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The Enigma Called Health for All

Nandini Chatterjee*

It is 2026, and we have another World Health Day at our doorstep—with a slogan for the betterment of health and well-being of the world at large. This time, the WHO slogan for World Health Day 2026 (April 7) is "Together for health, stand with science."

It is a clarion call for governments, health professionals, partners, and the public to stand with evidence-based guidance to protect the health of people, animals, plants, and the planet.

It is well established that the circle of life encompasses the interdependence of human health, the environment, and the zoonotic ecosystem.

The WHO is propagating the concept of "One Health," which is an integrated approach aiming to sustainably balance and optimize the health of not only humans, but also the domestic and wild animals, plants, and the wider environment (including ecosystems).

Health is closely related to food and water safety, climate, and environmental alterations, which require interdisciplinary collaborations to deal with health challenges such as the emergence of infectious diseases, antimicrobial resistance, increasing neglected tropical diseases, and threatened ecosystems.

The One Health approach is designed to help address the entire spectrum of disease control—from prevention to detection, preparedness, response, and management—and contribute to global health security, and is to be applied at the community, national, and global levels. The success of this initiative, however, depends upon effective governance, communication, and coordination.

The decision to dedicate a specific day—April 7—to a global health theme was made in 1948 during the First World Health Assembly with a noble intention to address the pressing health needs of the conflict-ridden humanity and give hope and direction to optimal healthcare a few years after the conclusion of the second World War.

But the 28th of February 2026 saw the world experiencing the devastating effects of another conflict on humanity, the environment, and ecobiology.

Whatever has been achieved in terms of Health for All by 2030 will take a backseat as war and destruction take upper hand in the months to come. To date, over 1,444 people have been killed, over 18,551 people have been injured, and the UN has reported that up to 3.2 million people have been displaced, representing between 600,000 and 1 million households.

Let us have a look at how conflict disrupts health, security, and long-term wellbeing.

Explosive weapons and combat lead to high mortality rates and destruction of infrastructure, causing shortages of medical supplies, an exodus of health workers, and a total system collapse.

Malnutrition due to starvation and increased risk of outbreaks of communicable diseases as a result of disruption of water, sanitation, and hygiene are the inevitable consequences. Refugees and internally displaced persons (IDPs) face overcrowding, lack of resources, and increased susceptibility to disease.[1]

It has been reported that over 70% of epidemic-prone diseases and 60% of preventable maternal deaths occur in conflict-affected areas. The vulnerable population, such as women, children, and the elderly, are the worst affected by gender-based violence, reproductive health risks, and malnutrition.[2] Chronic disease neglect is also a grave consequence due to interrupted care for conditions such as cancer, diabetes, and hypertension.

What is the Long-term Impact?

The disruption of health services and infrastructure often causes a spike in mortality that lasts for years or decades beyond the active conflict.

It also important not to overlook the enormous burden on mental health culminating in depression, anxiety, and PTSD in war-torn zones that has immense socioeconomic implications.[3]

Devastating environmental contamination directly results from damage to industrial sites, oil refineries, and use of toxic weapons polluting air, water, soil, and killing millions of aquatic and terrestrial animals and plants as well

What Needs to be Done

The World Health Organization (WHO) takes the lead in mitigating the far-reaching consequences of conflict on health. It endeavors to restore and strengthen health systems in crisis zones by providing emergency medical supplies, supporting mobile clinics, and advocating for the safety of health workers.

However, it is the responsibility of the local, national, regional, and global authorities to implement joint responses to health threats.

Apart from health aids, monitoring and surveillance of health crises and tracking attacks on health services, as well as developing shared databases across different sectors, are of prime importance.

So how do we stand together on World Health Day?

How do we stand together in health and science if there is no harmony in this world?

How do we achieve Health for All if half of the world is dying, starving, fleeing in terror?

Humanity is in grave danger, and only peace, stability, and empathy can save it.

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GUEST EDITORIAL

"Dead" Patients Coming Alive: A Case for a Foolproof Death Pronouncement in India

Sadananda B Naik[1*], Sangram Biradar[2]

Introduction

It is not a rare occurrence where a patient who has been declared dead in the hospital comes alive either during transport back home or while performing the last rites. But in recent times we are witnessing a steady rise in such incidences.[1–4] Though it is a global phenomenon, in our country it has brought a lot of negativity and adverse publicity against medical professionals and hospitals. These incidences are casting serious doubt in the minds of the public about the ability and knowledge of medical professionals in declaring someone dead and have eroded the public trust in doctors. On many occasions it is being perceived as serious negligence or total irresponsibility on the part of a medical professional. A patient who has been declared dead but comes alive could put medical professionals under serious mental stress with long-lasting emotional trauma as well. Beyond the medical realm, such cases raise legal and ethical dilemmas. Families go through unnecessary mental trauma, funeral services are disrupted, and, in some cases, patients wake up in morgues or coffins—an unimaginable horror. In India we have neither any data on such occurrences nor a well-accepted protocol or guidelines for the determination and declaration of death. While cases of the "dead" coming back to life remain rare, they highlight the gaps in medical practices that need urgent attention, and there is a pressing need for a foolproof protocol for pronouncement of death that is acceptable legally and medically and with a pan-India application.

