiella pneumoniae* at 12.50%.

There were more cases of CAUTI in male patients than in female patients in the intensive care unit. Different age ranges and sexes of patients had significantly different relative frequencies of CAUTI and Non-CAUTI. Males between the ages of 18 to 40 and females between the ages of 41 to 60 were most likely to catch CAUTI infections in MICUs, while Non-CAUTI infections affected males over the age of 60. The age ranges and relative frequencies of CAUTI and Non-CAUTI infections in HAI patients significantly differ among the different age group of patients (F = 39, $p<0.0002$, and F = 13.41, $p<0.006$).

Antimicrobial sensitivity pattern

In order to understand the impact of drug sensitivity patterns on various isolated microorganisms from patients in the surveillance unit, a two-way analysis of variance (ANOVA) was conducted. The majority of the experimental sets displayed a significant effect at a $p<0.05$ level.

The present study also evaluated the drug sensitivity patterns of the isolated microorganisms [Figure 2] and it was recorded

that *Enterococcus* spp. was found to be the most superior pathogen causing infections. Nitrofurantoin was found to be 77% sensitive in *Enterococcus* spp. Isolated from urine samples, followed by Doxycycline at 66.6% and Amoxy/clav at 50% sensitivity. Cefixime and Ceftriaxone were found to have 100% resistance to *Enterococcus spp.*, followed by Ciprofloxacin at 66.67%. Levofloxacin was 75% sensitive and Amikacin was 66.67% sensitive to *Escherichia coli*, while Piperacillin/Tazobactum and Ciprofloxacin (50%) had the lowest sensitivity. *Staphylococcus aureus* was completely susceptible to Nitrofurantoin and completely resistant to Gentamycin. Amikacin, Meropenem, and Ceftazidime had showed sensitivity rates of 75%, 58.33%, and 66.67%, respectively, against *Klebsiella pneumoniae*. *Enterobacter* spp. was found to be highly susceptible (100%) to Nitrofurantoin and Cefoxitin, followed by Doxycycline at 66.6%. For *Acinetobacter spp*. Isolated from urine samples showed the highest sensitivity of 100% against Colistin and Minocycline, while Imipenem showed 70% resistant. Piperacillin/Tazobactum and Imipenem were 100% susceptible to *Citrobacter freundii* and nitrofurantoin, followed by Amoxy/clav and Levofloxacin, which was 100% resistant. Ciprofloxacin and High Sensitive Gentamycin were 100% resistant to *Enterococcus faecalis*, which was identified from urine samples.

Present findings revealed that a total of 8 patients had died from CAUTI infections, out of this 8 patients 7 patients were male and 1 female. The MICU had the most deaths compared to the PICU and RICU. The present research also identified *Enterococcus spp*. was the most commonly isolated organism from the unit MICU and accounted that 50% of cases, whereas by *Klebsiella pneumoniae* at 25% as well as *Enterobacter spp*. and *Klebsiella spp*. also accounted as 13% and 12% of cases, respectively. Despite recent shifts in pathogen patterns towards gram-positive bacteria, our study showed that they continue to play a significant role in nosocomial infections in the ICU. The present investigation revealed that gram-

Figure 3: Different duration in days against various bacterial infections.
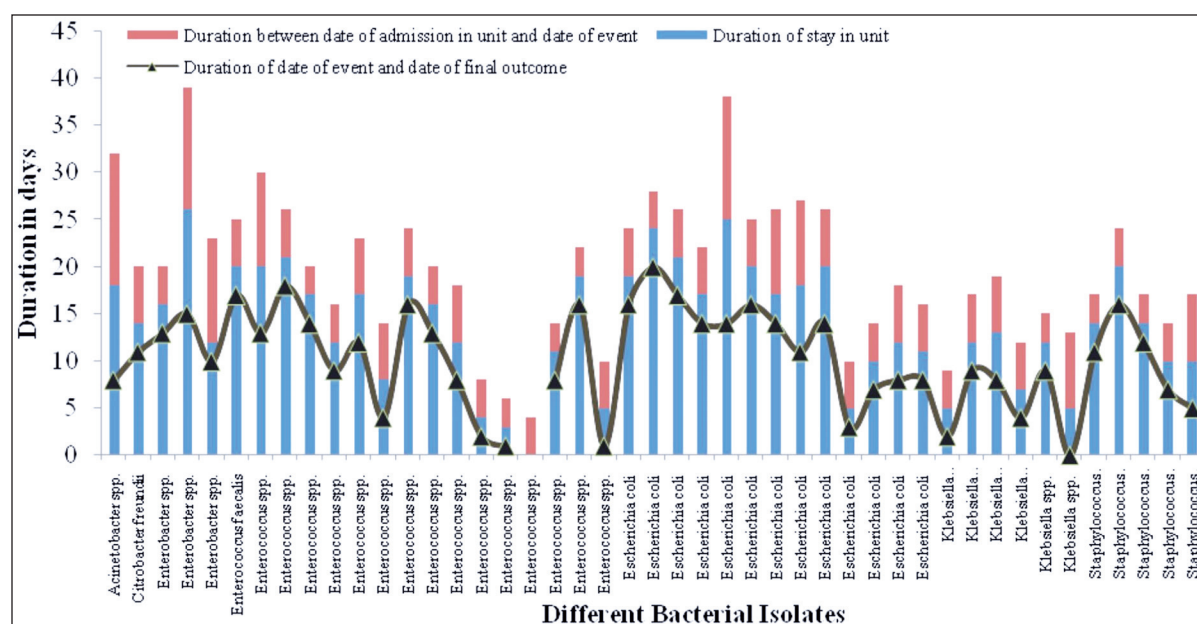
positive bacteria were the most frequently identified species and closely followed by *Enterococcus* spp.

This research work also documented that the duration of stay in the unit is the main factor affected by HAI organisms. In comparison to the date of the event and final outcome of the patients were already affected by the pathogens in the ward or unit before being transferred to the surveillance unit (ICU). According to the definition of nosocomial infection, the patient must be admitted to the hospital and must have completed 48 hours of hospital days. During these days, the maximum number of patients require life-saving devices during treatment. This research revealed that the majority of patients were affected by their individual units after admission. This might be due to a lack of sufficient understanding, as well as correct device care and handling (Interval of 95% Confidence: 7.89–16.07%) [Figure 3].

DISCUSSION

The prevention of HAIs is a crucial cause because as it requires a comprehensive understanding of the underlying causes, including the rate of infections per month, sources of infection, types of pathogens and risk factors that facilitate the growth of pathogenic organisms. The aim of this study is to identify the causative organisms responsible for CAUTI and Non-CAUTI infections in the ICUs of a tertiary care hospital located in the state of Tripura, India. The number of patients identified with hospital-acquired infections, the proportion of CAUTIs and non-CAUTIs, the number of samples tested, and the number of samples provided by different ICUs. Additionally, the sentence also informs us of

an accompanying figure that shows the age distribution of a few surveillance units.

Between July 2020 to June 2022, 150 hospital-acquired illness patients were identified in the selected surveillance units. A total of 45 samples were positive out of 150 samples. During this study period, 82.2% CAUTIs and 17.8% of non-CAUTIs were identified. Present findings showed that the distribution of age of selected surveillance units was highest in MICU. The findings of Saleem *et al.*[14] documented that a total of 1078 patients were admitted to the hospital ICU, out of which healthcare-associated infection was reported in 316 patients and CAUTI was reported only in 70 patients (22.15%), which showed slight dissimilarity with our findings. Our findings were also comparable to the prevalence rate of other research work such as H Bizuayehu *et al.*[4]

Findings of Magliano *et al.*[15] and Kiffer *et al.*[16] were comparable to our present research findings, in terms of the patient population (both males and females of any age), the number of isolates, and selected age groups. Present findings revealed that more male patients had CAUTI as compared to female patients,[14] whereas the most effective age ranges were 21-40 years in males and 41-60 years in females.

Isolation of bacteria

From the isolated samples, multiple *Enterococcus species* were isolated and accounted at 33.3%, followed by *Acinetobacter spp.* and *Escherichia coli* (29%), *Klebsiella pneumonia* (8.89%), and *Staphylococcus aureus* (11.1%), in that order. Additionally, 2.22 percent of *Enterococcus faecalis* and

Citrobacter freundii were recorded but findings of Rezai *et al.*[6] observed that *Escherichia coli* was the main agent for urinary infection (34.9%), followed by *Klebsiella* (15.3%), *Pseudomonas aeruginosa* (9.5%), and miscellaneous (40.3%). Present findings showed similarity with the findings of Magliano *et al.*,[15] where *Escherichia coli* recorded as 67.6% of all isolates, followed by *Klebsiella pneumoniae* (8.8%), *Enterococcus faecalis* (6.3%), *Proteus mirabilis* (5.2%), and *Pseudomonas aeruginosa* (2.5%). The results of the current study shows that the *Enterococcus spp.* microbial pathogen contributed 33.0% of the total isolates in catheter-associated urinary tract infection (CAUTI), followed by *Escherichia coli* (29.0%), *Staphylococcus aureus* (11%), *Enterobacter spp.* (7%), *Klebsiella pneumonia* were 9.0%, *Klebsiella spp.* 5.0%, and the least percentage was observed in *Acinetobacter spp.* In terms of non-CAUTI infections, *Enterococcus spp.* was the most common isolate, accounting for 37.5% of all isolates, followed by *Staphylococcus aureus* and *Escherichia coli* at 25% and *Klebsiella pneumonia* at 12.50%. Similar findings was observed by Saleem *et al.*,[14] where that *Klebsiella pneumoniae* (20%) was the predominant isolate, whereas *Serratia* (3%) and *Providencia* (3%) species were the least common isolates. Present observation revealed that the dominant isolate were *Enterococcus* sp. (50%) and *Klebsiella pneumoniae* (25%). Samples of *E. coli* isolated from patients were highly resistant to third-generation cephalosporin and aminoglycosides.

This research revealed that a total of 8 patients had passed due to CAUTI infection and there were 7 male patients and 1 female patient, additionally, it was also observed that few patients were passed away in the PICU, RICU and highest in the MICU unit. Furthermore, it was shown that *Enterococcus* spp. (50%) from the MICU, followed by *Klebsiella pneumonia* (25%), *Enterobacter* spp. (13%), and *Klebsiella* spp. (12%), were the most common isolates from the expired patient. Despite changes in the pathogen pattern in recent years toward Gram-positive bacterial infections and, they were consistently exist. The majority of research claims that Gram-negative bacteria are to blame for more than half of the nosocomial infections that occur in the ICU. Gram-positive bacteria were the most frequently identified species in the present investigation.

Antimicrobial sensitivity

In this study, the drug sensitivity patterns of isolated microorganisms from UTI patients were documented and found that E*nterococcus* spp showed 100% resistance to cefixime and ceftriaxone and 66% resistance to ciprofloxacin. Levofloxacin 75% and Amikacin. 66.67% were shown to have the highest sensitivity against *Escherichia coli*, while Piperacillin/Tazobactum and Ciprofloxacin (50%) showed the lowest sensitivity. It was also observed that *Staphylococcus aureus* was entirely susceptible to nitrofurantoin but

completely resistant to Gentamycin. As well as Amikacin, Meropenem, and Ceftazidime showed sensitivity rates of 75%, 58.33%, and. 66.67%, respectively, against isolated *Klebsiella pneumonia*. Enterobacter spp. were showed highly susceptible to Doxycycline at 66.67% and highly resistant to Nitrofurantoin and Cefoxitin(100%). Isolated *Acinetobacter* spp. showed 100% sensitivity against Colistin and Minocycline. Piperacillin/Tazobactum and Imipenem was 100% susceptible to *Citrobacter freundii*. Ciprofloxacin and High Sensitive Gentamycin showed 100% resistance to *Enterococcus faecalis*, which was isolated and identified from the urine sample. This type of research was performed by various scientists throughout the world and results were comparatively varied from the findings of each other researchers.[4,14] Aman *et al.*[7] observed that *Acinetobacter baumannii* and *Citrobacter* species were the most common multidrug-resistant gram-negative pathogens responsible for Device associated nosocomial infection (DANI). According to Dasgupta *et al.*,[17] *K. pneumoniae* (62.07%) was the most frequently discovered dominant organism in urinary tract infections, however, current data suggested that Enterococcus spp. (33%), caused the most number of urinary tract infections.

In this study, we discovered that the length of stay (days) in the unit is the most impacted by HAI organisms, in contrast to the date of the incident and the date of ultimate conclusion. Our findings revealed the maximum number of patients affected from their respective units after admission due to a lack of proper care and the maintained the device. Dasgupta *et al.*,[17] documented that 11.98% of patients had nosocomial infections. (Interval of 95% Confidence: 7.89–16.07%) and finding revealed that the nosocomial infection statistically lengthened hospital and intensive care unit stays, but no deaths, and where is our findings showed similarity accept the death of patients at MICU, RICU and PICU.

Based on the results of the present study, we observed that the duration of stay in the unit is the main factor affected by Healthcare-Associated Infections (HAI) organisms. We found that the patients were already affected by the unit before being transferred to the surveillance unit, which highlights the importance of early identification and management of HAIs.

CONCLUSION

A high-risk setting for UTIs is an intensive care unit. The frequent use of medical devices, the duration of hospitalization, and the severity of the patient's disease are only a few of the numerous variables that contribute to the high infection frequency in ICUs. The need to lower MDR in UTI patients is critical. Males were shown to be more likely than females to have a CAUTI infection in MICUs, whereas females aged 41 to 60 years were found to be more susceptible

to non-CAUTI infections. It would be best to avoid inserting unnecessary catheters in order to reduce morbidity and length of hospital stay. If a Foley catheter is required, the aseptic procedure must be applied. The procedure will be needed to improve through ongoing training, and education of the healthcare workers as well as surveillance reduces infection by the infection control committee. This research work will help future researchers to update/modify their institutional bundle care policy to prevent device-associated hospital-acquired infection looking forward to evaluating the genetic pattern for the MDR gene of isolated microorganisms. This research work may be helpful for earlier detection of microorganisms causing nosocomial infection and appropriate management would help in reducing mortality in the ICU's.

Ethical approval

The research/study approved by the Institutional ethical committee (IEC) at Agartala Government Medical College and GBP Hospital, number IEC Ref. No. 3935, dated 15th March 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that they have used artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript or image creations.

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Original Article

Influence of COVID infection or vaccination on pregnancy outcome

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ABSTRACT

Objectives: The study aimed to assess the effect of Covid infection or Vaccination on pregnancy outcomes.

Material and Methods: Infection and vaccination status of 372 women were collected during the pandemic period (March 2020 to March 2022) from medical records and personal interviews of pregnant women visiting two hospitals for antenatal care and through a survey form circulated online. Seventy-eight women were still on follow-up during the study.

The women were categorized into (i) Infected during gestation, (ii) Vaccinated before pregnancy, (iii) Vaccinated during pregnancy, (iv) Vaccinated after delivery (v) unvaccinated. Individuals in (iv) and (v) categories were taken as controls.

Results: Thirty-six women were infected during gestation, 156 were vaccinated before/during pregnancy, and 180 were kept as controls The result showed that 35 individuals from the sample size had adverse pregnancy outcomes such as Spontaneous abortions, MTPs (Carried out after an ultrasound detected abnormality), and Intrauterine deaths, 4 of them were infected and 23 were vaccinated before/ during pregnancy, and 8 were the controls, indicating that 77% of individuals with adverse pregnancy outcomes were exposed to either virus/vaccination. Eighty-nine women had mild complications during pregnancy, such as Oligo/Polyhydramnios, Abnormal USG, and biochemical markers. 56.1% of these individuals were exposed to the virus or vaccination, slightly higher than the control group.

Conclusion: In this preliminary follow-up study, an association was seen between SARS-CoV-2 infection, COVID-19 vaccination, and adverse pregnancy outcomes.

Keywords: Adverse pregnancy outcomes, Covid, Covid vaccination, Miscarriage, Pregnancy

INTRODUCTION

Covid-19 is a disease caused by a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified amid an outbreak of respiratory illness in Wuhan City, China. SARS-CoV-2 is a member of the coronavirus family, Coronaviridae, which includes other viruses that cause the common cold, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS).

Cases of Covid-19 were reported in India from the last week of January 2020. The government imposed a nationwide lockdown in March 2020 to curb the spread of the SARS-CoV-2 virus. The number of cases in each state varied with international traffic, inter and intra-state migration, and population density of the state, and districts. Case fatality and recovery were different based on population composition and the status of health services, including the vaccination drive.[1]

SARS-CoV-2 as a teratogen

Several viruses are known to be teratogenic in humans, such as Zika, cytomegalovirus, Rubella, and herpes simplex. The growing risk of pandemics is making it essential for us to understand the role of viral infections and vaccinations during pregnancy, as these may significantly affect the pregnant mother as well as the fetus. There is substantial epidemiologic evidence that pregnant women are at higher risk of severe illness and mortality from viral infections and that these may predispose them to spontaneous abortions, preterm labor, and congenital anomalies.[2]

The effect of COVID infection on the unborn fetus during pregnancy is still poorly understood. However, there have

been anecdotal reports of women infected with the virus during pregnancy, resulting in fetal distress. A study by Wong *et al* (2004),[3] on the effect of SARS on pregnancy outcomes revealed that the women who were infected with the virus during their gestation either had a first-trimester spontaneous abortion, delivered preterm, or the pregnancies were complicated by IUGR(Intra Uterine Growth Reduction).

Vaccination during pregnancy

Maternal immunization provides benefits to both pregnant mothers and fetuses. Immunization during pregnancy directly protects the fetus by transferring the antibodies from the mother to the fetus. Some vaccines, such as the ones for hepatitis A or B or the influenza virus, are safe to receive before and during pregnancy. Other vaccinations, such as the ones for chickenpox or Rubella, contain weakened but live versions of the virus/bacteria and are best given at least a month before a woman conceives.[4]

The effect of the COVID-19 Vaccine on the developing fetus has not been characterized. The Centers for Disease Control and Prevention (CDC), The American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal - Fetal Medicine (SMFM) say the Food and Drug Administration (FDA) has authorized COVID-19 vaccines for pregnant and/or lactating women since June 2021. The World Health Organization believes that the pros of vaccination during pregnancy outweigh the cons.

The present observational study assessed the effect of the SARS-CoV2 infection and COVID-19 vaccination before and during gestation on pregnancy outcomes during the pandemic.

MATERIAL AND METHODS

All pregnant women who attended the Out Patient (OP) and In Patient (IP) Department of three hospitals (two urban and one rural) from March 2020 to March 2022 were included in this study.

Data from the Radiology Department during the same period was also assessed for identifying abnormal cases through routine antenatal scans—nuchal translucency (NT) and Targeted imaging for fetal aneuploidies (TIFFA) at 11-13th weeks and 18-22 weeks, respectively.