Declaring death is one of the most definitive diagnoses a clinician makes, and there could be no scope for any ambiguity or error in this medical conclusion. However, medical science being a complex and unpredictable science, it is practically impossible for any medical professional to deliver healthcare error-free, be it in managing the patient or pronouncing death.

Causes for the Wrongful or Erroneous Death Declarations

- Absence of formal training during undergraduate and postgraduate medical studies.
- Many a time, death pronouncement is done by relatively junior or less experienced medical professionals.
- Absence of a universally accepted protocol to declare someone dead in India.
- Misunderstanding between the family members and the medical team regarding the patient's health condition. The word "may not survive" is misunderstood as "dead" by the family members.
- Lazarus syndrome, otherwise known as autoresuscitation, is a strange phenomenon named after a biblical character who was supposed to have come back to life 4 days after death. It refers to blood circulation returning spontaneously after a failed cardiopulmonary resuscitation (CPR). Survival time after autoresuscitation ranges from minutes to hours, days, and even months. Six patients with the Lazarus phenomenon reached full recovery without any neurological impairment. Hyperventilation, auto-positive end-expiratory pressure (PEEP), and delayed drug action are the popular explanations for this strange autorecovery of cardiac function and circulation. The hyperventilated lung due to prolonged CPR causes air trapping inside the lungs, which eventually raises the intrathoracic pressure to a level that leads to complete cessation of venous return to the heart and results in persistent cardiac arrest unresponsive to CPR. On stopping the CPR, there is a scope for the passive exhalation of the trapped air from the lungs and the reduction in intrathoracic pressure, which allows venous return as well as the inotropes injected earlier to return to the heart, resulting in cardiac function being reinstated to bring back the dead to life. This strange phenomenon could be avoided by keeping the cardiac monitor on at least for 10 minutes after cessation of resuscitation and disconnecting the endotracheal tube from the ventilator or artificial manual breathing unit (AMBU) bag.[5]
- Medical equipment malfunction: In rare cases, medical equipment such as monitors, defibrillators, or electrocardiogram (ECG) machines may malfunction, giving false readings and leading to a premature and erroneous declaration of death.

Key Guidelines Available to Medical Professionals in India for the Declaration of Death

- World Health Organization (WHO) guidelines on the definition and declaration of death.[6]
- Brain death criteria as outlined by the Uniform Determination of Death Act (UDDA) and the American Academy of Neurology (AAN).[7]
- Ethical principles from the World Medical Association (WMA) for organ donation and brain death determination.[8]
- World Medical Association Declaration of Istanbul.[9]
- Transplantation of Human Organs (Amendment) Act 2011.[10]

Definition of Death

"Death is the permanent loss of capacity for consciousness and all brainstem functions. This may result from permanent cessation of circulation or catastrophic brain injury." This is the popular and widely accepted definition of death, and here "permanent" refers to loss of function that cannot resume spontaneously and will not be restored through intervention.[11,12]

Gardiner et al.[13] advocate three sets of criteria to diagnose human death. Each set of criteria clearly establishes the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe. The three criteria sets are somatic (features visible on external inspection of the corpse), circulatory (after cardiorespiratory arrest), and neurological (in patients in coma on mechanical ventilation)

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and represent a diagnostic standard in which the medical profession and the public can have complete confidence. Despite all these guidelines or protocols, every now and then we find reports of dead patients coming alive in some parts of India, indicating that they are not foolproof.

In our country, a registered medical practitioner can only certify death, and the process could be really challenging when he is summoned to pronounce a patient or person dead at the residence of the deceased, and there is a lot of scope for errors during these home visits. Declaring the patient dead at the hospital could occur under two circumstances—pronouncing an inpatient as dead or declaring someone brought to the emergency as dead on arrival or brought in dead.

Survivor Medical Care

Unfortunately, most of the "dead" patients who come alive will eventually succumb in a few hours to a few days due to the critical illness they suffer from. In order to improve their long-term survival and recovery thereafter, an action plan should be formulated to treat such patients in nearby tertiary care hospitals rather than small hospitals in their hometown. The relatives of the patient should be elaborately counseled on the limitations of medical science regarding someone being declared dead erroneously. This would not only help the patients and their relatives come to terms with the facts but also revive and rejuvenate the doctor–patient relationship and trust in the medical profession at large.

Ethical and Legal Considerations

The certification of death is not only a medical issue but also an ethical and legal one. The misdiagnosis could be the bone of contention in a legal dispute and lead to legal consequences for the healthcare professionals, and it could pave the way for long-drawn and draining litigations in the court of law for the doctors. The media, which takes center stage in highlighting such incidences, loses interest as the spotlights fade.

Proposed Guidelines to a Foolproof Death Certification

In order to avoid erroneously diagnosing someone dead, medical professionals should follow strict guidelines to confirm that death has actually occurred. There is a need for Indian guidelines simulating best practices from different countries:

- A minimum of two experienced medical professionals should be involved in declaring the patient dead.[13]
- A mandatory minimum period of 10 minutes of waiting following a failed CPR, with cardiac monitors being on, to ensure that there is no spontaneous return of cardiac or respiratory function (autoresuscitation).[5,14]
- In similar lines, the endotracheal tube should be disconnected from the ventilator or AMBU bag to negate the effect of auto-PEEP and allow venous return.[5]

Policy Recommendations

As there are no data available on this important issue, incidences of "dead" patients coming alive should be made a notifiable medical condition. Hence, the state and union governments should issue a gazette notification in this regard. Accumulated data could help constitute special audit units to look into such cases and come out with useful protocols to make death certification a foolproof process to mitigate such events.

Conclusion

To prevent errors in diagnosing someone dead, hospitals and medical professionals must implement more rigorous death confirmation procedures, including extended observation periods and better training. Medical students and newly graduated doctors need mandatory special training or workshops to learn the clinical skill and knowledge to pronounce someone dead. The public should be made aware of the limitations of medical science, which could result in someone being erroneously declared dead. The medical fraternity should take utmost care and caution while pronouncing someone dead, and there should be no scope for any callous or casual approach in the best interests of the profession and society at large. The Ministry of Health and Family Welfare, in coordination with the National Medical Council of India, should come out with an error-free protocol for death declaration, which is legally and ethically acceptable.

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ORIGINAL ARTICLE

Thyroid Hormone Levels, even within the Euthyroid Range, are Associated with Lipid Levels

RS Sudharshini[1*], A Velayutharaj[2], Monisha Mohan[3], Praveen Kumar[4]

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Abstract

Background: Thyroid dysfunction of any magnitude is associated with dyslipidemia. But the relationship of thyroid hormones with lipid parameters among euthyroid population is still unclear.

Materials and methods: This is a cross-sectional study to assess relationship between measured [free T3 (fT3), free T4 (fT4), and TSH] and derived (free T3/free T4 ratio, and TSH index) parameters of thyroid profile with different components of lipid profile among euthyroid population.

Results: We included 100 patients (60 men and 40 women) in this study. The mean free T3, free T4, and TSH levels of our study population were 2.4 ± 0.5 pg/mL, 1.2 ± 0.2 ng/dL, and 3.0 ± 1.6 µIU/mL, respectively. Overall, fT3 had a significant positive correlation with HDL cholesterol (r = 0.4, p = 0.01) and a negative correlation with total cholesterol levels (r = –0.3, p = 0.04). While fT4 (r = 0.3, p = 0.04) and fT3/fT4 ratio (r = 0.5, p = 0.001) showed positive correlation only with HDL levels. In subgroup analysis, positive association of fT3 (r = 0.6, p = 0.008), fT4 (r = 0.4, p = 0.04), and fT3/fT4 ratio (r = 0.8, p = 0.001) with HDL cholesterol was significant only in men. And only in the subgroup with TSH ≥ 3 µIU/mL (N = 48), we found a significant negative correlation of fT3 with total cholesterol (r = –0.5, p = 0.01) and LDL levels (r = –0.7, p = 0.001) and a positive correlation with HDL levels (r = 0.5, p = 0.02).

Conclusion: Among euthyroid subjects, fT3 seems to have a significant and consistent favorable association with lipid levels, especially with HDL cholesterol. This positive association of fT3 with HDL is more marked in men and in subjects with TSH ≥ 3 µIU/mL.