Information was also collected by interviewing pregnant women who were currently visiting the Obstetric and Gynaecology outpatient (OBG OP) department, women in the labor room for delivery, and those who came to collect reports of Newborn Screening.

Information about COVID-19 virus infection and COVID-19 vaccination for antenatal cases during the COVID-19 period was collected from the Medical Records.

A survey form with the questions mentioned in the annexure was circulated on social media, targeting pregnant women during the COVID period and not associated with our hospitals (From March 2020 to March 2022) to increase the number of cases.

Individuals who got vaccinated after delivery and those who remained unvaccinated were kept as the controls for this study.

RESULTS

As they informed, the 372 pregnant women included in the study were categorized according to their Viral infection status based on RT- PCR or Rapid Antigen test and Vaccination status.

They were grouped into the following five categories.

- Women infected with the virus before or during their gestation (n = 36).
- Women who took the Covid vaccine less than 3 months before conception (n = 69).
- Women who took the Covid vaccine during pregnancy (n = 87).
- Women who took the Covid vaccine after delivery (these included individuals who took the Covid vaccine while/after breastfeeding, after a miscarriage/Termination of pregnancy) (n = 99)
- Women who were unvaccinated (n = 81)

36 women out of the 372 included in the study individuals were infected with the virus during their gestation. Ten were asymptomatic, while 26 had cough, cold, high-grade fever, body pain, etc.

Further into the study, the sample size was categorized according to their term of delivery and adverse outcomes such as miscarriages/medically terminated pregnancies and intra uterine death (IUD). The individuals who were unvaccinated and the individuals who took the vaccine after delivery were kept as controls.

At the time of data collection's completion, 78 individuals were still pregnant. Therefore, the analysis was carried out based on the remaining 294 individuals.

The infection or vaccination status does not affect the term of delivery. However, adverse outcomes like Medical Termination of Pregnancy (MTP) (Carried out after an ultrasound detected abnormality) and Spontaneous Abortions (SA) in individuals who were vaccinated before or during pregnancy were higher, while infection during pregnancy did not result in adverse outcomes.

Other complications such as oligohydramnios, polyhydramnios, Increased NT, Abnormal TIFFA, and Abnormal biochemical marker tests were observed in 89/372 (23.7%) individuals.

A higher number of women who took vaccination either before or during pregnancy had increased NT compared to the controls. All other complications were lower than the controls.

DISCUSSION

Viruses have long been studied for their teratogenicity. Viruses like Herpes, CMV, Rubella, etc., have been known to cause preterm births and congenital disabilities such as microcephaly, ocular abnormalities, hearing defects, and neural tube defects, among others.[5] The vaccination in pregnant women was studied separately for these viruses. Some types of vaccines are considered unsafe for pregnant women. Hence, vaccination during gestation and lactation is avoided. COVID-19 vaccine was offered to women from July 2021 without prior testing and was released into the market immediately.

The teratogenicity of SARS- CoV2 virus has been the subject of several papers, and the meta-analysis by Zaigham and Andersson (2020)[6] based on 108 pregnancies exhibited evidence that there may be vertical transmission of SARS-CoV 2 virus. A more recent meta-analysis on a larger sample of 4,38,548 pregnant women showed that COVID-19 may be associated with increased risks of preeclampsia, preterm birth, and other adverse pregnancy outcomes (Wei *et al.*, 2021)[7].

In this study, out of 372 pregnant women of different stages of gestation, 294 were individually followed up during the pandemic until delivery. Seventy-eight still had an ongoing pregnancy at the time of the end of data collection. Among these, 36 (9.7%) women were RT-PCR positive and considered infected with the virus during their gestation. 10/36 (27.7%) were asymptomatic, 26/36 (72.3%) had symptoms like cough, cold, fever, and body pains, and none had severe symptoms requiring hospitalization. However, it was noted that one of the individuals who was infected with the virus in her second trimester developed Bell's palsy during her third trimester.

According to other reports also, the clinical presentations of COVID-19 in pregnant women were not very severe and were similar to that seen in the general population[8,9]

We categorized the pregnant women into four groups [Figure 1] and considered those who were not infected or vaccinated after delivery as controls (n = 180). The results indicate that most deliveries were full-term (89.2%). However, the percentage of women who had a pre-term delivery after getting infected or vaccinated during pregnancy was the same [Table 1], and this percentage was lower than the controls. Adverse outcomes like MTP (Carried out after an ultrasound detected abnormality) and SA were seen in all four categories but were highest in women who were vaccinated before or during pregnancy, and the lowest frequency was in those who were infected during pregnancy [Table 1]. Other complications like oligohydramnios, polyhydramnios, Increased NT, Abnormal TIFFA, and Abnormal biochemical marker tests were observed in 89/372 (23.7%) individuals [Table 2]. However, none of the complications except increased NT had a higher frequency of occurrence when compared to the control. A review of COVID-19 vaccines in pregnancy reported that the vaccine is safe and it effectively protects them against the disease.[9] This paper only focuses on the fetal outcomes and does not include maternal aspects such as gestational diabetes and pre-eclampsia. The adverse fetal outcomes (if any) recorded in the sample size 372 have
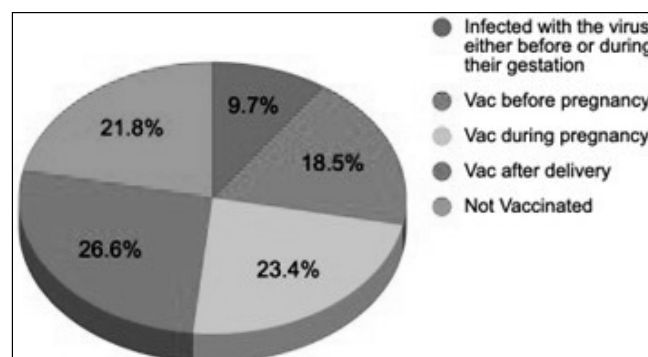
Figure 1: Pie chart representing women included in the study categorized according to their infection and vaccination (Vac) status.

Table 1: The individuals exposed to the virus either via Infection or vaccination are categorized according to their term of delivery and pregnancy outcome.

Type	Number of individuals	Delivered		Adverse pregnancy outcomes		
Total	**294**	**259**		**35 (11.9%)**		
		Full term (231)	Preterm (28)	MTP (18)	SA (13)	IUD (4)
Infected during pregnancy	32	24 (10.4%)	4 (14.3%)	3 (16.7%)	1 (7.7%)	0
VAC before pregnancy	36	22 (9.5%)	0	6 (33.3%)	6 (46.1%)	2 (50%)
VAC during pregnancy	66	53 (23%)	4 (14.3%)	5 (27.8%)	4 (30.8%)	0
VAC after deliver Y+ not vaccinated	160	132 (57.1%)	20 (71.4%)	4 (22.2%)	2 (15.4%)	2 (50%)

MTP: Medical termination of pregnancy, SA: Spontaneous abortions, IUD: Intra uterine death.

Table 2: Tabular representation of the individuals with mild complications categorized according to their infection and vaccination status

Type	Oligohydramnios	Polyhydramnios	Increased NT	Abnormal TIFFA	Abnormal biochemical markers
Total number of individuals	**21**	**2**	**12**	**35**	**19**
Infected during pregnancy	3 (14.3%)	1 (50%)	0	8 (22.8%)	6 (31.5%)
VAC before pregnancy	1 (4.8%)	0	5 (41.7%)	7 (20%)	3 (15.7%)
VAC during pregnancy	4 (19%)	0	4 (33.3%)	6 (17.2%)	2 (10.5%)
VAC after delivery + not vaccinated	13 (61.9%)	1 (50%)	3 (25%)	14 (40%)	8 (42.3%)

TIFFA: Targeted imaging for fetal anomalies, VAC: Vaccinated, NT: Nuchal translucency.

been categorized and analyzed according to their infection and vaccination statuses.

Therefore, this follow-up study of pregnant women during the COVID-19 pandemic exhibited that the symptoms of infection during gestation were not different from those seen in the general population. Pre-term deliveries in controls were higher; this may be because the norms for antenatal management were altered during this period. However, the same percentage of pre-term deliveries were seen in both women infected or vaccinated during pregnancy, suggesting that both interventions have similar effects. MTP (Carried out after an ultrasound detected abnormality) and SA were higher in women getting vaccinated before or during pregnancy compared to those infected during pregnancy. The two IUDs were also seen in women who were vaccinated before pregnancy. This is unlike some studies demonstrating that vaccination did not affect pregnancy outcomes.

CONCLUSION

We believe that caution is required before vaccinating women of reproductive age, especially those planning a pregnancy.

Ethical approval

Institutional Review Board approval is not required as it is a retrospective study.

Declaration of patient consent

Patient consent not required as the patient's identity is not disclosed or compromised.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that no artificial intelligence (AI)-assisted technology was used to assist in the writing or editing of the manuscript, and no images were manipulated using AI.

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Original Article

Serum phosphorus levels as a predictor and severity marker for mechanical ventilation in adults versus elderly patients – A cross-sectional study

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ABSTRACT

Objectives: Mechanical ventilation (MV) is a supportive therapy for patients with acute respiratory failure. Studies have shown direct relationship between serum phosphorus on admission and risk of respiratory failure requiring MV. This study aims to determine admission serum phosphorus level's ability to predict severity in 64 mechanically ventilated patients among two groups: Group A was designated to adults (<60 years of age) and Group B to elderly (60 years or older) admitted to the critical care unit (CCU). Study Design: It is a cross-sectional study.

Material and Methods: Data were collected from 64 adults admitted to CCU. The Sequential Organ Failure Assessment (SOFA) score and serum Phosphorus level on admission were assessed. Patients with Diabetic Ketoacidosis, Head Trauma, Renal Failure, Hyper or Hypoparathyroidism, Leukaemia, and Lymphoma were excluded.

Results: The study had 32 subjects in each group. The commonest indication for mechanical ventilation was Poisoning (31.25%) in Group A and Cerebrovascular Accident (34.37%) in Group B. The common complication among the study group was ventilator- associated pneumonia (14.06%). Out of 64 patients requiring mechanical ventilation, nine patients had hypophosphatemia, and eighteen had hyperphosphatemia. In the case of hypophosphatemia, 100% and in hyperphosphatemia, 55.5% mortality was observed.

Conclusion: Altered serum phosphorus levels on admission can be a potential indicator for requiring MV and mortality. Both hypophosphatemia and hyperphosphatemia are potential risk factors for the development of respiratory failure. Also, age-related variation in phosphorus levels has not shown any association with the outcome.

Keywords: Mechanical ventilation, Mortality, Serum phosphorus, SOFA score, Adults, Elderly

INTRODUCTION

The concept of artificial respiration was introduced by Vesalius in the sixteenth century and by the twentieth century it became a widely accepted modality for the management of acute respiratory failure.[1] Although mechanical ventilation is vital as supportive therapy in acutely ill patients, prolonged use of it can result in life-threatening complications like ventilator-associated pneumonia (VAP), barotrauma, sepsis, acute respiratory distress syndrome (ARDS), pulmonary edema, and embolism.[1,2]

Phosphorus was first discovered by Hennig Brandt in 1669 in Hamburg by condensation of the putrefied urine vapor.[3] It is one of the most important elements found mostly inside cells and is naturally contained in food. It is a crucial part of ribonucleic acid (RNA), deoxyribonucleic acid (DNA), bones, and teeth. Phosphorus, as phospholipids, is an important part of cell membranes and adenosine triphosphate (ATP), which is required for cellular activity in the body.[4] Many elements in the body exist in phosphorylated forms. Also, it is necessary for the storage and translation of genetic information in nucleotides, intracellular signaling via the phosphorylation or dephosphorylation of important enzymes, energy transfer, and acid-base buffering.[5]

Serum phosphate levels in adults typically range from 2.5 to 4.5 mg/dL.[4] Hypophosphatemia is characterized as serum phosphate levels below 2.5 mg/dL, and hyperphosphatemia is defined as levels above 4.5 mg/dL.[6]

The mortality in a critical care setup is directly related to the rate of organ failure and its severity. The Sequential Organ Failure Assessment (SOFA) score is a helpful tool for predicting the prognosis of the patient in the Intensive Care Unit (ICU).[7]

Mohammad Tinawi *et al*.[6] reported that abnormal phosphate levels are linked to a higher 180-day mortality rate. Hence, immediate action should be taken to stabilize the patient's phosphate profile and correct the phosphate values in case of any alterations.

Thongprayoon *et al*.[8] conducted the study on 37,728 hospitalized patients and concluded that there is an association between serum phosphate level on admission and the risk of respiratory failure requiring mechanical ventilation. A similar study was carried out by Miller *et al*.[9] who deduced that hyperphosphatemia can be a predicting factor for poor outcome in mechanically ventilated patients with severe sepsis or septic shock.

The literature proving the association of serum phosphorus with mechanical ventilation comparing the age-related changes in blood phosphorus with the outcome in mechanically ventilated patients is sparse. This study assessed the serum phosphorus level as a severity and prognostic marker in patients on mechanical ventilation among adults and the elderly.

MATERIAL AND METHODS

A cross-sectional study was conducted with the approval from the ethical committee obtained on 11th January 2021 (IEC/No. 9 /2021). The study was conducted for 18 months on all patients aged 18 years and above, irrespective of sex, admitted to the critical care unit of Bijapur Lingayat District Education Deemed to be University, Shri B. M. Patil Medical College, Hospital and Research Center and subsequently requiring mechanical ventilation, were recruited in the study. The consent for enrolling the case was obtained from a close relative of the patient. Patients with Diabetic ketoacidosis (DKA), malnutrition, hyperparathyroidism or hypoparathyroidism, leukemia and lymphomas, acute/chronic renal failure, and conditions requiring elective mechanical ventilation (e.g., neuromuscular syndrome) were excluded from the study.

The patients requiring ventilator support were divided into two groups based on their age. Group A was assigned to the adults (age 18–59 years) whilst the elderly (60 years or older) were assigned to Group B.

The Sequential Organ Failure Assessment (SOFA) scoring, which objectively described organ (dys)function in critically ill patients, was done on admission. Each organ system is assigned a point value from 0 (normal) to 4 (high degree of dysfunction/failure) in SOFA scoring. The relevant investigations, along with serum phosphorus, were assessed on the day of admission and the patient was followed for the need for ventilator support.

All the recruited patients were followed for their outcome and conclusions correlating the admission phosphorus levels with the results were drawn. The data were obtained in a Microsoft Excel sheet, and statistical analysis was done using a statistical package for the social sciences (Version 20). Categorical variables were compared using the Chi-square test. The p-value of <0.05 was considered statistically significant. All statistical tests performed were two-tailed.

RESULTS

A total of 64 critically ill patients who required mechanical ventilation over a period of 18 months were included in the study. The patients were divided into groups based on their ages. Thirty-two patients were in Group A (adults) and the other 32 were in Group B (elderly) [Table 1]. In Group A, most patients (18.74%) belonged to the age group 30–39 years. While in Group B, the majority (28.12%) of patients were in the 60–69 years age group. The study had male predominance. The oldest subject in the study was a 90-year-old male.

Patients in the study had one or more pre-existing comorbidities. In Group A, among patients requiring mechanical ventilation, 9.37% had diabetes mellitus and epilepsy each, 6.25% had rheumatoid arthritis and depression each, 3.12% had hypertension and bronchial asthma each, 6.25% had coexisting diabetes and hypertension while remaining 56.25% had no comorbidities [Table 2].

On the contrary, of patients in Group B, 9.37% patients had hypertension, 6.25% had bronchial asthma, 3.12% had Parkinson's disease, diabetes, and old cerebrovascular accidents each while 25% of patients had multiple coexisting comorbidities like diabetes, hypertension, ischemic heart disease, chronic obstructive pulmonary disease, and the remaining 50% were devoid of any comorbidities [Table 2].

The majority of Group A patients requiring mechanical ventilation in our study were diagnosed as poisoning in

Table 1: Age and sex distribution.

Group	Male	Female
Young (18–59 years) (Group A) (n = 32)	24	08
Elderly (60 years or above) (Group B) (n = 32)	24	08
Total	48 (75%)	16 (25%)

Table 2: Diagnosis, comorbidities, and Complications.

	Group A	Group B
Diagnosis		
Poisoning	10 (31.25%)	3 (9.37%)
Cerebrovascular accident	6 (18.75%)	11 (34.37%)
Seizure disorder	5 (15.62%)	-
Infections	4 (12.50%)	-
Musculoskeletal injuries	2 (6.25%)	-
Alcoholic liver disease	2 (6.25%)	1 (3.12%)
Carcinoma	2 (6.25%)	-
Autoimmune disease	1 (3.12%)	-
Ischemic heart disease	-	8 (25.00%)
Septic shock	-	4 (12.50%)
Carbon dioxide narcosis	-	2 (6.25%)
Megaloblastic anemia	-	1 (3.12%)
Bronchial asthma	-	1 (3.12%)
COPD	-	1 (3.12%)
Comorbidities		
Diabetes mellitus	15.62%	21.87%
Hypertension	9.37%	28.12%
CAD	3.12%	9.37%
Bronchial asthma	3.12%	6.25%
Epilepsy	9.37%	-
Rheumatoid arthritis	6.25%	-
Depression	6.25%	6.25%
COPD	-	3.12%
Parkinson's disease	-	3.12%
None	56.25%	50%
Complications		
Ventilator-associated pneumonia (VAP)	9.37%	18.75%
	-	-
Pleural effusion	6.25%	-
Pulmonary edema	6.25%	-
No complications	78.12%	81.25%

CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease.

31.25% of cases, cerebrovascular accident in 15.62%, seizure disorder in 15.62%, sepsis in 15.62%, musculoskeletal disease in 6.25%, alcoholic liver disease in 6.25%, carcinomas in 6.25%, and autoimmune disease in 3.12%. The most common diagnosis among Group B was cerebrovascular accident in 34.37% followed by ischemic heart disease in 25%, septic shock in 12.50%, poisoning in 9.37%, carbon dioxide narcosis in 6.25%, alcoholic liver disease in 3.12%, megaloblastic anemia in 3.12%, bronchial asthma in 3.12%, and chronic obstructive pulmonary disease in 3.12% [Table 2].

The serum phosphorus levels were categorized as normal (2.5–4.5 mg/dL), hypophosphatemia (<2.5 mg/dL), and hyperphosphatemia (>4.5 mg/dL). Normal serum phosphorus levels were seen in 20 patients in Group A and 17 in Group B. Of nine hypophosphatemic patients, six belonged to Group A and three to Group B. Among 18 patients with increased serum phosphorus levels on admission, six were in

Group A and 12 in Group B. The levels were compared to the two groups and no association (p-value = 0.198) was found between the age groups and admission serum phosphorus. Regarding the duration of ventilation, 22 patients were on a ventilator for 1 day, while one elderly with left capsule ganglionic ischemic stroke stayed on a ventilator for 17 days.

The SOFA score was applied and it showed that 14 patients presented with a SOFA score of 8. Of these 14, eight were young and six were elderly. Out of these eight young, five died and three recovered while among six elderly, one died and the other five recovered. Among the 64 patients in our study, two elderly patients had the highest SOFA score of 13 on admission. There was no significant association between the SOFA score on admission and the outcome of our study.

In Group A, 78.12% and in Group B 81.25% of subjects had no complications following mechanical ventilation while 9.37% in Group A subjects and 18.75% in Group B developed ventilator-associated pneumonia (VAP). Patients in Group A have developed additional complications like pulmonary edema (6.25%) and pleural effusion (6.25%) secondary to mechanical ventilator. Whereas in Group B, no other complications were seen [Table 2].

Blood phosphorus levels at admission were also compared with the outcomes of the patients. In Group A, 12 patients had abnormal serum phosphorus on presentation, of which 50% had hypophosphatemia, and the other 50% had hyperphosphatemia. Among the patients with low blood phosphorus levels, 100% mortality was noticed, whereas in the patients with hyperphosphatemia, mortality was seen in 50% of them.

In Group B, 15 patients presented with deranged phosphorus levels, of which 20% had hypophosphatemia with 100% mortality, while among 80% hyperphosphatemic patients, mortality was 58.3%. It was noticed in our study that there was a significant relation between serum phosphorus levels on admission and the outcome of the patient (p-value <0.05) [Table 3].

DISCUSSION

Our study assessed the severity and prognostic value of the serum phosphorus level in mechanically ventilated patients on admission among adults (<60 years) and elderly (60 years or older).

Critically ill patients who develop acute respiratory failure are managed by supportive therapy like mechanical ventilation, but prolonged mechanical ventilation is itself associated with deleterious effects. Hence, the key to survival in such cases is early weaning from the ventilator support.[10,11] Removal of the endotracheal tube and withdrawal of ventilator support are both steps in the process of weaning from invasive ventilation.

Table 3: Association of serum phosphorus levels with the outcome of the patient.

Serum phosphorus		Outcome		Total (n = 64)	Chi-square value	p-Value
		Recovered	Died			
<2.5	Count	0	9	9	16.617	<0.05
	%	0.00%	100%	14.06%		
2.5–4.5	Count	27	10	37		
	%	72.97%	27.02%	57.81%		
>4.5	Count	8	10	18		
	%	44.44%	55.55%	28.12%		

It can only be started once the underlying issue or respiratory failure has been addressed.[12] Boles *et al.*[13] have mentioned in their study that one of the crucial causes of respiratory failure is hypophosphatemia and other metabolic derangements. In a similar study, Dooley *et al.*[14] have stated that the inability to wean from a mechanical ventilator may be caused by insufficient 2,3 diphosphoglycerate (2,3-DPG) synthesis, which shifts the hemoglobin dissociation curve to the left and reduces oxygen supply to the tissues. Also, phosphorylated intermediates like ATP are not produced adequately in hypophosphatemic states which hampers diaphragmatic contractility. Gravelyn and colleagues[15] studied 23 patients and concluded that respiratory muscle weakness is common among the patients with hypophosphatemia which can be improved with phosphate repletion. Furthermore, a number of studies[16–22] have demonstrated that, in the absence of any underlying lung pathology, a correlation exists between respiratory muscle weakness and altered serum phosphorus levels. Miller *et al.*[9] have concluded that time-weighted hyperphosphatemia is directly associated with increased mortality.

Hypo- and hyperphosphatemia is difficult to diagnose as it presents with nonspecific symptoms. Therefore, it is crucial to get the baseline serum phosphorus levels for all patients admitted to a critical care unit.

The study has male dominance (75%) which was similar to Miller *et al.*[9] Identical to Alsumrain *et al.*[23] most of the individuals in our study belonged to the age group of 60 to 69 years. Also, the common comorbidities in the study were diabetes mellitus and hypertension which resembled our analysis. Unlike other studies,[4,9,23] the common diagnosis in our subjects was poisoning and cerebrovascular accidents. Compared to Moitra *et al.*,[24] only 12.5% of patients spent a day in the ICU. In contrast, most of the patients (14.06%) in our study have been hospitalized for 8 days while a maximum length of hospital stay of 55 days was recorded. Nine patients in Group A and 13 in Group B were mechanically ventilated for a single day.

Sequential Organ Failure Assessment (SOFA) score was used as the tool to predict the mortality of admitted critically ill patients. It was found that most of the patients had a score of 8 on admission which was in contrast to the low on admission SOFA score (median SOFA score of 3.38+/-0.39 and 2.89+/-0.31) documented by Talakoub *et al.*[4]

The most common complication among the patients on ventilators was ventilator-associated pneumonia (VAP) seen in 14.06%, among these 18.75% were elderly while 9.37% belonged to the young adult group which was similar to Vincent *et al.*[25]

A significant association (p-value <0.05) between serum phosphorus at admission and outcome was established as all the patients who had presented with low blood phosphorus needed mechanical ventilation and subsequently died.

There was no relation found between serum phosphorus levels and age group during the study.

Limitations

The study has a limited number of subjects involved; the hypothesis can further be evaluated by a cohort-type study involving a larger group. Though our study did not recognize the levels of serum phosphorus and the need for ventilator support on admission with statistical significance, we recommend serial measurements of serum phosphorus levels in critically ill patients for accurate prediction of ventilator support needs.

CONCLUSION

Patients admitted in critical care units are at risk of respiratory failure or sudden cardiac death. The assessment of serum phosphorus levels at the time of admission in critical care setup helps us to identify the group of patients who are at risk for respiratory failure and may require artificial ventilation. Both hypophosphatemia and hyperphosphatemia are potential risk factors for the development of respiratory failure.

Ethical approval

This cross-sectional study was conducted with the approval from the ethical committee obtained on 11th January 2021 (IEC/No. 9 /2021).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

Perspectives of Indian medical students regarding the competency based medical education curriculum – A qualitative, manual, theoretical thematic content analysis

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ABSTRACT

Objective: A competency-based undergraduate curriculum for the Indian Medical Graduates has been introduced since August 2019. The objective of this study was to capture the perspectives of students regarding the competency-based medical education curriculum.

Material and Methods: We present the qualitative findings from a multicentric cross-sectional study conducted among first-year MBBS students of selected medical colleges in India (2019–2020 batch) enrolled using a multistage random sampling method between February and March 2020. Qualitative data were analyzed using manual, theoretical thematic content analysis following the steps endorsed in Braun and Clarke's six-phase framework.

Results: Of the 336 medical students, 175 (52.1%) were from the government and 154 (45.8%) were from private medical colleges. The initiatives that were perceived to be most useful by students were sports, including extracurricular activities; attitude, ethics and communication (AETCOM) modules; yoga sessions;field visits; and skills modules (especially basic life support training). The duration of the foundation course, documentation of early clinical exposure, self-directed learning in the form of logbooks, records and related assignments for each subject, and pattern of assessment methods were initiatives that required modifications from student's perspective. Also, the suggestions provided by students to improve the curriculum has been summarized in this article that included changes in pattern of question papers, introducing skill certification, capturing subject based – student centered reflections, making available a mental health counselor, introducing literary clubs, and inter medical college visits.

Conclusion: The introduction of competency based medical education for undergraduate curriculum is a step in the right direction. But the need of the hour is to continuously adapt – based on the experiences of teachers, administrators, other stakeholders and students in particular.

Keywords: Competency based medical education, Medical education, India, Students, Qualitative

INTRODUCTION

Medical education is under constant evolution.[1] In 1910, Abraham Flexner proposed a model of medical education where scientific knowledge of biological understanding was given importance at the expense of its social and humanistic characteristics.[2,3] Hugh Rodman and E. Gurney Clark, in the mid-1950s introduced the concept of a natural history of disease and urged the physicians to differentiate and understand the individual illness from community health problems.[4,5] The concept of medical education further evolved when H.L. Blum and Marc Lalonde introduced a model where

health processes depended on four groups of factors, namely genetics, behavior, health services and the environment.[6] The later modifications in the medical curriculum were aligned with the principles of the Alma Ata declaration (1978) and the Ottawa charter (1986).[4,7,8]

In India, the history of medical education can be traced back to the era of Charaka and Sushrutha, who had their own doctrines in treating and teaching indigenous systems of medicine. However, it was during the British rule when Indians received formal training in medical science in the backdrop of colonialism and hegemony. Though the country

succeeded in establishing government and private medical colleges across the country to meet the societal need of doctors, who were exceptional in the management of diseases but failed in providing healthcare that is comprehensive – preventive, promotive, curative, rehabilitative and palliative.[9,10] The National Medical Commission (NMC) commenced the new competency-based medical education (CBME) in August 2019 with the objective of covering all three domains of learning – cognitive, affective and psychomotor.[9,11] The set of core competencies expected from an Indian Medical Graduate (IMG) are being a clinician, lifelong learner, communicator, leader and professional.[12-14] This provides an effective outcome-based, student-centered strategy for medical education. A module on attitude, ethics and communication (AETCOM) has been introduced as a forerunner in the transition to CBME for undergraduates.[15] CBME also includes foundation courses, early clinical exposure and integration, self-directed learning, electives, a family adoption program, revamped examination, and assessment patterns.[16-20] However, the perspectives of students (in terms of usefulness, shortcomings, and suggestions) regarding the newly introduced competency-based medical education curriculum is yet to be documented. Against this background, the objective of this study was to capture perspectives of students regarding the competency-based medical education curriculum.

MATERIAL AND METHODS

We present the qualitative findings from a multicentric cross-sectional study conducted among first-year MBBS students in India (2019–2020 batch), between February and March 2020. Detailed study methodology has been published earlier.[21] In short, the study adopted a multistage random sampling method – of the total 542 medical colleges in India, 420 were listed (standalone postgraduate institutes and those colleges awaiting recognition were excluded). In the next step, 74 medical colleges were selected by simple random sampling (lottery method). In the final step, we implemented universal sampling and enrolled all first year students of these 74 medical colleges – provided that they consented to participate in the study. A total of 987 students participated in the study. The earlier publication focuses on perspectives of teachers at medial colleges and these data were different from what is being presented in the present manuscript.[21]

The study incorporated a predesigned, semi-structured, pre-tested questionnaire that included both open- and closed-ended questions to elicit learners' perceptions on various facets of a competency-based undergraduate curriculum. The data collection was done using the Google Forms online survey platform. Out of total 987 participants, 336 (34.0%) responded to the open-ended questions –

sessions or initiatives in the curriculum that were perceived to be most useful or that require modification or withdrawal, and suggestions to improve the curriculum from the student's perspective were captured.

We analyzed this qualitative data using manual, theoretical thematic content analysis following the steps endorsed in Braun and Clarke's six-phase framework.[22,23] We read and re-read the transcripts to ensure familiarity with the data corpus and any other data being used for the purpose. Also, we made notes and jotted down early impressions. We then organized our data in a systematic, meaningful way by generating codes. Because each open-ended question was thematically enquired about, the data were thematically sorted to start with. However, we ensured whether the data supports these themes, we are trying to fit too much into a theme, there are any overlaps, any sub themes within predetermined themes, or other novel themes within the data. The results were presented according to themes (n = 3). Under each theme, codes and supportive manually chosen verbatims were provided.

The study was approved by the Institute Human Ethics Committee, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu, India (IHEC/04/2020). The Participant Information Sheet (PIS) in English language was provided to the study participants digitally, and they were enrolled in the study only after obtaining informed digital consent.

RESULTS

The results included perspectives of 336 medical students on the newly introduced CBME curriculum. Of the 336 medical students, 175 (52.1%) were from government medical colleges, and 154 (45.8%) were from private medical colleges [related data was missing for 7 participants (2.1%)].

Theme 1 – Initiatives that were perceived to be most useful by students: The initiatives found useful by medical students are presented in Table 1 in order of their preference. Sports, including extracurricular activities were mandated (sports, four hours per week; extracurricular activities, two hours per week) as a part of the Foundation course. Students felt that these sessions relived them of stress, which in turn increased their concentration and efficiency while reading, helped them in building relationships, and instilled confidence. Attitude, Ethics, and Communication (AETCOM) sessions were able to sensitize students of their responsibilities – being an observer and a performer for the same or similar scenario helped students in scenario analysis and introspection [Table 1].

The students perceive that early clinical exposure is aiding them in clinically correlating the concepts taught in basic sciences. Specific mentions were provided for sessions that stressed the importance of documentation in the existing

Table 1: Initiatives that were perceived to be most useful by students.

Codes	Participant responses (verbatims)
Sports	Verbatim 1.1: *"Physical Education gave us some leisure time to relax; actually, it increased our efficiency while reading"* Verbatim 1.2: *"Sports helped me connect with my batchmates better"* Verbatim 1.3: *"Sports and games should be a part of curriculum throughout the entire period of MBBS education"*
Ice breaking session	Verbatim 1.4: *"Ice breaking sessions because it made us to express ourselves"* Verbatim 1.5: *"My batchmates became familiar to me through various interactive sessions and especially the ice breaker session helped me open up"*
AETCOM	Verbatim 1.6: *"I have interacted with doctors before for personal illness; but to observe a doctor patient interaction knowing that I am going to be a doctor made me understand the responsibilities I have"* Verbatim 1.7: *"Though the sessions are simulated, I am able to understand my shortcomings in communication skills. I gain confidence in my communication skills with each session"* Verbatim 1.8: *"The session on how to break bad news was useful"*
Yoga	Verbatim 1.9: *"The talk on yoga and its demonstration was useful. But it would be very helpful if an expert can guide us on a daily basis (at least for 15 minutes)"*
Visits	Verbatim 1.10: *"I usually come across various health centers in my locality. But never understood its importance. After visiting the nearby PHC with community medicine faculty I realized the importance of health centers in providing healthcare service"*
All	Verbatim 1.11: *"The session on disability competencies made me realize the huge population with disabilities and their special needs"* Verbatim 1.12: *"Foundation course helped me to adapt to this college easily"*
Experiences	Verbatim 1.13: *"I found inviting eminent doctors who are excelling their role for a talk with us very inspiring"* Verbatim 1.14: *"The visit of the eminent Doctors, they themselves sharing their views and their experiences, what it takes to be a Doctor, what it takes to become 'The Fittest Doctor', how to manage the critical complaints posted against the treating Doctors by the patient attenders was very useful"*
BLS	Verbatim 1.15: *"Learning CPR technique and BLS gave me confidence. It felt doctorish"*
MBBS: Bachelor of medicine, bachelor of surgery, AETCOM: Attitude ethics and communication, BLS: Basic life support, PHC: Primary health center, CPR: Cardiopulmonary resuscitation	

scenario of doctor-patient relationship and/or violence; patients' perspective of disease, their aversion or anxiousness against hospital and doctors; doctors having a patient perspective, need for empathy; disability competencies; gender sensitization; and lived experiences of eminent doctors. Students also perceived that the visits within the medical college and hospital campus helped them understand the coordinated functioning of a hospital ecosystem.

Initiatives and/or aspects in CBME curriculum that requires modification – students perspective: The idea of a foundation course is exemplary. However, students perceived that the duration is one month, adding stress and creating aversion towards the subject and curriculum. Students perceived that the effectiveness of self-directed learning largely depends on their colleagues who may or may not prepare for any particular session. Provided that the documentation of self-directed learning is similar to assignments, students prefer only assignments to self-directed learning [Table 2].

Regarding the pattern of assessment in the new curriculum, students perceive that exams of 100 marks would be difficult to complete in three hours – suggesting a reduction in total

marks of assessment (to 50 marks) or substantially increasing the multiple-choice questions in the assessment (MCQs for 50 and theoretical questions for 50). They also noted that this would benefit them in the long run in their preparation for NEXT exams.

The multitude of writing work has clearly added to the burden of medical students. They perceive that the write-ups being maintained for self-directed learning, early clinical exposure, logbooks, and record books for each subject do not add much to the objectives of a new curriculum. These are in addition to the regular assignments being provided after completion of each topic in each subject. However, few suggested that if these activities cannot be completely ignored, the mode of activity and submission can at least be made online – adding importance to other related objectives in the curriculum like enhancement of computer skills.

Suggestions to improve the curriculum from students' perspective: We have enumerated the suggestions provided by the students to improvise the curriculum as follows:

Table 2: Initiatives and/or aspects in CBME curriculum that requires modification – students perspective.

Codes	Participant responses (verbatims)
Sessions	**Foundation course** Verbatim 2.1: *"Being first batch who attended foundation course we want to say that after foundation course there is sudden burden of academics. It depresses many students in my batch who can perform extremely well but they can't do this thing due to sudden burden and phobia created by faculty"* Verbatim 2.2: *"Duration of foundation course can be reduced. Towards the end of the month, we found repetitive sessions boring"* **Self-directed learning** Verbatim 2.3: *"SDLs are similar to assignments so either one of the above needs to be removed. Assignments on specific topics with additional reference can be done. But such preparation in an SDL session is useless if others in the group do not prepare a prior"* **Others** Verbatim 2.4: *"The integrated sessions and ECE are really good. Helps us in better understanding. It makes us go to library and look for reference books. But the frequency of such sessions should be increased"* Verbatim 2.5: *"Visits show us the real-world scenario. Need more visits"*
Assessment pattern	**Regarding logbooks, records, and assignments** Verbatim 2.6: *"The maintenance of reflective writing for ECE and SDLs, logbooks, records for each subject is too much time consuming and it's actually a burden. I feel like I am just writing the whole day and night and not actually reading"* Verbatim 2.7: *"Assignments can be submitted through an online portal instead of being handwritten. This saves a lot of time as the current generation is more Tek savvy"* Verbatim 2.8: *"Record submission needn't be a criteria for assessment as only a few people are artistically inclined in medical colleges"* **Need for additional MCQs** Verbatim 2.9: *"I feel that multiple choice questions must be provided so that wide range of syllabus can be covered"* Verbatim 2.10: *"MCQs if provided right from the beginning will be very useful and help us preparing for NEXT in future"* **Regarding total marks and duration of examination** Verbatim 2.11: *"Writing a paper for 100 marks in 3 hours will not give us time to think logically. We will not be able to correlate for answers. Quality will be compromised"* Verbatim 2.12: *"Please help us with writing 100 marks paper. It's really not easy for me to write such lengthy paper in a stipulated time"*

SDL: Self-directed learning, ECE: Early clinical exposure, MCQs: Multiple choice questions, NEXT: National exit test

- Introducing two-mark questions in the question papers asking for concepts to be explained in words or pictures or flow diagrams should be explored.
- The possibility of having each theory class for a maximum of 45 minutes and utilizing the next 15 minutes in the assessment of the then-conducted session should be explored
- To complement the introduction of integrated teaching and early clinical exposure, the question papers for summative and internal assessments should be made integrated and not as separate subject papers.
- The concept of skill certification (for example, 'basic suture techniques trained' certificate, 'intravenous catheterization trained' certificate, 'electrocardiogram interpretation trained' certificate) should be implemented
- In addition to session-based reflections, subject based–student centered reflections should be encouraged
- The internal marks should not just be cumulative of all internal assessments but should also include assessment of activities like seminars, case presentations, participation and involvement in creative works, projects, early clinical exposure focus group discussions, field trips and sports.
- The curriculum is being perceived as stressful, and students opined that a counselor should be available in the academic wing of each medical college. This is in addition to the mentor assigned to each student.
- Students appreciated the introduction of local and English language programs. However, they stressed the need to sustain these initiatives beyond foundation courses by starting formal literary clubs in medical colleges.
- During the course of the curriculum, students must be made aware of (and preferably to handle) the routine machines used in a hospital setting (can be a pulse oximeter ranging up to automated external defibrillator or ventilator).
- The possibility of mandating a research project (or thesis) during the tenure of MBBS, along with training in basic research methods, should be explored. This may inculcate the habit of scientific thinking and reasoning of concepts and facts they read.