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Introduction

Thyroid dysfunctions have a profound impact on lipid levels.[1] Thyroid hormones (TH) promote synthesis, mobilization, and degradation of lipids. But their effect on degradation is slightly more pronounced than their effect on synthesis and mobilization.[2] These effects are more pronounced in cases of thyroid dysfunction with higher lipid levels in hypothyroidism and lower lipid levels in hyperthyroidism.[3] These changes are also noticeable in cases of subclinical thyroid dysfunction as well.[4] The impact of thyroid dysfunction on lipid levels is usually reversible with treatment.[5] While the effect of TH and TSH on lipid levels in thyroid dysfunction is well established, their impact on lipid levels among euthyroid population remains controversial.[6–10]

Recently, acquired mild resistance to TH has been postulated as a contributor to metabolic syndrome, including dyslipidemia, in the general population.[11] The resistance to TH can be central (at the level of pituitary) or peripheral (at tissue level). The sensitivity to thyroid hormones can be indirectly assessed through composite indices derived from routine thyroid function tests. The central sensitivity to thyroid hormones can be assessed with the help of TSH index (TSHI), the Thyroid Feedback Quantile-based Index (TFQI) index, and the thyrotrophic T4 resistance index (TT4RI), while peripheral sensitivity to thyroid hormones can be inferred from the free T3/free T4 ratio (fT3/fT4 ratio).[11,12] Higher values of these indices have been shown to be associated with obesity, diabetes, and hypertension among the euthyroid population in previous studies.[11,13] The possible pathogenic association of thyroid insensitivity with altered lipid metabolism has been highlighted by previous studies showing a positive association of thyroid insensitivity with dyslipidemia and metabolic dysfunction associated with steatotic liver disease (MASLD).[13]

In this study, we tried to assess the potential relationship between TH, TSH, and indices of thyroid sensitivity (fT3/fT4 ratio and TSHI) with different components of lipid profile among the euthyroid population.

Materials and Methods

This cross-sectional observational study was carried out in a tertiary care hospital in Southern India over a period of ten months from March 2023 to December 2023. The study subjects were mostly patients attending our medicine outpatient department. All consenting apparently healthy adults aged more than 19 years of both sexes were included. Subjects with a previous history of any known thyroid illness were excluded from the study. Subjects who were taking medications that directly or indirectly affect TH (such as steroids, interferons, amiodarone, lithium, etc.) or lipid levels (such as anti-lipid therapies) were also excluded from this study.

In a similar previous study from South India, Gopalakrishnan et al.[14] had shown the correlation coefficient between TSH and triglyceride (TG) to be 0.675 (r-square = 0.45). Assuming a similar level of correlation coefficient, for a total of eight study variables, the minimum sample size for 80% power at 5% level of significance of the study was calculated to be around 70. We included a total of 100 subjects in our study.

After informed consent from the participants, a detailed case history with demographic data was obtained. A fasting blood sample was collected and centrifuged for serum separation. Separated serum was stored at –20°C. Serum fT3, fT4, and TSH levels were measured using chemiluminescence immunoassay (CLIA). Fasting lipid profile, including total cholesterol (TC), TG, HDL, LDL, and VLDL cholesterol levels, was measured using a fully automated analyzer (Roche cobas c311-Enzymatic colorimetric method).

The following formulas were employed for calculating indices of TH sensitivity: TSHI = Ln TSH (µIU/mL) + 0.1345 × fT4 (pmol/L). TSHI is inversely proportional to central sensitivity to TH (the higher the value of TSHI, the lower the central sensitivity to TH). fT3/fT4 ratio = fT3 (pmol/L)/fT4 (pmol/L). The fT3/fT4

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ratio is directly proportional to peripheral TH sensitivity, indicating a higher ratio corresponds to greater peripheral sensitivity to TH.[15,16]

All statistical analyses were performed using SPSS 25th version software. Mean ± standard deviation (SD) was used to express continuous variables. The correlation analysis between lipid levels and TH was done using Pearson's correlation method. All tests were two-tailed, and a *p*-value less than 0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of our institution, Trichy SRM Medical College Hospital and Research Centre, vide letter no. LII-IRB-09 dated 05 April 2023.

Results

We included 100 subjects, with 60 male and 40 female participants, in this study. Table 1 shows the demographic, anthropometric, and biochemical parameters of study participants. We found no significant difference with regard to any of the studied parameters in both sexes. The results of correlation analysis between measured and derived parameters of thyroid function with different parameters of lipids are shown in Table 2. We found a significant positive correlation of HDL cholesterol with fT3 (r = 0.4, p = 0.01), fT4 (r = 0.3, p = 0.04) and fT3/fT4 ratio (r = 0.5, p < 0.001). fT3 also showed a significant negative correlation with TC (r = −0.3, p = 0.04). We did not find any correlation between TSH and any of the studied lipid parameters.