- Along with early clinical exposure students must be provided with clinical scenario banks.
- In routine practice, small groups or batches are divided in accordance with roll numbers. However, students expressed concerns that such grouping limits their interaction with various other individuals in the batch, resulting in monotonicity (interaction is limited to the same set of students) – groups based on random numbers can be preferred
- The possibility of having inter-college visits for medical students – to understand the learning environment and sharing experiences should be explored
- Sessions on stress management, time management, talks from eminent speakers, activities like sports and yoga should be sustained across all phases

DISCUSSION

The study documents the perspectives of the 2019–2020 batch of medical students in selected medical colleges of India regarding the competency-based medical education curriculum – initiatives that were perceived to be most useful, that require modification and their suggestions to improve the curriculum.

Students perceived that the introduction of mandatory sports and extra-curricular activity sessions in the foundation course was the most useful.[17] However, they recommended that these sessions should be sustained across all phases of medical education. Literary evidence also supports such a notion – sports help an individual much more than in the physical aspects alone; it builds character, teaches, and develops strategic thinking, analytical thinking, leadership skills, goal setting and risk-taking.[24-26] A recent publication highlighted that the majority of Phase I MBBS students (83.6%) were academically stressed, and around 90.0% opined that additional time within the curriculum should be allotted for sports and extra-curricular activities.[21] The AETCOM modules were well received by the students. The basic principle of these modules is that a change in a person's attitude may change his or her own behavior.[15] This attitude may in turn be directed by cognitive and affective attitudes. It is important to note that ethical dimensions play a crucial role in the behavioral evolution of an individual, and the basic building block of effective communication is the feeling that every human being is unique and of value.[27] The visits to Anganwadi centers, subcenters, and primary and community health centers had the ability to orient students to the existing public healthcare service delivery system in the country. Interaction with healthcare providers, patients and their families were also a part of these visits. An earlier publication also highlighted that the majority of the students had a

positive feedback on field visits at the start of their medical education.

The objective of a foundation course at the start of MBBS course is to sensitize the incoming medical students with the required knowledge and skills – assisting him or her to acclimatize to the new professional environment. However, the minimum required components of a foundation course (orientation, skills module, field visits and professional development including ethics) and levels of flexibility provided for local adaption has made sure that students are intimidated by the medical education.[28] It is the need of the hour to enlist items that students should be made aware of, trained in at the start of medical education from those that they will be made aware of or trained in during the subsequent phases of medical education. The difference in conducting self-directed learning sessions and routine assignments, and their evaluation should be explicitly spelled in the CBME curriculum. Also, students perceive that documenting early clinical exposure, SDLs in the form of logbooks, records and related assignments for each subject is a burden in terms of effort and time, without adding much to the learning component. The new curriculum should work out the initiatives from a value for time perspective as well. Students have also stressed upon the pattern of examination proposed in the CBME curriculum. In short, they perceive that the total marks of each examination should be reduced, and number of MCQs should be increased. It should also be documented that CBME faces several challenges. It includes (but not limited to) lack of norms regarding the number and composition (in terms of qualification and eligibility) of faculty in each medical institution; higher student to teacher ratio in medical colleges; inadequate training of medical faculty in implementing the CBME curriculum; lack of adequate infrastructure to teach students in multiple small groups and parallel assessments; and importantly, lack of time for an effective, complete implementation.[9]

The study is not without limitations. First, to ensure a sample that is externally valid, we used Google Forms to reach students across the country (various districts and States) – in-depth interviews or focused group discussions would have been better. Second, only 336 of the total 987 participants documented their perceptions regarding the competency-based medical education curriculum (34.0%). However, being a qualitative study data saturation was observed within the available responses. Third, the nature of study implementation (web-based survey) would have resulted in volunteer bias and/or reporting bias. Also, these may have limited the generalizability of the study findings. Fourth, the study captures the perspectives of Phase I MBBS students only – their perspectives may be limited only to the initiatives in Phase I – but the CBME curriculum covers the entire duration of medical education, including internship.

Finally, the present study did not collect information regarding the provisions of the medical colleges towards CBME.

CONCLUSION

The introduction of competency based medical education for undergraduate curriculum is a step in the right direction. But the need of the hour is to continuously adapt – based on experiences of teachers, administrators, other stakeholders and students in particular.

Ethical approval

The research/study was approved by the Institute Human Ethics Committee at KMCH Institute of Health Sciences and Research, number (IHEC/04/2020), Coimbatore, Tamil Nadu, India.

Declaration patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

Vitamin A, E, and C levels in maternal blood of patients with idiopathic preterm premature rupture of membranes, spontaneous preterm birth, and term birth

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ABSTRACT

Objectives: To compare vitamin A, E, and C levels in cases with idiopathic preterm premature rupture of membranes (pPROM), idiopathic spontaneous preterm birth with intact membrane (sPTB), and term birth (TB).

Material and Methods: There were three groups in this study: pPROM, sPTB, and TB. The sample size was 60 patients in each group (n = 60, Total = 180). Serum vitamin A and E levels and leucocyte vitamin C levels were measured using commercially available research kits.

Results: The mean (SD) vitamin A levels were 49.56 (18.66) µg/dL in the pPROM group, 48.67 (10.28) µg/dL in the sPTB group, and 52.69 (24.39) µg/dL in the TB group. The mean (SD) vitamin E levels were 19.17 (9.23) µg/dL in the pPROM group, 16.94 (10.17) µg/dL in the sPTB group, and 17.47 (11.19) µg/dL in the TB group. The mean (SD) vitamin C levels were 47.89 (9.53) µM in the pPROM group, 45.78 (7.92) µM in the sPTB group, and 42.35 (6.14) µM in the TB group. Vitamin C levels were significantly higher in mothers who developed pPROM (p<0.05) when compared with TB and tended toward significance in mothers who developed sPTB compared with TB.

Conclusion: Vitamin A and E levels were comparable in all three groups. Higher leucocyte vitamin C levels, observed in patients with pPROM (vsTB) and sPTB (vsTB), were not able to protect against pPROM and sPTB. Thus, supplementation of these vitamins during pregnancy is questionable and needs further exploration.

Keywords: Vitamin A, Vitamin E, Vitamin C, pPROM, Fetal membranes

INTRODUCTION

Poor nutritional status is linked to poor pregnancy outcomes. Micronutrients like vitamins and minerals are required for the normal development of not only the fetus but also of the extra fetal tissue, which helps support the conceptus throughout pregnancy. Micronutrient deficiency can affect both the growth of the fetus (leading to Intrauterine Growth Restriction (IUGR)) and the integrity of fetal membranes.[1] Preterm premature rupture of membranes (pPROM) is such a condition arising due to premature weakening of fetal membranes prior to completion of gestation. It is defined as a rupture of membranes from the age of viability to 36 weeks plus 6 days of gestation and prior to the start of delivery.[2] One of the most common complications associated with pPROM is preterm birth. Preterm birth is defined as any birth that occurs before the completion of 37 weeks gestation.[3] Established risk factors of pPROM include prior preterm labor, cigarette smoking, polyhydramnios, urinary and sexually transmitted infections, prior PROM, work during pregnancy, low body mass index, bleeding, low socio-economic status, etc. However, in many cases, risk factors still remain unknown.[4]

Vitamin A and E are fat-soluble vitamins mainly obtained from dietary sources. Vitamin A is mainly responsible for vision, but its isoforms also play a role in keratinization and regulation of gene expression. Vitamin E is an important

lipid-phase antioxidant, a deficiency of which could lead to oxidative stress–induced damage to fetal membranes leading to pPROM.[5]

Vitamin C is a water-soluble vitamin with various physiological roles, most notably increasing the tensile strength of collagen. The health-promoting effects of vitamin C can be attributed to its biological functions as a co-factor for a number of enzymes (hydroxylases involved in collagen synthesis) and as a water-soluble antioxidant. It is involved in the synthesis and degradation of collagen and is important for maintaining the integrity of chorioamniotic membranes.[6] Vitamin C is also recognized as a cofactor for collagen post-transcriptional modification[7] and a down regulator of the gene transcription of type IV collagenase, matrix metalloproteinase 2 in the amnion cells.[8] A study has suggested that altered patterns of collagen synthesis and diminished leucocyte concentration of vitamin C in gestation have been associated with the subsequent occurrence of pPROM.[9] This indicates that vitamin C probably plays a role in the maintenance of fetal membranes. Therefore, the prediction and prevention of pPROM would offer the best opportunity to prevent its complications. Keeping this in mind, this study was designed to estimate the levels of vitamin A, E, and C in patients of pPROM, sPTB, and healthy term birth (TB).

MATERIAL AND METHODS

This study was conducted in the Department of Biochemistry and Department of Obstetrics and Gynecology of a tertiary care center from March 2017 to September 2019 in accordance with guidelines laid down in the Declaration of Helsinki. Ethical clearance was obtained from the Institutional Ethics Committee – Human Research (IEC-HR). Written informed consent was obtained from all the patients.

Sample size calculation

The sample size was first determined by using the values of vitamin C. From our extensive literature search, we did not find any study on vitamins A and E in the groups we were considering. The mean ± SD in term delivery for vitamin C was 0.58±0.05mg/dl. Considering 1 SD as significant difference, a minimum sample size of 22 subjects with 80% power and 2% level of significance was required. Since we have three groups, type I error was considered as per Bonferroni correction (0.05/3+0.017). Keeping in mind the frequency of patients and fixed time period, a sample size of 60 subjects per group was selected.

Participant selection and sampling

This study consisted of three groups. Group 1 included patients with idiopathic pPROM. pPROM was defined as

the rupture of membranes prior to $37^{0/7}$ weeks' gestation and was confirmed by tests including amniotic fluid pooling, ultrasound for amniotic volume, and positive Amnisure® dipstick test. Group 2 included idiopathic spontaneous preterm birth with intact membrane (sPTB) and Group 3 included TB. Idiopathic sPTBs were defined as the presence of regular uterine contractions at ≤ $37^{0/7}$ weeks' gestation (2 contractions/10 minutes with documented cervical change) followed by delivery. Normal TBs were age-matched women with normal labor and delivery at term (≥$37^{0/7}$ weeks) without medical or obstetrical complications and no prior history of pPROM or sPTB or previous cesarean section.

In all the three groups, gestational age was determined by the last menstrual period and corroborated by the first-trimester ultrasound. Exclusion criteria were women with preeclampsia, multiple gestations, placental previa, poly- or oligohydramnios, gestational diabetes, and a history of surgical intervention (surgeries like cerclage, laparotomy, and diagnostic interventions like amniocentesis, chorionic villus sampling, etc.) in the present pregnancy. Patients with clinical evidence of chorioamnionitis and those with uterine abnormalities, systemic morbidities, fetal growth restrictions, and fetal anomalies were also excluded. Baseline variables, including age, mean gestational age, socioeconomic status, previous obstetric history, blood pressure, and routine investigations, were recorded. Maternal blood was collected for pPROM (at the time of diagnosis), sPTB (early labor, i.e., cervical dilatation < 3 cm), and normal TBs (early labor, i.e., cervical dilatation < 3 cm).

Estimation of vitamin A, E, & C levels

Vitamin A and E levels were estimated in maternal serum using commercially available research kits (Elabsciences, USA) following manufacturer protocol after appropriate dilution. The detection range of vitamin A ELISA kit was 0.16–10 ng/mL with a sensitivity of 0.09 ng/mL. The detection range of vitamin E ELISA kit was 1.563–100 μg/mL with a sensitivity of 0.938 μg/mL.

Leucocyte levels of vitamin C were estimated using Ascorbate Assay Research Kit (Cayman Chemical Co., USA), following manufacturer protocol with a detection range of 0–150μM.

Statistical analysis

Data were analyzed with Microsoft Excel as well as SPSS version 20. Quantitative variables were analyzed as mean and standard deviation (SD). Detection of difference was done by one-way ANOVA test. $p < 0.05$ indicated a statistically significant difference.

RESULTS

General baseline characteristics of study group:

All participants belonged to the lower or lower middle socioeconomic status according to the Kuppuswamy's scale. There was no history of low birth weight or abortions and all were housewives.

The general baseline variables and biochemical characteristics of the participants are summarized in Table 1. The mean levels of vitamins A, E, and C in the three groups are depicted in Tables 2a–2c. There was no significant difference in the serum levels of vitamins A and E in all three groups. The leucocyte levels of vitamin C are significantly higher in pPROM than TB [$p<0.05$], while leucocyte levels of vitamin C tended toward

Table 1: Patient parameters (Demographic profile, serum total calcium and serum vitamin D levels) in TB, sPTB and pPROM.

	TB Mean (SD) (n=60)	sPTB Mean (SD) (n=60)	pPROM Mean (SD) (n=60)	p value
Age (years)	23.98 (3.05)	23.77 (2.44)	24.42 (3.43)	TB: sPTB=0.924 TB: pPROM=0.730 sPTB: pPROM=0.494
Mean gestational age in weeks	39.00 (1.15)	35.34 (1.63)	32.73 (2.11)	TB: sPTB =0.000* TB: pPROM=0.000* sPTB :pPROM=0.000*
Total calcium (mg/dL)	8.69 (0.54)	8.65 (0.52)	8.79 (0.60)	TB: sPTB =0.912 TB: pPROM=0.640 sPTB: pPROM=0.390
Serum vitamin D (ng/ml)	17.38 (6.65)	18.83 (6.07)	13.75 (7.21)	TB: sPTB =0.462 TB: pPROM=0.009* sPTB: pPROM=0.000*

*Statistically significant ($p<0.05$); Patients' parameters (group wise, n = 60 in each, total = 180) are shown as mean (SD). pPROM: Idiopathic preterm prelabor rupture of membranes, sPTB: idiopathic spontaneous preterm birth with intact membrane, and TB: term birth, SD: Standard deviation.

Table 2a: Vitamin A levels (μg/dL) in pPROM, TB and sPTB.

Vitamin A levels (μg/dL)	No. of subjects (n=180)	Mean (SD)	p value
TB	60	52.69(24.39)	TB-sPTB=0.467 TB-pPROM=0.964 sPTB-pPROM = 0.628
sPTB	60	48.67(10.28)	
pPROM	60	49.56(18.66)	

Statistically significant ($p<0.05$); pPROM: Preterm prelabor rupture of membranes, sPTB: Spontaneous preterm birth with intact membrane, and TB: term birth. SD: Standard deviation.

Table 2b: Vitamin E levels (μg/dL) in pPROM, TB, and sPTB.

Vitamin E levels (μg/dL)	No. of Subjects (n=180)	Mean (SD)	p value
TB	60	17.47(11.19)	TB-sPTB=0.957 TB-pPROM=0.634 sPTB-pPROM = 0.459
sPTB	60	16.94(10.17)	
pPROM	60	19.17(9.23)	

Statistically significant ($p<0.05$); pPROM: Preterm prelabor rupture of membranes, sPTB: Spontaneous preterm birth with intact membrane, and TB: term birth. SD: Standard deviation.

Table 2c: Vitamin C levels (μM) in pPROM, TB, and sPTB.

Vitamin C levels (μM)	No. of subjects (n=180)	Mean (SD)	p value
TB	60	42.35(6.14)	TB-sPTB=0.051 **TB-pPROM=0.001*** sPTB-pPROM = 0.322
sPTB	60	45.78(7.92)	
pPROM	60	47.89(9.53)	

*Statistically significant ($p<0.05$); pPROM: Preterm prelabor rupture of membranes, sPTB: Spontaneous preterm birth with intact membrane, and TB: term birth. SD: Standard deviation, Bold: signifies a highly statistically significant difference.

significance in mothers who developed sPTB compared with TB [p = 0.051].

DISCUSSION

pPROM is a multifactorial disease characterized by defects in collagen synthesis causing loss in tensile strength, resulting in a weak chorioamniotic membrane.[10]

In this study, we did not find any significant difference between vitamin A & E levels between the three groups. A study[11] has reported that vitamin A supplementation has no effect on the development of preterm birth while another study[12] demonstrated no difference in the levels of retinol in amniotic fluid and serum between pPROM and healthy pregnant controls. In our study, it has been further shown that there is no difference in the vitamin A levels between pPROM, sPTB, and TB. Thus, supplementing vitamin A for the prevention of pPROM and, in addition, sPTB may not be beneficial.

In our study, the levels of vitamin E were comparable in all three groups. The findings are similar to the previous studies done[12, 13, 14] Thus, supplementing vitamin E for the prevention of pPROM and sPTB may not be beneficial.

Vitamin C is known to play a key role in the synthesis of collagen and a deficiency could lead to premature weakening of membranes. In our study, we report a higher leucocyte level of vitamin C in cases of pPROM compared to sPTB and TB groups and in sPTB compared to TB. There was no statistically significant difference between sPTB and pPROM.

The exact role of vitamin C in pPROM is still a gray area, with some studies[15-17] reporting lower serum vitamin C levels in cases of pPROM and others[18-20] reporting no difference in serum vitamin C levels in cases when compared to healthy controls. These studies have also not reported the nutritional intake of patients and have measured vitamin C levels in serum, which are considered to be an inaccurate test when compared to leucocyte vitamin C levels as they are easily affected by acute intake of the vitamin via diet.[21] A study[22] has also suggested that measuring vitamin C levels isn't reliable due to high instability. Our finding is contrary to the findings of studies done till date. A possible explanation for our finding is the effect of gestational age. It was observed that the mean gestational age (weeks) for pPROM was significantly lower (p<0.000), i.e., 32.73 (2.11), and that of sPTB was 35.34 (1.63), and for TB it was 39.00 (1.15). Vitamin C levels fall as pregnancy advances; higher levels in the pPROM group could be explained by the early gestational age in these patients.

Reference values of vitamins A, E, and C in adults are 30–80 µg/dL, 0.5–1.8 mg/dl, and 0.4-1.5mg/dL, respectively.[23] Their

values are known to change as pregnancy advances, and no clear deficiency cut-offs exist. We, therefore cannot compare our values with the reference value in addition to the fact that research-based kits were used in this study.

CONCLUSION

Vitamin A and E levels were comparable in all three groups. Higher leucocyte vitamin C levels, observed in patients with pPROM (vsTB) and sPTB (vsTB), were not able to protect against pPROM and sPTB. More detailed studies should be performed before recommendations on supplementation of these vitamins in patients of pPROM.

The following were the limitations of our study: Single sample was obtained and analyzed at the time of delivery, while vitamin C levels in pre-pregnant, pregnant, and post-pregnant states and fetal levels were not measured. It is also worthwhile to measure and compare vitamin C levels in gestational age-matched controls.

Implications and future prospects: Probably vitamin A and E supplementation is not required nor will it be of any benefit in patients of pPROM. Our findings suggest that high vitamin C levels were not able to protect against pPROM or sPTB. Supplementation of vitamins A, E, and C is hence questionable and must be done with caution. Vitamins A & E being fat-soluble are stored in the body and therefore excess could lead to hypervitaminosis and vitamin C is known to be toxic at higher doses. Therefore, supplementation should be scientific.

Ethical approval

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent

Financial support and sponsorship

Conflicts of interest

Dr. Rajarshi Kar and Dr. Amita Suneja are on the Editorial Board of the Journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

Association of KCNJ11 gene (rs5219) polymorphism with HOMA-IR and HOMA B values in type 2 diabetes mellitus in India: A case-control study

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ABSTRACT

Objectives: Type 2 diabetes mellitus (T2DM) is a complex illness that results from either insulin resistance or insufficient insulin, which raises blood sugar levels. Numerous genes interact to influence the secretion of insulin. A gene of great interest is KCNJ11 of subfamily-J, member 11, which functions as an inwardly rectifying ATP-sensitive potassium (KATP) channel in pancreatic beta cells and is involved in glucose-stimulated insulin release.

Material and Methods: The present case-control study attempts to delineate the genetic impact of KCNJ11 (rs5219) gene polymorphism on the risk of T2DM in the Indian population. It involves 55 patients with type 2 diabetes (fasting plasma glucose of >126 mg/dl, 2-h glucose of >200 mg/dl, or HbA1c level of >6.4%) and 55 healthy controls (fasting plasma glucose of <100 mg/dl, 2-h glucose of <140 mg/dl, or HbA1c level of <6.4%). polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) was used to study KCNJ11 polymorphism through a standard protocol. Enzyme Linked Immunosorbent Assay (ELISA) was used to estimate serum Insulin levels. HOMA-IR & HOMA-β values were calculated. Statistical analysis was done using *t*-test, Chi-Square test, and One-way analysis of variance (ANOVA) test.

Results: Serum insulin levels and HOMA-IR values were significantly decreased in cases than in the control group. Logistic regression analysis showed that the frequency of KK genotype in T2DM individuals (21.8%) was higher than the control group (9%) ($p = 0.01$). Frequency of K allele (38%) in patients was higher than the control group (18%) ($p = 0.001$). The K allele risk in diabetic patients was 9.9 times higher as compared to controls ($p = 0.001$, OR 9.9, 95%Cl 0.036–0.36). Homeostatic model assessment β (HOMA-β) values of KK genotype (59.9±27.8315) were lower than that of EK (76.8±33.23) and EE (127.9±44.59) genotypes ($p < 0.001$).

Conclusion: The presence of KCNJ11 (rs 5219) gene polymorphism shows a noteworthy correlation with the likelihood of developing T2DM among the North Indian population. K allele is more likely to be present in individuals with T2DM than the control group. Moreover, HOMA-β values of those with the KK genotype were found to be lower than the individuals having EK and EE genotypes.

Keywords: KCNJ11, Type 2 Diabetes mellitus, rs5219 gene polymorphism, Insulin, HOMA-β, HOMA-IR.

INTRODUCTION

The multifactorial illness known as type 2 diabetes mellitus (T2DM) is characterized by either insufficient insulin secretion or insufficient insulin activity, which hinders the body's ability to maintain glucose homeostasis. Worldwide, the incidence of T2DM is on the rise.[1] With over 250 million cases worldwide, T2DM is more widespread than it was a few decades ago.[2] T2DM etiology has been linked to interactions between many genetic determinants and environmental variables. A deeper knowledge of the genetic architecture of type 2 diabetes has been made possible by the identification of at least 75 distinct genetic loci for the disease over the course of the last ten years thanks to advancements in genetic association studies.[3] Some genes that are particularly good indicators of T2DM susceptibility include those that encode proteins essential for pancreatic beta cell functions, such as those linked to insulin secretion. The route leading to the release of insulin begins with glucose inhibiting ATP-sensitive potassium (KATP) channels. This is followed by the β-cell membrane depolarizing, an increase in calcium ion inflow, and intracellular calcium stimulating the exocytosis of insulin-containing granules. This KATP channel is an

inwardly-rectifying K+ channel composed of two structurally unrelated subunits of an octamer protein complex with four pores. Potassium inwardly-rectifying channel, subfamily J, member11 (KCNJ11) subunits are linked to four high-affinity sulfonylurea receptor (SUR1, ABCC8) subunits.[4] Recent years have seen a great deal of attention in KCNJ11 as a potential gene for Type 2 diabetes. The NCBI (National Centre for Biotechnology Information) database for humans has 180 single nucleotide polymorphisms (SNPs) related to this gene. It spans two kilobases, is located at 11p15.1, contains one exon that encodes 390 amino acids, and controls the amount of insulin secreted by pancreatic beta cells in response to glucose.[5] It has been demonstrated that the reduction in KATP sensitivity caused by the substitution of the amino acid lysine (K) for glutamate (E) in codon 23 of the KCNJ11 gene causes the channel to open for a longer period of time, hence reducing insulin production.[6,7] As a result, several researches found a strong correlation between the E23K variation of KCNJ11 and T2DM susceptibility.[8–10]

Previous research reports have indicated that Asians seem to have a fairly common KCNJ11 polymorphism (rs5219). Small and medium-sized researches were conducted in this community, and conflicting findings about the link between this variation and type 2 diabetes were found.[11–16] The influence of rs5219 on susceptibility to type 2 diabetes is not fully explored due to the published research's limitations in terms of sample size and ethnic diversity, and their small sample size may make it impossible to draw meaningful conclusions. The conclusive determination of the connection between KCNJ11 polymorphism (rs5219) and T2DM in South Asian populations requires the completion of sufficient thorough meta-analyses and genome-wide association studies (GWAS).

The current study was conducted to assess the relationship between KCNJ11(rs5219) gene polymorphism and associations between this genetic variation and diabetes susceptibility in T2DM in India, as the genetic background for this genetic variant has not been investigated much for T2DM in this population.

MATERIAL AND METHODS

Study Population

This case-control study was done in the Department of Biochemistry and the Department of Medicine, V.M.M.C. & Safdarjung Hospital in New Delhi, India, after clearance from the Ethical Committee of Vardhman Mahavir Medical College and Safdarjung Hospital. Informed written consent was obtained from each subject before enrolling them in the study. The sample size was calculated using the formula as shown below.[17]

Calculation

$$\text{Sample size formula: } n = \left[\frac{P_A(1-P_A)}{k} + P_B(1-P_B) \right] \left(\frac{Z_{\alpha/z} + Z_\beta}{P_A - P_B} \right)^2$$

$$K = nA / nB = 1$$

$$\alpha = 0.05\%, CI = 95\%$$

$$\beta = 0.2, \text{Power of study} = 80\%$$

Where n is the sample size.

P_A is proportion of cases and P_B is proportion of controls.

$$n = \left[0.84(1-0.84) + 0.95(1-0.95) \left(\frac{1.96+1.28}{0.84-0.95} \right)^2 \right] = 113$$

Final Sample Size = sample size/[1+(sample size−1/population)]

$$= 226/[1 + (226−1/200)] = 107$$

According to the above formula, the sample size is calculated as 113 by taking the finite population of T2DM to be 200. In view of hospital statistical data and after inclusion and exclusion criteria, the minimum sample size is kept as 55 cases and 55 controls.

The study subjects included 55 patients having T2DM and 55 healthy age- and sex-matched controls. The diagnosis of type 2 diabetes was done on the basis of symptoms of polyuria, polydipsia, and polyphagia. Relevant investigations included fasting plasma glucose more than 126 mg/dl, plasma glucose more than 200 mg/dl after 2-h oral glucose (1.75 g/kg), or HbA1c $\geq 6.5\%$.[18]

Exclusion criteria

Patients with type 1 diabetes mellitus or gestational diabetes, pancreatitis, patients on oral hypoglycaemic and insulin therapy, patients with other endocrine diseases and impaired renal and hepatic function, and those receiving hypercholesterolemia, hypertension, or corticosteroid medications were excluded from the study.

Sample collection

After an overnight fast, study participants had their blood drawn via venepuncture. Each of the three vacutainer types—Ethylenediamine tetraacetic acid (EDTA), plain (without an anticoagulant), and NaF—was used for the collection of 2 mL of blood. Samples of EDTA were kept at −20°C to extract DNA. After allowing the blood in the ordinary vacutainer to coagulate, the serum was extracted and centrifuged for additional examination. Prior to batch analysis for the enzyme assay, these samples were kept at −70°C. As soon as the blood

was drawn, it was utilized to estimate serum glucose in a NaF vacutainer.

Biochemical measurements

Biochemical parameters, fasting blood Glucose, and postprandial glucose levels were processed using Siemens ADVIA Germany, a fully automated chemistry analyzer.

Estimation of Serum Insulin Levels, HOMA-IR, and HOMA-β

Serum insulin levels were estimated using a commercially available enzyme-linked immunosorbent assay (ELISA) kit manufactured by Calbiotech Inc (Catlog no. P1099D), following the instructions from the manufacturer. This utilizes a two-step protocol for enzyme immunoassay in quantitative measurement of serum insulin. The absorbance was read at the wavelength of 450 nm. The optical density that was measured was directly proportional to the insulin concentration. Homeostasis Model Assessment IR (HOMA-IR) index is calculated by the product of basal glucose and insulin levels divided by 22.5,[19] and is considered to be a simple, inexpensive, and reliable surrogate measure of insulin resistance. Homeostasis Model Assessment β (HOMA-β) value was determined as shown below in the formula to analyze fasting insulin level reflecting pancreatic β-cell function.

$$\text{HOMA-}\beta(\%) = \frac{\text{Fasting insulin } (\mu\text{IU/mL}) \times 360}{\text{Fasting blood glucose } (\text{mg/dL}) - 63}$$

Genotyping

DNA Extraction Kit (Krishgen) was used to extract genomic DNA from nucleated blood cells. The extracted DNA was amplified using polymerase chain reaction (PCR) by utilizing the following primers-forward=5'-GACTCTGCAGTGAGGCCCTA-3' reverse=5'ACGTTGCAGTTGCCTTTCTT-3'.[20] The Indian company "Eurofins Scientific" created the primers. The amplification of DNA was done using a PCR reaction mixture with the help of a thermal cycler (Himedia Eco-96). This 25 μL PCR reaction mixture contained 3 μl of genomic DNA, 0.25 μl of each primer, 6.5 μl of nuclease-free water, and 10 μL of Dream Taq green PCR Master-mix manufactured by Thermo fisher-scientifc (Catalog no. K1081), which had 3.2 μM Taq DNA polymerase, 3.2 μM 2X bufer, 32 μM MgCl2, and 3.2 μM of each dNTPs. The following PCR conditions were used: initial denaturation at 95°C for 5 min, followed by 30 cycles of denaturation at 95°C for 30 sec; annealing at 57°C for 30 sec, then extension at 72°C for 30 sec. The final extension step was at 72°C for 5 min and kept for temporary storage at 4°C. The PCR amplification was confirmed by gel electrophoresis (2% agarose gel and Ethidium bromide

staining). The amplified PCR product of 210 bp in 1 μl quantity was incubated with *BanII (Catlog no. R0119S)* (New England, Biolabs, England) restriction enzyme[20] at 37°C for 60 min in 50 μl reaction mixture that contained 10 × NE buffer. The digested PCR products were then resolved on 2% agarose gel electrophoresis for the E23K genotypes. The Homozygous KK Genotype was digested into two fragments of 178 bp and 28 bp. Homozygous EE Genotype was cut into three fragments of 150 bp, 32 bp, and 28 bp in heterozygous subjects. With the EK genotype, the PCR product breaks into four fragments of 178 bp, 150 bp, 32 bp and 28 bp. On 2% agarose gel electrophoresis, 32 bp and 28 bp being very small are not visible on gel as depicted in Figure. 1.

Statistical analysis

The Statistical Package for the Social Sciences for Windows (SPSS), version 25.0 (Chicago, IL, USA), was used to do the final analysis after the data were imported into a Microsoft Excel spreadsheet. The categorical variables were displayed as percentages (%) and numbers. The means ± SD were used to present the quantitative data. P values less than 0.05 were regarded as statistically significant. Using the Chi-Square test, any divergence from the Hardy–Weinberg equilibrium was assessed. A 95% confidence interval (CI) was used to compute the odds ratio (OR) in order to assess the relationship between T2DM genotypes and the KCJN11 gene polymorphism. The Independent *t*-test was utilized to assess quantitative variables. The Chi-Square test was used to assess qualitative characteristics.

RESULTS

This study confirmed the association between *KCNJ11* (rs5219) gene polymorphism in HOMA-IR and HOMA-β values in 110 participants. Of these, 55 patients were diagnosed with T2DM. As per ADA criteria, mean age was 46 ± 10.24 years where 40% were males and 60% were females. The control group comprised 55 age- and gender-matched healthy individuals with mean age of 42 ± 10.7 years, where 47.27% were males and 52.73% were females. The demographic profile along with the clinical and laboratory parameters of the study population is depicted in Table 1. The difference in age and gender between cases and controls was not statistically significant. However, weight and body mass index were significantly higher in cases than controls (p<0.001). Subgroup analysis of biochemical markers between T2DM and control group in this study showed statistically significant difference in HbA1C (p<0.001), fasting blood glucose (p<0.01), and postprandial blood glucose (p<0.001) with values greater than in the control group.

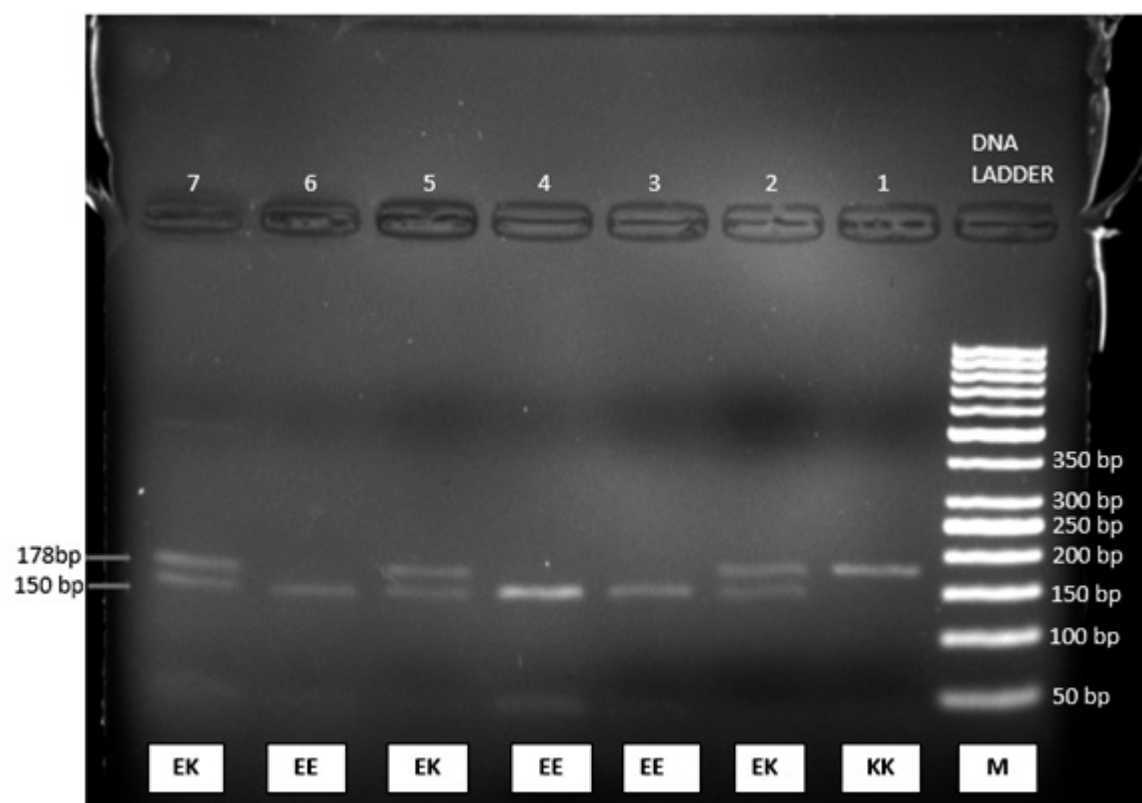Table 2 depicts the serum insulin levels, HOMA-IR, and HOMA-β values in T2DM patients and controls. Serum

Figure 1: KCNJ11 gene polymerase chain reaction (PCR) products were broken down using the BanII restriction enzyme. At 150 bp, homozygous EE has a single band. There are two bands at 178 bp and 150 bp in heterozygous EK. The homozygous KK sample was electrophoresed on a 2% agarose gel, revealing a single band at 170 bp. Lane 1 displays the homozygote KK genotype, lanes 2, 4, and 7 the heterozygote EK genotype, and lanes 3, 4, and 6 the homozygote EE genotype. M is a DNA ladder (50 bp ladder). Due to their extremely small size, the bands corresponding to sizes 32 and 28 bp are invisible in the gel.

Table 1: Biochemical, Clinical and Demographic characteristics of study population.

Characteristics	Cases (n=55)	Controls (n=55)	P-value
Age (years)	46±10.24	42.34±10.7	0.071
Males, %	40	47.27	0.442
Weight (kg)	72.65±10.76	62.15±8.58	<.0001
Height (m)	1.6±0.04	1.8±0.02	0.678
BMI (kg/m^2)	28.98±3.87	24.75±3.45	<0.0001
HbA1C (%)	7.8±0.57	4.3±0.2	<0.0001
FBS (mg/dL)	104.9±13.2	90.3636±9.6	0.01
PP (mg/dL)	189±13.8	127±2.4	<0.0001

Data are expressed as Mean ± SD or percentage.

HbA1C: Glycated hemoglobin, BMI: Body mass index, FBS: Fasting blood sugar, PP: Postprandial blood sugar

Table 2: Serum insulin, HOMA-IR, and HOMA-β in T2DM and control group.