We also performed subgroup analysis based on gender and TSH levels. We arbitrarily chose 3 µIU/mL as the TSH cut-point for subgroup analysis, as it led to even distribution of subjects in both groups (less than 3 µIU/mL = 48 subjects; ≥ 3 µIU/mL = 52 subjects). Table 3 shows the results of correlation analysis between thyroid and lipid parameters among men versus women. The statistically significant positive correlation of fT3 (r = 0.6, p = 0.008), fT4 (r = 0.4, p = 0.04), and fT3/fT4 ratio (r = 0.8, p < 0.001) with HDL cholesterol was seen only in men, while the positive association did not reach statistical significance among women. We found a significant positive correlation of TSH with TC in men (r = 0.7, p < 0.001) and LDL cholesterol in both men (r = 0.6, p = 0.001) and women (r = 0.5, p = 0.04).

Table 1: Demographic, anthropometric, and biochemical parameters of the study population

Parameters	*Men (n = 60)*	*Women (n = 40)*	*Overall*	*p-value*
Age (years)	48.9 ± 16.1	51.9 ± 10.3	50.4 ± 13.2	0.6
BMI (kg/m^2)	28.0 ± 1.0	28.8 ± 0.8	28.4 ± 0.9	0.8
Total cholesterol (mg/dL)	158.8 ± 46.3	176.7 ± 45.6	166.9 ± 46.4	0.2
Triglycerides (mg/dL)	152.1 ± 81.2	162.8 ± 93.4	157 ± 86.2	0.7
HDL (mg/dL)	39.6 ± 17.6	38.8 ± 12.4	39.2 ± 15.3	0.9
LDL (mg/dL)	91.3 ± 43.6	108.7 ± 36.9	99.2 ± 41.2	0.2
VLDL (mg/dL)	31.7 ± 15.8	29.9 ± 14.7	30.9 ± 15.2	0.7
Free T3 (pg/mL)	2.5 ± 0.6	2.4 ± 0.5	2.4 ± 0.5	0.4
Free T4 (ng/dL)	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.4
TSH (µIU/mL)	2.9 ± 1.7	3.2 ± 1.5	3.0 ± 1.6	0.6
Free T3/free T4 ratio	2.0 ± 0.6	2.0 ± 0.6	2.0 ± 0.6	0.9
TSH index	1.1 ± 0.5	1.3 ± 0.4	1.1 ± 0.7	0.2

Table 2: Results of correlation analysis between measured and derived parameters of thyroid function with different parameters of lipids

Thyroid parameters	*Correlation coefficient (p-value in parentheses)*				
	Total cholesterol	*Triglyceride*	*HDL*	*LDL*	*VLDL*
Free T3 (pg/mL)	−0.3 (0.04)*	−0.1 (0.2)	0.4 (0.01)*	−0.3 (0.1)	−0.2 (0.2)
Free T4 (ng/dL)	−0.2 (0.2)	0.1 (0.7)	0.3 (0.04)*	−0.2 (0.3)	−0.1 (0.5)
TSH (µIU/mL)	0.2 (0.1)	0.04 (0.8)	0.2 (0.1)	0.2 (0.2)	0.1 (0.9)
Free T3/T4 ratio	−0.1 (0.5)	−0.1 (0.4)	0.5 (0.001)*	−0.2 (0.3)	−0.1 (0.7)
TSH index	0.1 (0.7)	0.1 (0.4)	0.1 (0.5)	0.1 (0.6)	0.1 (0.4)

*p-value < 0.05

Table 3: Results of correlation analysis between thyroid and lipid parameters among men versus women