Study Group	Insulin (μIU/mL)	HOMA-IR (%)	HOMA-β (%)
T2DM	9.95±3.12	2.6±0.9	96.3255±47.7
Control	15.1±4.6	3.3855±1.1	224.56±107.5
P value	<0.0028	<0.03	<0.0001

T2DM: Type 2 diabetes mellitus, HOMA-IR homeostasis model assessment IR.

HOMA-β homeostasis model assessment β.

insulin levels were found to be significantly lower in cases than in the control group (9.95±3.12 vs 15.1±4.6 μIU/mL, p<0.0028). Similarly, HOMA-IR and HOMA-β and values showed a significant decrease in cases than controls (2.6±0.9 vs 3.3855±1.1 μIU/mL, p <0.03) and (2.6±0.9 vs 3.3855±1.1 μIU/mL, p <0.03), respectively.

Table 3 displays the distribution of genotypes and alleles for the KCNJ11 rs 5219 (E23K) polymorphism. In the T2DM group, the frequencies of the EE, EK, and KK genotypes were 25%, 18%, and 12%, respectively, compared to 40%, 10%, and 5% in the control group. The homozygous KK genotype of KCNJ11 rs 5912 SNP has a 3.8-fold greater risk of type 2 diabetes in the Indian population, according to logistic regression analysis (odds ratio OR = 3.84, 95% Cl 1.21–12.21, p = 0.01). In the Indian population, the heterozygous EK genotype likewise demonstrated a 2.8-fold elevated risk of

Table 3: Comparison of genotypic frequency between cases and controls.

	Cases	Controls	P-value	OR	(95% CI)
Genotypic frequency					
EE	25 (45.45%)	40 (80%)		**Reference**	
EK	18 (32.73%)	10 (18%)	0.02	2.88	1.15–7.23
KK	12 (21.82%)	5 (9%)	0.01	3.84	1.21–12.21
Total	55	55			
Genotypic frequency					
EE	25 (45.45%)	40 (72%)			7.37
EK & KK	30 (55%)	15 (27%)	0.0066	2.88	(0.06–0.47)
Total	55	55			
Allelic frequency					
E	68 (62%)	90 (82%)	0.001	9.9	0.036–0.36
K	42 (38%)	20 (18%)			

OR: Odds ratio, Cl: Confidence interval.

Table 4: The difference of HOMA-β among individuals in the present study.

Variable	Mean ± SD			P
	KK (n=12)	EK (n=18)	EE(n= 25)	
HOMA-β	59.9±	76.8±	127.9±	<0.0001
(%)	27.8315	33.2314	44.5975	

Values are expressed as Mean ± standard deviation (SD)

type 2 diabetes (odds ratio OR = 2.88, 95% Cl 1.15–07.22, p = 0.02). Individuals with type 2 diabetes showed a noticeably higher prevalence of the K allele than in controls (OR 9.9, 95% Cl 0.036–0.36. p = 0.001).

The inter-genotypic variation of the HOMA-β in T2DM and controls is shown in Table 4. Our results showed that HOMA-β in KK, EK, and EE genotypes of the patients with T2DM was 59.9±27.83, 76.8±33.23, 127.9±44.60%, respectively. The inter-genotypic difference in HOMA-β values was statistically significant in T2DM patients.

DISCUSSION

One of the most common noninfectious diseases in the world, type 2 diabetes has been getting more and more common over the past few decades. Susceptibility to T2DM is influenced by both environmental susceptibility and genetic background. The illness has been linked to several genes.[21] The KCNJ11 protein encodes a crucial role in the production of insulin from pancreatic β-cells, suggesting that it may be a susceptibility gene for type 2 diabetes. However, E23K polymorphism in KCNJ11, plays an important role in suppression of insulin secretion.[22,23] The amino acid substitution, replacing lysine (AAG) with glutamic acid (GAG) resulting due to E23K polymorphism leads to altered physiochemical properties wherein the negative charge replace the positive charge. This

prolongs the opening of KATP channel and decreases its sensitivity to ATP and suppresses insulin production.[24,25]

When stratified by ethnicity, a meta-analysis study by Takeuchi *et al.*[26] revealed a significant connection between the E23K (rs5219) polymorphism and T2D risk among East Asians and Caucasians; no significant associations were detected among South Asians and other ethnic populations. Given the variability in associations and scarcity of literature from the Indian subcontinent, we tried to investigate the correlation of this SNP with HOMA-β and HOMA-IR in the Indian population for T2DM patients and controls.

Our findings support previous research on the Russian, Syrian, and Iranian populations, which indicated that patients had a higher frequency of the KK genotype than controls.[27–29] In the study done by Li YY in 2013,[29] it was found that E23K contributed to T2DM susceptibility.

In addition, our data showed that KK genotype carriers were significantly more likely than controls to develop type 2 diabetes. Furthermore, HOMA-β was used as a model to analyze pancreatic β-cell activity and evaluate the insulin secretion of the study participants. The results showed that there was a statistically significant difference in HOMA-β values between the KK, EK, and EE genotype groups. These findings are consistent with the research conducted by Sunita *et al.*[30] Our study's K allele prevalence of 38% is comparable to that of research conducted in Asian and Caucasian populations.[31–34]

A range of models were used to assess the relationship between the KCNJ11 rs5219 polymorphism and the risk of type 2 diabetes. The results showed that the dominant genetic model (EE vs. KK + EK) was linked to a sevenfold increased risk of developing diabetes compared to controls, with an OR of 7.37 (95% CI 0.06 to 0.47, P = 0.006). Wang *et al.*'s meta-analysis study[34] indicates that the KK genotype is consequently linked to an eightfold increase in the risk of T2DM. In a similar vein, other studies have also been published[30,35–38] showing a link between the KK genotype and an increased risk of diabetes.

The KK genotype's HOMA-β values (59.9±27.83) in our study were found to be lower than those of the EK (76.8±33.23) and EE (127.9±44.60) genotypes. A One-Way ANOVA analysis revealed a significant difference (P<0.0001) in the HOMA-β value between the EE, EK, and KK genotypes. The effects of a single genetic component on the development of T2DM varies throughout individuals due to differences in environmental circumstances. T2DM is recognized as a complex condition caused by the interaction of several hereditary and environmental factors. In India, a large number of people experience varying degrees of stress and generally have poor eating habits. This might account for the high-risk value (nine times) in our study in a sample of the Indian population in comparison to other groups, since these

potent environmental factors may magnify the influence of the genetic component in the risk allele carriers.

CONCLUSION

This study showed an association between rs5219 polymorphism of the KCNJ11 gene with susceptibility to develop T2DM in the Indian population. Also, K allele is more likely to be present in individuals with T2DM than the control group. However, additional studies with a larger sample size will be required to confirm this marker in the Indian population.

The limitation of the present study is that it did not consider the interactions between the gene and its protein. The study was conducted only on a single SNP of the KCNJ11(rs5219) gene. Hence, further studies on other SNPs of KCNJ11 should be carried out to prove the significant association between genetic markers and biochemical markers in T2DM. Moreover, a large cohort study is required to validate the expression of these genes in diverse populations in a country like India.

Ethical approval

The research/study is approved by the Institutional Ethics Committee at Vardhman Mahavir Medical College and Safdarjung Hospital, number IEC/VMMC/SJH/Project/2021-10/CC-192, dated 06th November 2021.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation:

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Case Report

A rare incidence of cerebral venous thrombosis in a case of immune thrombocytopenia on eltrombopag

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ABSTRACT

Immune Thrombocytopenia (ITP) typically presents with mucocutaneous bleeding. Splenectomy, rituximab, and thrombopoietin receptor agonists (TPO-RAs) are the recommended second-line therapy. Eltrombopag is one of the TPO-RAs used for the treatment of steroid-refractory ITP, with a response rate of 70–80%. Though rare, yet various cases of venous thromboembolism have been reported from clinical trials as well as real-world studies. We present a case of ITP that was refractory to corticosteroid and second-line drugs; however, it responded to eltrombopag. While having a complete response on eltrombopag, the patient developed Cerebral Venous Thrombosis.

Keywords: Cerebral venous thrombosis, CVT, Eltrombopag, Immune thrombocytosis, ITP

INTRODUCTION

Immune Thrombocytopenia (ITP) is a diagnosis of exclusion. Clinically, it is characterized by low peripheral blood platelet (<100,000/cmm) and typically presents with mucocutaneous bleeding.[1,2] The first-line therapy consists of corticosteroids with or without immunoglobulins with a response rate of 70–90%.[3] However, the majority of patients have a loss of response and require second-line therapy. Splenectomy, rituximab, and thrombopoietin receptor agonists (TPO-RAs) are the recommended second-line therapy.[4–6] Eltrombopag is one of the TPO-RAs used for the treatment of steroid-refractory ITP, with a response rate of 70–80%.[7] Though rare, yet various cases of venous thromboembolism (VTE) have been reported from clinical trials as well as real-world studies. Cerebral venous sinuses are an uncommon and rare site of thrombosis. There are limited numbers of case reports of cerebral venous thrombosis (CVT) in the literature and all are from the Western world.[8] We present a case of refractory ITP that developed CVT while on eltrombopag therapy.

CASE REPORT

A 27-year-old lady was diagnosed with acute ITP in September 2021. Her Antiphospholipid Antibody (APLA) antibodies were negative. She received dexamethasone 40 mg once daily for four days without any response. Due to wet purpura, she was given immunoglobulin with transient improvement in platelet. In view of no response with a corticosteroid, she was started on romiplostim 3 mcg/kg. The dose was increased to 10 mcg/kg (1 mc/kg increase every week) with no response. Due to persistent disease and poor response, she underwent an extractable nuclear antigen test (ENA), which was negative. She was given rituximab 375 mg/m² weekly × four doses without any response. She was started on eltrombopag 50 mg once daily (empty stomach) and increased to 75 mg OD (in view of no response after four weeks). Eight weeks on eltrombopag 75 mg OD, she had shown response with platelet counts increasing up to 36,000/cmm. She was continued on eltrombopag 75 mg OD.

Two months later, she reported to emergency with acute onset severe headache, which gradually progressed over the last three days. She took some over-the-counter painkiller pills without any relief. She also had multiple episodes of projectile vomiting. On ophthalmoscopy, she had grade two papilloedema, and an urgent Non-contrast Computed Tomography (NCCT) head was suggestive of left parieto temporal SAH with an extension into the ventricle. She was admitted to the intensive care unit and treated with mannitol, levetiracetam, and supportive care. Her blood reports were hemoglobin 9.3 g/dL, MCV 67.5fL

WBC 19500/cmm, and platelet 2.91 L/cmm. In view of a rapid increase in platelets since the last follow-up and no risk factors for subarachnoid hemorrhage, a clinical diagnosis of CVT was contemplated. She was taken up for cerebral angiography. The CT angiography images of the brain showed extensive venous thrombosis [Figure 1]. The findings were confirmed on MR images of the brain [Figure 2]. There was no family history of VTE. She was started on enoxaparin 1 mg/kg SC twice daily,
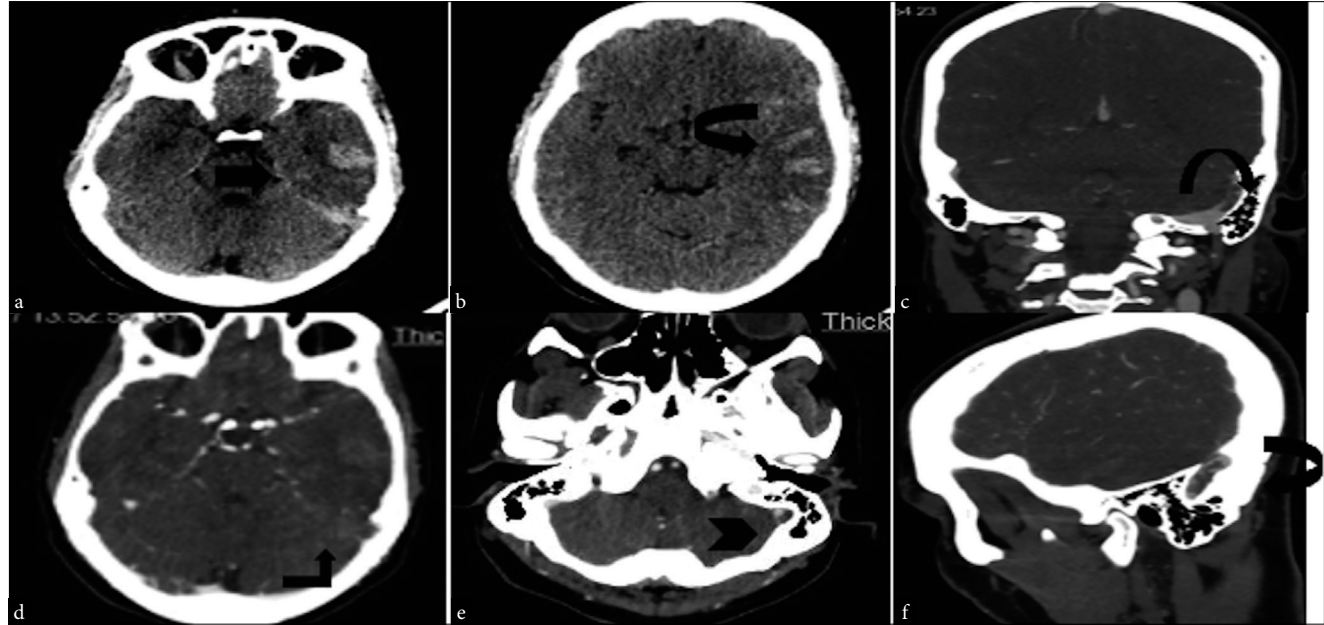

Figure 1: NCCT head (a and b) axial section—hyperdense contents (black arrow) (suggestive of SAH) involving the sylvian fissure and sulcal spaces and parenchyma of the left temporoparietal lobe. (c, d, e, and f)—CT angiography second phase—hypodense partially occlusive patchy and linear areas of filling defects suggestive of thrombus seen in the left sigmoid sinus (black arrowhead in e). NCCT: Non-contrast computed tomography, SAH: Sub-arachnoid hemorrhage
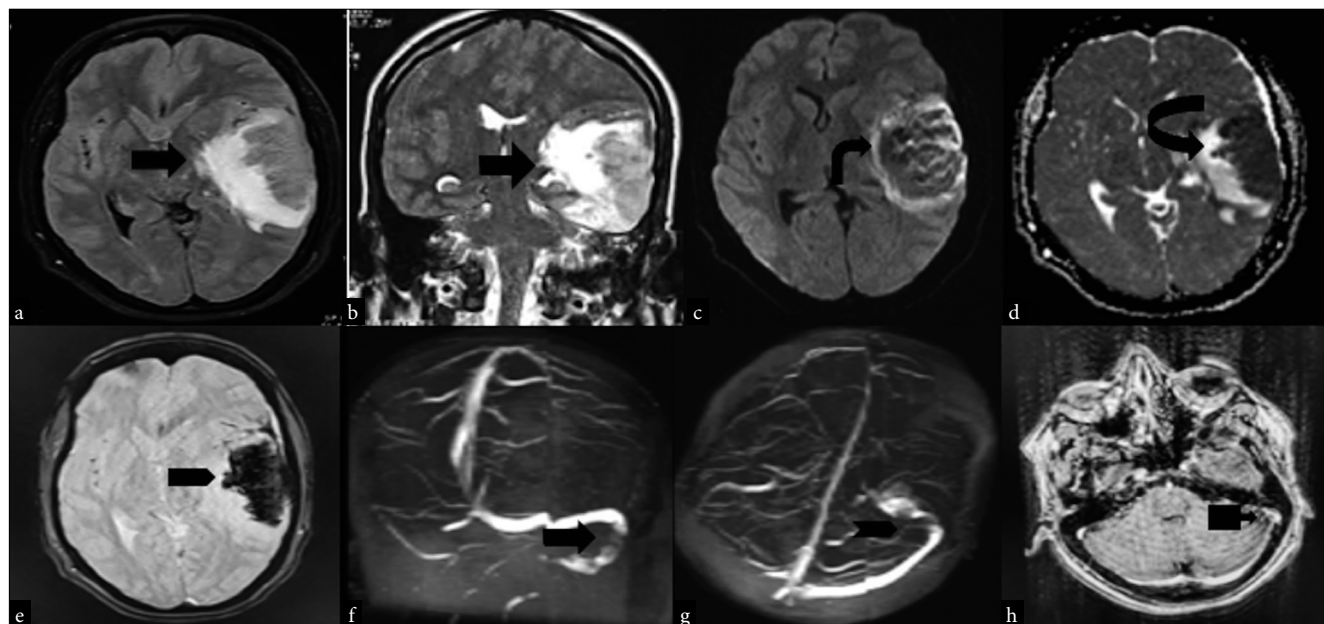

Figure 2: MRI (a and b) FLAIR axial and T2 coronal—hyperintense area of altered signal intensity involving the cortex and underlying white matter of the left temporoparietal lobe (black arrow). (c and d) DWI and ADC maps—lesion is showing a patchy area of restriction of diffusion with corresponding reduced ADC values (black arrow). (e) GRE axial—diffuse are of signal loss/blooming as seen suggestive of intraparenchymal hemorrhage (black arrow). (f and g) 2D TOF MRV coronal and axial—hypointense filling defects with peripheral hyperintensity within the left sigmoid sinus (black arrow) (black arrowhead). (h) Gadolinium-enhanced T1 Axial—central filling defect in left sigmoid sinus with peripheral post-contrast enhancement (black arrow). FLAIR: Fluid-attenuated inversion recovery, DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient, GRE: Gradient recalled echo, TOF: Time-of-flight, MRV: Magnetic resonance venography.

and the supportive care continued. However, she had a rapidly worsening course in the hospital and succumbed to her illness.

DISCUSSION

CVT in steroid-refractory ITP on eltrombopag is rare, and so far, only eight cases have been reported in the literature.[8–13] Our case is only the second from India and overall ninth in the world. Eltrombopag increases the platelet by direct action on megakaryocytes as well as immunomodulation by acting on T-regulatory cells. Though it has a very good safety profile, VTE has been reported from the clinical trials initially and real-world case reports subsequently. The sudden rise in young platelets, which are bigger in size and have more granular cytoplasms, predisposes to thrombus formation at various venous beds. This may pertain to the better platelet function reported in cases of ITP preventing bleeding despite having critically low platelet[14,15] Though CVT is rare, it results in severe morbidity and rarely results in death. To prevent this situation, we, in our clinical practice, start patients on ecosprin once the patient achieves complete response (platelet >100,000/cmm) on eltrombopag. However, a multicenter trial is required to evaluate the benefit and safety of such preventive intervention. The index case emphasizes that for any patient of ITP on eltrombopag presenting with unexplained headache, focal neurological deficit, or neuroimaging suggestive of ischemic changes with or without hemorrhage, CVT must be considered as one of the possibilities, and prompt anticoagulation can be lifesaving.

CONCLUSION

CVT is a rare but life-threatening complication in ITP patients on eltrombopag. High degree of suspicion is required for early diagnosis and therapy.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

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Case Report

Atypical progress of tuberculosis in the peripartum period: Report of a paradoxical reaction

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ABSTRACT

Central nervous system involvement is noted in approximately 1% of all Tuberculosis (TB) cases. Worsening of pre-existing tubercular lesions following antitubercular treatment in the absence of disease relapse or any other diagnosis is called a paradoxical reaction. We detail an atypical evolution of TB in a pregnant woman. We report the case of a woman admitted with respiratory symptoms at 35 weeks of Pregnancy. She had a spontaneous onset of labor within 48 hours and delivered a 1.6 kg live baby. Investigations confirmed pulmonary TB. She was started on antituberculosis treatment. Post-partum, she developed persistent headaches, and the imaging confirmed tuberculoma in the left inferior frontal gyrus with leptomeningeal enhancement. She was started on steroids. She was readmitted after two weeks due to a new onset holocranial headache, and MRI detected a new large tuberculoma in the temporal region hence, a diagnosis of Pleuropulmonary with Extrapulmonary tuberculosis with a Paradoxical reaction was made. Anti-edema measures were added, and the patient was managed in hospital for another 2 weeks. The case details and the possibility of flare due to puerperium and steroids are discussed. In pregnant women with active TB disease, complications of perinatal death, preterm birth, acute fetal distress, and low birth weight are increased. The risks of untreated active disease in a pregnant woman are higher than the risks of its treatment. A high index of suspicion, avoiding over-crowding, proper nutrition, timely and appropriate initiation of treatment may have a favorable pregnancy outcome.

Keywords: Paradoxical reaction, Pregnancy and puerperium, Tuberculosis

INTRODUCTION

Worsening of preexisting lesions following antitubercular treatment (ATT) in the absence of disease relapse or any other diagnosis is called a paradoxical reaction.[1,2] Increased incidence of paradoxical reaction has been reported in patients with autoimmune disease on immunomodulators like monoclonal antibodies, lymph node tuberculosis, and human immunodeficiency virus (HIV) co-infected population.[1,3–5] It is more likely to flare up in the postpartum period once the immunological changes of Pregnancy start reverting to normal. It is important to be aware of this entity while treating patients with Tuberculosis as it can be confusing with possible wrong diagnosis or treatment failure due to drug resistance. We discuss a case with atypical progress of TB from lungs to brain and postpartum brain spread despite appropriate treatment.

CASE REPORT

A 20-year-old G2P0L0A1 (Second gravida with no living children and history of previous abortion) was referred to us at 35 weeks of gestation from a nearby district with complaints of occasional cough with minimal expectoration for 6 months, shortness of breath, intermittent low-grade fever, and loss of appetite for 1 week duration. She had a positive history of contact with TB with her father, who was on ATT. General physical examination showed a poor nutrition status, tachycardia, low-grade fever, and pallor. There was no generalized lymphadenopathy; she was mildly dyspneic with a respiratory rate of 28 per minute, and the oxygen saturation was 93% in room air. Auscultation revealed normal cardiac sounds, decreased breath sounds, and bronchial breathing on the right lower lung field. Obstetric examination suggested a clinically growth-restricted fetus, further confirmed by ultrasonogram, and the admission cardiotocograph (CTG) was normal. She was immediately admitted to the intensive care unit (ICU), propped up and positioned with oxygen on flow, and management was planned with a multidisciplinary team of obstetricians, anesthetists, respiratory physicians, general physicians, and neonatologists. Her hemoglobin was 8.2g%, total leukocyte count (TLC) was 2430/μL, and platelets were 3.06 lakh/μL. Renal and liver function tests were within

Figure 1: Chest X-Ray showing right lower zone opacity with pleural effusion.

normal limits. Chest X-ray showed a right lower zone opacity with pleural effusion [Figure 1]. She was kept under vigilant vital monitoring and started on round-the-clock antipyretics, hydration, and optimum calories. Sputum was sent for culture sensitivity, gram stain, Acid Fast Bacillus (AFB) stain, and Gene Xpert. COVID-19 testing was negative. Post-admission, she spontaneously went into preterm labor and delivered a 1.6 kg female baby uneventfully. The baby was shifted to the neonatal ICU for observation. Subsequently, her Gene Xpert was reported positive for *Mycobacterium tuberculosis* (MTB) with sensitivity to Rifampicin and was started on Category I ATT comprising fixed-dose combination of isoniazid, rifampicin, pyrazinamide, and ethambutol, three tablets a day based on her weight band. On postnatal day 4, she complained of severe unremitting generalized headache, and prolonged period of lethargy and drowsiness. There was no history or record of febrile spikes, convulsions, urinary tract infection, breast engorgement, leg pain, chest pain, breathlessness, or foul-smelling lochia. A general physical examination revealed tachycardia and pallor. Neurological examination showed a confused patient with a slow response but otherwise normal higher mental functions. Muscle bulk, tone, power, and sensory system were normal, and plantar reflex was extensor. There was no evidence of any facial nerve palsy and no positive signs suggestive of meningitis, papilledema, or tubercles on fundus examination. The liver function tests were normal. Magnetic resonance imaging (MRI) of the brain was done, which showed a sub-centimetric well-defined ring enhancing T2 hypointense lesion with subtle perilesional edema in the left inferior frontal gyrus suggestive of tuberculoma along with leptomeningeal enhancement [Figure 2]. The diagnosis was expanded to extrapulmonary Tuberculosis with tubercular meningitis and tuberculoma. Analgesics and oral dexamethasone 6 mg at a frequency of twice a day for 2 weeks followed by weekly tapering doses over 5 weeks, were added to the preexisting treatment. Her headache and drowsiness improved after the addition of steroids and analgesics. She
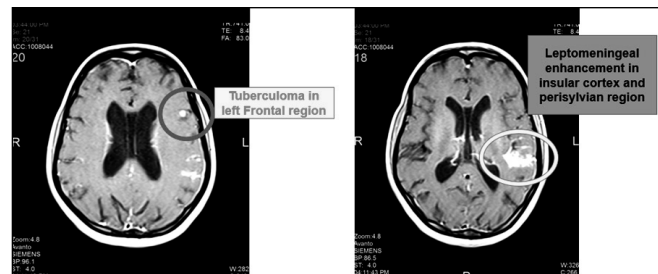

Figure 2: Post-contrast magnetic resonance imaging (MRI) brain showing tuberculoma in left inferior frontal gyrus with leptomeningeal enhancement.
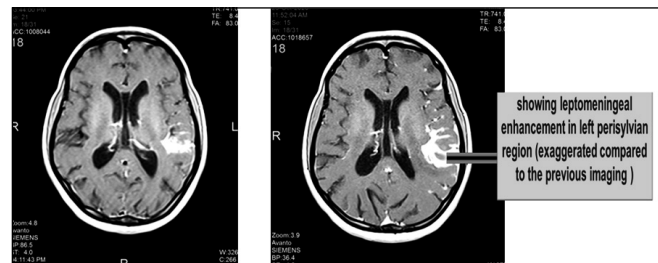

Figure 3: Follow-up MRI showed new tuberculoma and exaggerated leptomeningeal enhancement in the left temporal region.

tolerated drugs well, liver function tests were normal, and she was discharged home 20 days later, with directly observed treatment short-course (DOTS) registration and Isoniazid prophylaxis for the neonate. After 2 weeks of discharge, she reported back to the hospital with a recurrence of severe holo cranial, yet predominantly left-sided headache and vomiting. She was taking 4 mg oral Dexamethasone twice a day when she developed the recurrence of headache. There were no seizure episodes, fever, neck pain, limb weakness, or visual disturbance. A repeat chest X-ray showed a reduction in pleural effusion than the previous one. Fundus examination showed signs of early papilledema, and repeat MRI showed new, large tuberculoma and exaggerated leptomeningeal enhancement in the left temporal region [Figure 3] hence, a diagnosis of pleuropulmonary with extrapulmonary tuberculosis with a paradoxical reaction was made. She was under observation and along with ATT, oral steroids were replaced with an injection of Dexamethasone 4 mg intravenous eighth hourly, and oral Acetazolamide 125 mg twice a day was added as the anti-edema measure. Her headache improved and she was discharged home after ensuring compliance. In the follow-up visits, she was declared cured at the completion of treatment.

DISCUSSION

The principles for the treatment of Tuberculosis in a pregnant woman with presumed drug-sensitive disease are the same as in the nonpregnant state. In pregnancies in women with active TB disease, there is an increased risk of perinatal death,

preterm birth, acute fetal distress, and low birth weight.[6] A state of vague ill health may be present for 2 to 8 weeks prior to the development of meningeal irritation,[7,8] which may often be confused with the nonspecific complaints in Pregnancy. Moreover, the weight gain during Pregnancy can mask the weight loss accompanying tuberculosis, thereby giving a false sense of reassurance.[6] A review[9] of 29 cases published in 2003 documented that tuberculosis developed a median of 10 days after delivery, with 76% of the patients experiencing symptoms within 10 days postpartum. About 93% of the patients with tuberculosis during the postpartum period had extrapulmonary involvement, and of these patients, 69% had central nervous system (CNS) infection. Nevertheless, the progress of the disease to newer lesions, even after the commencement of ATT is rare. A recent case report[10] from Central America described a young postpartum woman who succumbed to the reactivation of undiagnosed prepartum latent Tuberculosis. Pregnancy is a relatively immunocompromised state due to the maternal immune tolerance to prevent fetal rejection; however, the immune reconstitution in the postpartum period can lead to the flare-up of the disease.

In our case, there was fetal growth restriction and she had pulmonary symptoms. She had a spontaneous preterm delivery. The postpartum flare-up involved the nervous system. Maybe she already had disseminated tuberculosis at the time of presentation. The neurological symptoms manifested once the lung symptoms subsided. It is also possible that addition of steroids for the neurological disease would have further spread the TB to form yet another tuberculoma. Such a flare has not been reported. Poor nutrition, poor socioeconomic status, postpartum immune-modulation, and heavy tubercle bacilli load could have resulted in this atypical flare.

CONCLUSION

The risks of untreated active tuberculosis in Pregnancy outweigh the risks of the treatment of the disease. A high index for suspicion of flare-ups despite treatment, timely and appropriate initiation of and compliance with treatment may have a favorable pregnancy outcome and complete recovery in women with TB in the peripartum period.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Case Report

Loss of lateral femoral condyle following sepsis of knee region in infancy: The hypothesis of vascular pathogenesis and clinical course

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ABSTRACT

Complete loss of lateral femoral condyle of the femur following sepsis of the knee region in infancy is a well-recognized entity. The etiopathogenesis of the sequelae is poorly understood with synovial plicae and post-septic growth disturbance postulated as possible causes. Two illustrative cases are presented to elucidate the clinical effects of condylar loss in the pediatric age group. There is a typical pattern of unicondylar damage, loss of adjacent metaphysis, and metaphyseal spur in involved cases. Abnormal loading of the knee, ligament laxity, and the presence of a physeal bar contribute additionally to deformity. The deformity progression can be as rapid as 2.8 degrees per month. The lesion is most often treated by balancing the knee mechanics using osteotomies and growth modulations. The lesion progresses downhill due to the absence of lateral support of the knee joint configuration. The anatomical region supplied by the superior lateral genicular vessels closely matches with the lateral unicondylar femoral loss seen post-sepsis. A vascular etiology is therefore hypothesized for the lesion.

Keywords: Infection, Lateral femoral condyle, Loss, Sepsis

INTRODUCTION

Complete loss of one femoral condyle of the femur is recognized as one of the most devastating complications of osteoarticular infection of the knee region in infancy.[1–7] Loss of lateral condyle of femur post sepsis is the more frequently recognized entity.[2-4] What follows is a course of progressive angular deformity, joint instability, and limb length discrepancy. The described interventions for the pathology either require several repetitions or, at best are salvage procedures aimed at reducing disability.[2,7]

The anatomical description of this entity is strikingly similar in various series.[2-4] Following infection in infancy, an area of destruction appears in the epiphysis and adjacent metaphysis in a few days.[2] With the settling of soft tissue swelling, a well-circumscribed defect involving epiphysis and metaphysis manifests a few weeks later. The margins of the defect are well-defined almost resembling the loss of one-half of the distal end femur, including the epiphysis and adjacent metaphysis [Figure 1]. The proximal margins of the bony defect may spread out a bit in the form of a "metaphyseal" spur.[2] This appearance persists for several years post-infection.

The etiopathogenesis of the above sequelae remains ill-understood. It is variably described as a consequence of osteomyelitis or septic arthritis of the knee region.[2-7] Strong *et al.* put forward the concept of metaphyseal infection spreading to the epiphysis through transphyseal blood vessels.[8] However, the above theory could not explain the sparing of the medial femoral articular cartilage while the whole joint was infected. To explain the "unicondylar" involvement, Tercier *et al.* postulated the synovial septum hypothesis wherein the opposite condyle was shielded from the proteolytic effect of bacteria.[7] The trans-synovial septae could however be demonstrated only in about 15% of knees. The "loculation" hypothesis again could not explain the unicondylar damage as once the infection spreads into epiphysis and metaphysis, there are no absolute barriers to the spread of infection.

Lately, there have been extensive studies on the vascular supply of the distal femur with osteochondral flaps and genicular artery embolization for knee osteoarthritis.[9–12] The present manuscript aims to revisit the etiopathogenesis of post-infective lateral unicondylar femoral loss with a vascular origin hypothesis. Two representative cases are presented to illustrate the clinical course following such lesions.
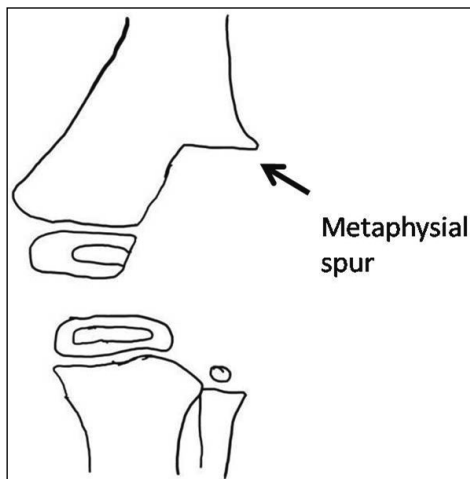
Figure 1: The typical sequelae observed following infection of the knee region in infancy: There is a loss of one-half of the distal end femur including the epiphysis and adjacent metaphysis. The proximal margins of the bony defect may spread out a bit in the form of a "metaphyseal" spur.

CASE REPORTS

Case 1

A 1.5-year-old girl presented with complaints of progressive valgus deformity of the right knee [Figure 2]. Her previous records revealed management for septic arthritis of the right knee joint at 10 days of life. The joint was decompressed by arthrotomy under the cover of intravenous antibiotics. The cultures isolated *Staphylococcus aureus*. The infection settled by 6 weeks. Serial radiographs showed partial loss of lateral femoral epiphysis by 6 months of age. The typical pattern of unicondylar damage, loss of adjacent metaphysis, and metaphyseal spur were obvious by 12 months. Computed tomography and MRI imaging reaffirmed the plain radiological findings. At the time of presentation to our institution, the lateral distal femoral angle (LDFA) had worsened to 30 degrees. The approximate rate of deformity progression was 2.8 degrees per month since the septic event. She underwent a distal medial closing wedge femoral osteotomy supplemented with growth modulation to prevent an early recurrence. She has also been advised to a hinged long knee brace post-operatively. The tension band plate was removed when the limb was aligned to neutral at 18 months post-surgery. At follow-up of 31 months, the deformity had already partially recurred (LDFA 74 degrees). The child continues to use the brace and is in regular follow-up.

Case 2

A 2.5–year-old girl was seen with severe valgus deformity of the right knee region [Figure 3]. The parents reported the

Figure 2: Illustrative case 1: (a) Anteroposterior view of right knee joint at age 10 days when septic arthritis of the joint was diagnosed. (b). Partial loss of epiphysis visible by 6 months. (c) Typical unicondylar loss of distal femur and adjacent metaphysis on lateral side at 12 months. Metaphyseial spur could also be appreciated (white arrow). (d) Computed tomography (e) MRI images of the lesion. (f,g) Clinical deformity and knee range of movement at 1.5 years. (h) Combined procedure distal medial closing wedge femoral osteotomy and tension band plating of medial side. (i,j,k) Follow- up 31 months – clinical and radiological findings of recurrent deformity.

onset of deformity soon after the child initiated walking. This child had a history of severe neonatal sepsis (Organism: *Streptococcus*) at age 15 days of life with multifocal involvement of the left shoulder, left elbow, and right knee joint. The interventions involved multiple aspirations of the joints and

Figure 3: Illustrative case 2: (a,b) severe neonatal sepsis with multifocal joint involvement. Radiographs at 2 months. Lesions are obvious in the right knee and lateral metaphysis, left shoulder, and elbow region. (c,d) Child at 2.5 years of age. Clinical deformity and radiological appearance. (e,f) Medial closing wedge osteotomy of the distal femur was performed at age 3 years. Healed osteotomy and corrected limb alignment at this stage. (g,h,i) Child at 6 years. The deformity had recurred. Partial regeneration of the lateral condyle is obvious. There was evidence of an eccentric physeal bar in the distal femur which was excised and a medial side tension band plating was added. (j,k) Follow up at skeletal maturity at age 14 years. Residual valgus at knee and limb length discrepancy. Knee range of movements fairly preserved. (l,m) Scanogram of the limb and the fate of other affected joints at the same follow-up.

intravenous antibiotics. The loss of the right lateral femoral condyle was obvious as early as 2 months in this child. At the time of presentation to our institution, the LDFA was 56.4 degrees. At age 3 years, the child underwent a distal medial closing wedge femoral osteotomy. Deformity at this time was 80 degrees. At 6 years, with the onset of recurrent deformity, an eccentric physeal bar was detected. The bar was excised and growth modulation of the medial femoral side was added. The limb length discrepancy at this time had progressed to 5 cm and therefore, concomitant left distal femoral complete epiphysiodesis was also performed. At the last follow-up, when the child had achieved skeletal maturity (at age 14 years), the right knee movements were relatively preserved, but there was a residual valgus of 12.4 degrees. The limb length discrepancy was 4 cm at this time. The patient is being planned for deformity correction and limb length equalization surgery.

DISCUSSION

The pathogenesis of loss of lateral femoral condyle following sepsis of the knee joint in children is debated. The primary site of infection – metaphysis or joint space; the presence of synovial plicae and loculation or post-septic growth disturbance all have been postulated.[1–7] None could, however, fully explain the characteristic appearance of the lesion.