Thyroid profile	*Correlation coefficient (p-value in parentheses)*									
	TC		*Triglyceride*		*HDL*		*LDL*		*VLDL*	
	Men	*women*	*Men*	*women*	*Men*	*Women*	*Men*	*women*	*Men*	*women*
Free T3	−0.2 (0.3)	−0.3 (0.1)	−0.2 (0.5)	−0.3 (0.3)	0.6 (0.008)*	0.09 (0.7)	−0.2 (0.5)	−0.4 (0.1)	−0.2 (0.5)	−0.3 (0.3)
Free T4	−0.4 (0.1)	0.01 (0.9)	−0.2 (0.3)	0.3 (0.2)	0.4 (0.04)*	−0.2 (0.4)	−0.2 (0.3)	−0.02 (0.9)	−0.2 (0.3)	0.1 (0.7)
TSH	0.7 (<0.01)*	−0.4 (0.07)	0.2 (0.3)	−0.2 (0.4)	0.3 (0.09)	0.1 (0.8)	0.6 (0.01)*	0.5 (0.04)*	0.1 (0.5)	−0.2 (0.4)
fT3/fT4	0.03 (0.9)	−0.3 (0.3)	0.03 (0.9)	−0.3 (0.2)	0.8 (< 0.001)*	0.1 (0.6)	−0.1 (0.8)	−0.3 (0.2)	0.03 (0.9)	−0.2 (0.5)
TSH index	0.4 (0.2)	−0.4 (0.2)	−0.2 (0.5)	−0.2 (0.6)	0.4 (0.2)	−0.1 (0.6)	0.4 (0.1)	−0.5 (0.1)	−0.2 (0.5)	−0.1 (0.7)

TC, total cholesterol; fT3/fT4, free T3/free T4 ratio; *p-value < 0.05

Table 4: Results of correlation analysis between thyroid and lipid parameters between TSH subgroups (< 3μIU/mL vs ≥ 3μIU/mL)

Thyroid profile	*Correlation coefficient (p-value in parentheses)*									
	TC		*Triglyceride*		*HDL*		*LDL*		*VLDL*	
	< 3	*≥ 3*	*< 3*	*≥ 3*	*< 3*	*≥ 3*	*< 3*	*≥ 3*	*< 3*	*≥ 3*
Free T3	−0.1 (0.6)	−0.5 (0.01)*	−0.3 (0.3)	−0.2 (0.4)	0.3 (0.2)	0.5 (0.02)*	0.04 (0.9)	−0.7 (0.001)*	−0.3 (0.2)	−0.2 (0.4)
Free T4	−0.1 (0.5)	−0.3 (0.2)	0.4 (0.1)	−0.1 (0.5)	−0.3 (0.2)	−0.3 (0.1)	−0.3 (0.3)	−0.1 (0.7)	−0.1 (0.9)	−0.1 (0.5)
TSH	0.2 (0.3)	0.4 (0.1)	0.2 (0.4)	0.4 (0.1)	0.1 (0.6)	0.3 (0.1)	0.2 (0.3)	0.2 (0.5)	−0.1 (0.6)	0.4 (0.1)
fT3/fT4	−0.1 (0.8)	−0.2 (0.5)	−0.4 (0.1)	0.1 (0.8)	0.4 (0.1)	0.6 (0.003)*	0.1 (0.6)	−0.4 (0.1)	−0.3 (0.2)	0.1 (0.8)
TSH index	0.1 (0.8)	0.3 (0.1)	0.3 (0.2)	0.5 (0.03)*	0.01 (0.9)	0.2 (0.3)	0.1 (0.8)	0.1 (0.6)	0.2 (0.5)	0.5 (0.02)*

TC, total cholesterol; fT3/fT4, free T3/free T4 ratio; *p-value < 0.05

Table 4 shows the results of the correlation analysis between thyroid and lipid parameters across TSH subgroups (< 3 μIU/mL vs ≥ 3 μIU/mL). Again, fT3 showed statistically significant positive correlation with HDL ($r = 0.5$, $p = 0.02$) and negative correlation with TC ($r = -0.5$, $p = 0.01$) and LDL ($r = -0.7$, $p = 0.001$) in TSH ≥ 3 μIU/mL group. While fT3/fT4 ratio showed a significant positive correlation with HDL ($r = 0.6$, $p = 0.003$) in TSH ≥ 3 μIU/mL group. TSH index showed positive correlation with TG ($r = 0.5$, $p = 0.03$) and VLDL ($r = 0.5$, $p = 0.02$) in the subgroup with TSH ≥ 3 μIU/mL. There was no association noted between any of the studied thyroid and lipid parameters in the TSH < 3 μIU/mL group.

Discussion

Overall, fT3, fT4, and fT3/fT4 ratio show consistent positive association with HDL cholesterol, especially in men and subjects with TSH ≥ 3 μIU/mL. FT3 also showed significant negative correlation with total cholesterol.

TH plays a vital physiological role in regulating the production, transport, and breakdown of lipids. They impact lipid metabolism by binding to TH receptors (THR), mainly THRβ isoforms, which are highly expressed in liver. TH directly enhances lipid synthesis in liver by inducing the expression of rate-limiting enzyme in cholesterol synthesis, HMG-COA reductase (HMGCR).[17] They can also promote lipogenesis indirectly by enhancing expression of transcription factors involved in lipid synthesis such as carbohydrate response element-binding-protein (ChREBP) and the sterol regulatory element-binding protein 1c (SREBP1c), etc.[18] On the other hand, TH promotes catabolism of TG in white adipose tissue as well as in liver by promoting activity of adipose triglyceride lipase and hepatic lipase, respectively. TH also upregulates expression of key enzymes involved in fatty acid β-oxidation in the liver, such as carnitine O-palmitoyl transferase 1 liver isoform (CPT1-Lα), pyruvate dehydrogenase kinase isoform 4 (PDK4), medium-chain acyl-CoA dehydrogenase (MCAD), and uncoupling protein 2 (UCP2).[19] TH also plays a vital role in the turnover of serum cholesterol levels via synthesis and export of cholesterol in the form of LDL from liver, reverse transporting cholesterol from peripheral tissues, reuptake of cholesterol via hepatic LDL receptors and conversion of cholesterol into bile acids for excretion into the intestine.[20]

Previous studies have shown contradictory and inconsistent impact of TH and TSH on lipid profile in euthyroid adults. Most studies have focused only on TSH and fT4. Only very few studies have included fT3 in the analysis. TSH has shown a consistent positive association with TC, TG, and LDL cholesterol in previous studies.[9,10] Even TSH levels in the high normal range have been shown to be associated with dyslipidemia and other components of metabolic syndrome among euthyroid subjects.[10,21,22] The causality of these findings has been proven in a few Mendelian randomization studies as well.[23,24] Overall, we found no association of TSH with any of the lipid parameters in this study. But we did find a positive association of TSH with LDL in both sexes and with TC in men alone.

After TSH, fT4 has been shown consistently to impact lipid parameters among euthyroid adults in previous studies. Most studies have found a negative association of fT4 with TC, TG, and LDL.[6–10] Low normal fT4 has been shown to be associated with atherogenic lipid profile,[7,10] insulin resistance[8] and components of metabolic syndrome.[6] Lower fT4 among euthyroid subjects has shown a causal association with increased TC and LDL in a Mendelian randomization study.[24] We did not observe any association of fT4 with TC, TG, and LDL cholesterol overall, as well as in subgroup analysis. But fT4 showed a positive association with HDL cholesterol, especially in men. Only few studies have shown a similar association of fT4 with HDL,[8,10] while others have failed to show any association.

fT3 is the only thyroid parameter in our study that showed a consistent positive association with HDL, more so in men and in euthyroid subjects with TSH ≥ 3 μIU/mL. We also found a negative correlation of fT3 with TC. These findings contradict results from previous studies, which usually found high fT3 to be associated with an unfavorable lipid profile characterized by lower HDL and higher TC.[9,10] The difference in ethnicity and anthropometric characteristics of our study population could be the reason for this contradictory observation. Our study subjects had higher body mass index (BMI) compared to previous studies, and BMI has been found to be a major confounding factor in assessing the association of thyroid parameters with lipids in euthyroid subjects.[10]

Another interesting finding of our study is that HDL seems to be the most affected lipid parameter, showing consistent association with most thyroid parameters, unlike previous study results.[6–10] Though TH significantly impacts HDL metabolism, they show inconsistent association with HDL levels because TH affects both synthesis and catabolism of HDL cholesterol.[25] TH strongly promotes reverse cholesterol transport. TH increases cholesterol efflux from peripheral tissues and macrophages to HDL by inducing the expression of ApoA1 and ATP-binding cassette transporter A1 protein, respectively. On the other hand, TH promotes HDL degradation by stimulating hepatic lipase.[26]

We calculated the fT3/fT4 ratio and TSHI to assess peripheral and central TH sensitivity, respectively. Overall, we observed a significant positive association of the fT3/fT4 ratio with HDL levels. This association was noted only among men and subjects with TSH ≥ 3 μIU/mL in subgroup analysis. Similar findings were noted in some studies where a higher fT3/fT4 ratio was associated with a favorable lipid profile,[16,27] while other studies have shown contradictory results.[9,11–13] Subjects with established dyslipidemia-associated comorbidities, such as morbid obesity, NAFLD, usually have higher fT3 and fT3/fT4 ratio. The increase in fT3 in these conditions is generally regarded as a failed adaptive response. This may explain the association of the fT3/fT4 ratio with unfavorable lipid profiles in studies where the participants had advanced

diseases, such as morbid obesity or NAFLD.[12,13] Unlike the fT3/fT4 ratio, TSHI has shown a consistent association with an unfavorable lipid profile in previous studies.[16] In our study, TSHI showed a positive correlation with TG and VLDL cholesterol in the subgroup with TSH ≥ 3 µIU/mL.