Singson *et al.* hypothesized a possible ischemic cause as the destructive changes typically seen due to proteolytic activity were not evident in the epiphysis and adjacent metaphysis.[6] Additionally, the partial regrowth of the affected region demonstrated over time in a few cases supported the ischemic etiology. Newer insights into the vascular anatomy of the distal femur may provide an answer to the occurrence of typical destruction patterns noticed in the said pathology.[9–12] The superior lateral genicular artery (SLGA) is the main vascular supply to the lateral femoral condyle[9,13,14] [Figure 4]. As a consistent branch from the popliteal artery, it originates approximately 4 cm proximal to the knee joint line. It runs laterally on the posterior aspect of the femur to reach the lateral intermuscular septum. Posterior to the septum, it gives out a superficial branch and a deep branch. The superficial branch travels anteriorly, giving off skin perforators, and ends at the superolateral patella. The deep branch pierces the intermuscular septum to travel anteriorly on the lateral surface of the femur, giving branches to the vastus lateralis, the lateral head of the gastrocnemius muscle, the biceps femoris muscle,
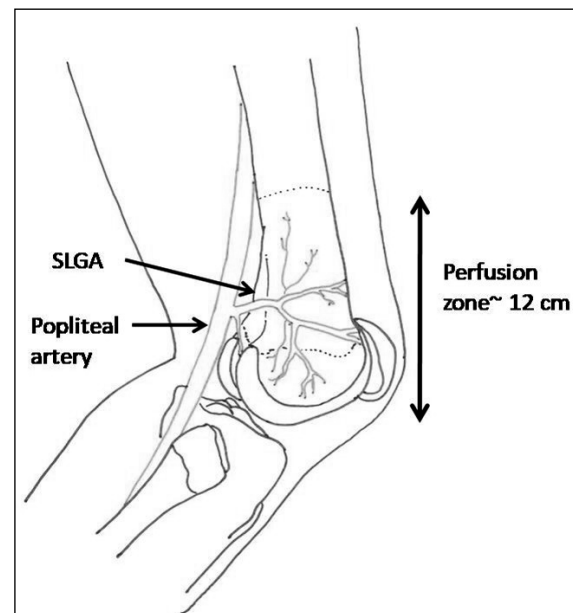

Figure 4: The area supplied by superior lateral genicular artery (SLGA). It is branch of popliteal artery and arises on the posterior aspect of knee. Approximately 12 cm of lateral half of distal femur is completely supplied by this vessel.

periosteum of the femur and ends by terminal end branches supplying the lateral femoral condyle. Overall the area supplied by SLGA extends approximately 12 cm above the lateral femur condyle in adult dissections. This very anatomy of SLGA forms the basis of vascularized lateral condylar graft used for reconstruction of non-union and defects of the hand, tibia, mandible, etc.

The lateral condyle of the distal femur is shown to be far more vascular than its medial counterpart in experimental studies.[15] This may predispose lodgement of infection in the lateral region. The SLGA vessel has a much larger bore of 1.5 mm compared to a medial vessel of size 1.2 mm. Thus, the lateral condyle grabs the larger share of the blood supply of the distal femur. Studies have shown that the application of a lateral locking plate over the distal femur resulted in a mean 21% total reduction in distal femoral arterial contribution.[15] When an additional medial plate was applied, it reduced the blood supply of the distal femur further by only 4%.

The chief mechanisms through which osteoarticular infection damages tissues are ischemia (vasculitis/thrombus/pressure tamponade), lysis by bacterial and inflammatory toxins and in some cases by host immune response. The lateral distal femoral supply is dedicated yet precarious. The anatomical area supplied by SLGA closely matches the loss of articular cartilage and the metaphyseal region associated with sepsis of the knee region in children. It is, therefore justified to hypothesize that an ischemic phenomenon occludes the SLGA early in infection. The occlusion of the vessel prevents further invasion by bacterial and host responses and, therefore the resultant clear demarcation of the involved region. Partial regeneration as noticed in several series, is theoretically possible with the dissolution of the thrombus, regeneration of newer vessels, or formation of collaterals from the surrounding vasculature.

Clinically, post-infective damage of the femoral condyle is associated with loss of lateral support of the knee joint configuration. What follows is a downhill course with progressive angular deformity and joint instability, as shown in the illustrated cases. The deformity progression can be as rapid as 2.8 degrees per month (Case 1). Abnormal loading of the knee, ligament laxity, and the presence of a physeal bar contribute additionally to deformity. The lesion is most often treated by balancing the knee mechanics using osteotomies and growth modulations.[2] The ongoing growth soon overcomes the correction achieved and in most patients, and throughout the disease, multiple osteotomies may be required. Langenskiöld documented that up to six osteotomies may be needed before skeletal maturity in these children.[4] In illustrated case 1, an early removal of tension band plating resulted in partial recurrence of deformity as

early as 13 months post removal. In the second case, the child's benefits of the first osteotomy were lost within 3 years. The use of contralateral growth modulation in concurrence with osteotomy may lessen the number of osteotomy procedures but add to the existing limb length discrepancy. In most cases, the regeneration of the lost part is delayed and its extent is unpredictable. Anticipating the unpredictable regeneration of lost femoral condyle, Tercier *et al.* advocated reconstruction of a lost articular surface using patella and osteoarticular graft from proximal fibula.[7] Either way, the outcome is never optimal or satisfactory.

The main technique through which the vascular territories have been commonly mapped is dye studies in cadavers followed by surgical dissection or high-resolution imaging. The infantile nature of post-infective vascular insult may preclude the determination of the exact sequence of events at that time and the lesion manifests only several weeks later. Either way, post-infective loss of lateral femoral condyle qualifies as one of the most disastrous sequelae of knee sepsis. The vascular hypothesis may pave the way for preventive interventions in the form of adequate hydration, anticoagulant medications, and decompressions if the site of vascular occlusion can be localized.

CONCLUSION

The superior lateral genicular artery-based vascular insult explains the typical anatomical pattern of post-sepsis lateral femoral condylar loss to a large extent. Advances in science may delineate the precise site in the future. This sequelae of knee sepsis results in recurrent angular deformities and is difficult to treat.

Ethical approval

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Perspective

Importance of thoughts—how bias derails smart choices

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The clinicians have two important tasks at hand. Arriving at a diagnosis is the most challenging and stimulating task to provide pain relief to suffering patients. When a symptomatic patient interacts with a clinician, a working hypothesis of a differential diagnosis is arrived at to investigate the patient for a definitive diagnosis.[1] The other task of the clinician is to answer a query once it remains unsolved by conducting a series of research studies to generate evidence. The researcher conceptualizes and designs a study, collects, analyses, and interprets data and compares it with available evidence. This systematic approach, if unbiased, may provide a new solution to the clinical puzzle of arriving at a credible diagnosis and effective treatment.

Bias is described as an error which may occur in clinical settings to arrive at a diagnosis and treat a patient. The bias may occur in the conception or design of a study or in the collection, analysis, interpretation, and reporting of research outcomes, which leads to conclusions that are systematically different from truth. The bias could be cognitive bias or publication bias.

COGNITIVE BIAS

It is described as systematic errors in thinking occurring due to limited human processing/inappropriate mental models.[2] Humans have two types of thinking to make decisions: the analytical thinking takes time and is slow but concise, while intuitive thinking is fast and practical. A balance is required to make appropriate decisions; however, when intuitive thinking predominates over analytical thinking, cognitive errors occur.[2]

The clinical judgment guided by an intuitive understanding of probabilities combined with cognitive processes is called heuristics.[3] Heuristics means rules of thumb, educated guesses, or mental shortcuts, which usually involve pattern recognition occurring due to subconscious integration of somewhat haphazardly gathered patient data and with prior experience. This may lead to several types of unconscious (cognitive) errors.

When we identify a set of clinical signs/symptoms representing a common disease based on rapid mental processing, taking cues from memory stores and intuition, it is called pattern recognition.

EFFECT OF BIASES ON HEALTH CARE DECISIONS

To err is human. Mistakes can occur in every field. In medicine, the diagnostic errors can have dire consequences. The strategies to prevent diagnostic errors lead us to a path of diagnostic excellence. Rebecca *et al.*, after a systematic review in psychology (N-149 studies), concluded that the quality, consistency, and accuracy of decision-making in allied health practice can be seriously impacted by biases.[4] The need to conduct further research in other disciplines to assess the impact of bias in healthcare decisions in real life was reiterated. Six to seventeen percent of diagnostic errors are reported in hospitals, out of which 70% occur due to cognitive biases, while knowledge deficit accounts for very few diagnostic errors.[5,6]

The biased approach is fast, intuitive, and irrational and may occur due to mental shortcuts, social influences, emotional motivation, and cognitive predisposition, ending in clinical decision bias/publication bias. Bias in clinical practice may affect clinical decision-making while publication bias of various kinds may lead to flawed research outcomes. The debiasing strategies need to be adopted, which may be a part of the education system, training, or motivation, or by making a memory checklist or decision algorithm to develop an unbiased approach which is analytical, slow, and rational.[7]

Various cognitive biases are:

a) **Aggregate bias:** Here, the physician disregards the clinical practice guidelines, believing that aggregate data do not apply to individual patients. Their belief that their patients are atypical or exceptional may lead to an error of commission. Tuberculosis (TB) gold does not help in making a diagnosis of TB according to various guidelines, while the clinicians continue to get the test done in their clinical practice. The fluoroquinolone as first-line antituberculosis (ATT) is continued to be prescribed despite the guidelines against its use. The TB spine lesions continued to be evaluated by monthly follow-up magnetic resonance imaging (MRI) after starting ATT when available evidence did not support it.

b) **Anchoring bias:** The tendency to stick to one probable suspected diagnosis based on early symptoms/signs despite getting new clinical information about the patient is described as anchoring bias.

c) **Confirmation bias:** Here, there is a tendency to look for evidence to support an initial diagnosis and not try to look for evidence against it.[6] It means physicians are trying to look to see something that they want to see. It leads to a mistaken diagnosis and is passed on to other colleagues without questioning the validity.

d) **Congruence bias:** Once a hypothesis/tentative clinical diagnosis is made, the clinician continues to conduct direct testing to prove it and does not consider other indirect tests to refute it without considering it, and it seems we do wish to consider alternative diagnoses.

e) **Gambler fallacy:** Instead of relying on the patient's clinical symptoms/signs, one is relying on personal belief. When a clinician faces a situation and believes that since the last few clinical patients belong to one condition, hence will not get another patient with similar diagnoses next time. Here, pretest probability is influenced by the preceding event despite it being independent.

f) **Overconfidence bias:** When the clinical decision is based on overconfidence, then that personal knowledge of oneself is more than others. Hence the decision is taken based on incompletely gathered evidence of signs/symptoms/investigations and on intuition/hunches rather than on carefully collected details of physical signs and investigations.

g) **Premature closure:** This bias is one of the most powerful biases and is the reason for a high proportion of missed diagnoses. Here, one tends to apply premature closure to decision-making and accept a diagnosis before it is verified; hence, we tend to stop further investigation. It is a common human tendency "to stop thinking when diagnosis is made."

h) **Base-rate neglect:** This is described as a tendency to ignore the true prevalence of the disease. Sometimes, uncommon/rare diagnoses are suggested, disregarding the common condition. The clinician may tend to inflate knowingly or unknowingly the uncommon diagnosis on the pretext of "ruling out the worst case scenario" or avoiding a rare diagnosis. In clinical situations, it is important to keep differentials based on gathered evidence in history/physical findings/imaging/laboratory findings and also consider the true prevalence of the disease.[5]

i) **Zebra retreat:** Contrary to base rate neglect, here, even if there is a possibility of a rare diagnosis based on gathered evidence, the clinician tries to retreat because of various reasons. This may be because of self-consciousness or low confidence. The clinician may not be keen to entertain a rare/remote possibility and does not want to be the first to investigate costly/special tests, given the inertia of the system. The clinician may be scared of being seen as esoteric or unrealistic, a person wasting resources. The clinician may not like to be seen as someone underestimating or overestimating a remote or unusual diagnosis. The clinician may be too busy to spend the required time to pursue a rare diagnosis or other team members may have diluted his convictions and insisted on not pursuing a rare possibility. Rarely does unfamiliarity with the diagnosis force the person not to pursue an unfamiliar road.

PUBLICATION BIAS

The publication bias leads to delay in the acceptance of key research or dissemination of distorted truth or delay in effective therapies and suboptimal outcomes.[2] It has far-reaching consequences. It distorts the conclusions and becomes the basis of future flawed hypotheses. The publication biases are of various types:[2]

a) Affinity bias: This occurs when one relies on the study based on a high-ranked institution/researcher/organization and not based on evidence drawn in the article.

b) Positive outcome bias: The tendency to rely on/prefer literature with positive outcomes is described as positive outcome bias.

c) Status quo bias: This occurs when one favors the opinion in support of current thoughts and does not consider evidence in support of a change.

d) Self-serving bias denotes support for the opinion expressed by reviewers or colleagues. Academic publication bias is where we favor studies which benefit personal institutions and peers.

CLINICAL DECISION-MAKING

While making a clinical decision, a hypothesis (differential diagnosis) is generated based on history and clinical examination. The differential diagnosis is tested by various investigations to arrive at a probable/final diagnosis. The probability of diagnosis with the investigation undertaken as well as probability estimation for the treatment suggested, is undertaken. In the presence of some uncertainty about the diagnosis, the treatment may be instituted considering the benefit of treating a sick person against the risk of erroneous treatment to a person with some other ailment.

The cognitive predisposition, mental shortcuts, social influences, and emotional motivation in clinical settings lead to intuitive, fast, and irrationally biased clinical approaches. Publication biases lead to delays in the acceptance of key research, dissemination of distorted truth, and delay in effective therapies. We need to undertake debiasing strategies to make it an unbiased, analytical, slow, and rational approach.

STEPS TO DECREASE BIAS

Reducing cognitive errors may be a challenge in healthcare facilities. Cognitive errors may be reduced by multi pronged strategies, which include increasing awareness about cognitive biases. The working conditions are improved to detect, protect, and recover from cognitive errors and associated risks.

The knowledge and awareness of cognitive biases can be imparted by discussing clinical cases to expose biases and raise awareness about their occurrences and also by providing simulation and training highlighting biased thinking.

TRAINING

We have to train students for metacognition. We have to inculcate among trainees the habit of asking questions to themselves: "Could it be explained by anything else?" We need to develop the systematic methods of reasoning, critical thinking, and presenting. The experience can be increased by the use of simulation methods. We should learn to tolerate feedback regarding diagnostic decision-making so that insight is developed into our reasoning and is recalibrated.[7]

Enhance work system conditions and workflow design that affect cognition

Working conditions should promote/facilitate perception/recognition/decision-making and should limit cognitive loading to produce task saturation/fatigue. Adequate time is available to collect data, review it, and discuss it. We should allow access to clarity of information. Health information technology should be available and accessible to incorporate into the system. We should aim to facilitate real-time decisions and memory reliance will be reduced. Teamwork is developed to verify assumptions, interpretations, and conclusions. The system at the workplace should be resilient so as to help in detecting/recovering from cognitive biases.

Promote an organizational culture that supports the decision-making process

The organization should be developed and strengthened with all the tools for a successful journey. We should support a safe, non punitive reporting culture to learn from near misses and incidents. We should consider including cognitive bias in patient safety incident analysis to enhance understanding of how it contributes and can be mitigated. We should encourage people working to speak up. The patients and families should be engaged and empowered to partner in their care so that they understand diagnosis and can ask questions and speak up.

STEPS TO REDUCE OUR BIAS

We need to be aware of our own bias, which, in turn, enhances our clinical decision-making and improves patient care as also to improve future research. A small step that can reduce cognitive errors and improve clinical decision-making is slowing down to give adequate time for rational clinical diagnosis. While proposing differential diagnosis, we need to keep the base rate in mind. We should consider only relevant data (history/physical findings/investigations). We should actively seek alternative diagnoses. We should not forget to ask ourselves a question to disprove our diagnosis. Always remember that you may be wrong and consider the implication of cognitive error/wrong diagnosis. We should have a checklist/protocol so that cognitive errors, if occurring, can be corrected and damage avoided.[6]

While making a clinical decision, various factors influence clinical knowledge, including clinical epidemiology, heuristics, evidenced-based medicine, inductive reasoning, Bayesian reasoning, and hypothesis deductive reasoning. With the interplay of metacognition, one can reach sound clinical reasoning. In the end, "How you think and what we think makes a difference."

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Letter to Editor

The woes and challenges of medical publications in India

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Dear Editor,

Apropos the editorial in your esteemed Journal.[1]

The content makes interesting reading of a long and fascinating journey of 59 years, expressing a variety of highly informative, balanced, unbiased, wholesome, and comprehensive articles to medical professionals.[1] In the "Editorials" too from the earlier issues, you have highlighted the "Woes" of medical publications.[2,3] You have rightly championed for robust "Review", regularity in publication, shortening of the submission–decision time frame, the need for an "Indian Indexing Platform", and rescue from the catch 22 situation.[4,5] With the dawn of the new year, ANAMS Journal has moved towards new publishing house promising user friendly manuscript submission system. Sure, these new initiatives are bound to encourage the research fraternity.

The earliest version had 156 print pages, but over the years, that number has reduced. As a new feature, you have introduced the "Task Force Report," and we observe that two-thirds of the pages in an issue are devoted to TFR. The TFR is lengthy, factual, and similar to textbook pages. We do need TFR, but perhaps not too many at a time.

Time alone is a witness to new technologies, resources, and tools of the new publishing house giving a new look to your esteemed journal. We sincerely appreciate your efforts to take this "Journal" to a world-class position.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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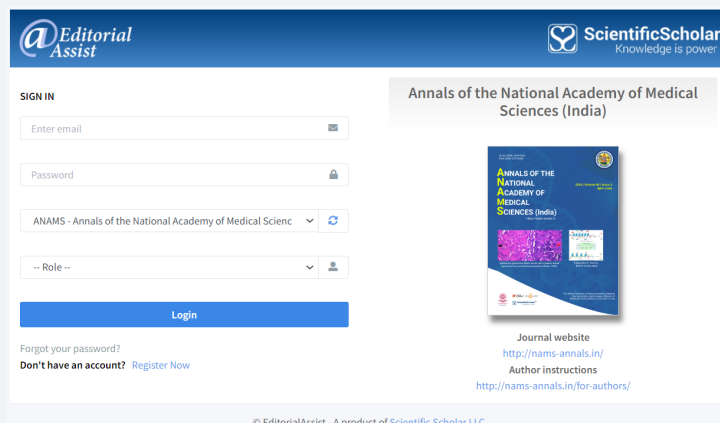5. Satyanarayana K, Sharma A. Biomedical journals in India: Some critical concerns. Indian J Med Res 2010;132:119–22.

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