In subgroup analysis, most observed associations between thyroid and lipid levels were seen only in men. One plausible explanation for this gender difference could be sex hormone-related discrepancy in the TSH-fT3 feedback and differential effects of sex hormones on TH metabolism.[28] In our study, the majority (97%) were premenopausal women. All the noted significant associations of thyroid parameters with lipid levels were significant only in subjects with TSH ≥ 3µIU/mL in our study. We hypothesize that subjects with TSH ≥ 3µIU/mL may have mild acquired TH resistance and TH may impact lipid levels significantly only in these subjects.

Our study had a few limitations. Thyroid autoantibody levels were not measured, and previous studies have shown that antithyroid peroxidase antibody status could compound association of thyroid parameters with lipid levels among euthyroid subjects.[7] Our findings need validation in further large-scale studies. Association does not imply causation, as is the case with any observational research. We could not perform logistic regression analysis due to small sample size of our study.

Conclusion

To conclude, we found a significant association of thyroid parameters with lipid levels, especially with HDL cholesterol. We observed higher fT3, higher fT4, higher fT3/fT4 ratio, lower TSH, and lower TSHI associated with an unfavorable lipid profile, characterized by higher TC, TG, LDL, VLDL, and lower HDL levels. Resmetirom, an oral, liver-directed, thyroid hormone receptor beta-selective agonist, has recently been approved for treatment of adults with non-alcoholic steatohepatitis (NASH) with moderate to advanced liver scarring (fibrosis).[29] Similarly, in the future, hepato-selective T3 or T4 analogs could be employed for treating dyslipidemia, considering their intimate association with lipid parameters.

Source of Support

Nil.

Conflicts of Interest

None.

Acknowledgments

None.

Authors' Contribution

SRS was responsible for patient management, data analysis, manuscript drafting, and revisions. VA handled analysis, manuscript drafting, and revisions. MM and PK managed patients, collected and analyzed data, and drafted and revised the manuscript.

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ORIGINAL ARTICLE

Perioperative FLOT Chemotherapy in Resectable Gastric Adenocarcinoma: A Single-center Retrospective Observational Study

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Abstract

Introduction: Gastric cancer (GC) is a leading cause of cancer-related mortality worldwide. Perioperative chemotherapy improves tumor downstaging and survival rates. The FLOT regimen was proven superior in the FLOT4-AIO trial, establishing it as the standard care for resectable gastric adenocarcinoma. Despite these encouraging results from randomized controlled trials, real-world data on the feasibility and outcomes of FLOT in diverse patient populations, particularly in low- and middle-income settings, remain limited. This study aimed to assess the feasibility, safety, and clinical outcomes of perioperative FLOT chemotherapy in patients with resectable gastric adenocarcinoma at a tertiary care center.

Materials and methods: We conducted a retrospective review of the medical records of patients diagnosed with resectable gastric adenocarcinoma who received perioperative FLOT chemotherapy between April 2019 and April 2025. The primary outcomes were the feasibility of perioperative FLOT chemotherapy and pathological complete response (pCR). The secondary outcomes were surgical outcomes, treatment adherence, and adverse events (AEs).

Results: The results showed that 64.4% of patients completed at least four cycles of neoadjuvant FLOT, while only 24.4% underwent surgical resection. No pathological complete responses were observed. Grade 3–4 AEs occurred in 18.1% of patients, primarily cytopenias. A high rate of loss to follow-up (45.4%) was noted in the preoperative phase.

Conclusion: While FLOT demonstrated an acceptable safety profile, the lower-than-expected surgical resection rate and high attrition highlight the challenges in managing locally advanced gastric cancer in real-world settings. This study emphasizes the need for strategies to improve treatment adherence and optimize patient selection to maximize the benefits of perioperative chemotherapy for gastric cancer.

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Introduction

Gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide despite global advances in early detection and treatment strategies. According to GLOBOCAN 2022, GC ranks fifth in terms of incidence and cancer-related deaths,[1] with the highest burden reported in East Asia, Eastern Europe, and parts of South America. The prognosis of patients with GC is largely determined by the stage of the diagnosis. Unfortunately, a substantial proportion of patients present with locally advanced disease beyond the scope of immediate curative resection.

Surgical resection with adequate lymphadenectomy remains the cornerstone of curative-intent therapy for gastric adenocarcinomas. However, surgery alone yields suboptimal long-term outcomes due to the high risk of micrometastatic spread and disease recurrence. Consequently, multimodal treatment strategies have evolved to improve survival outcomes. The integration of perioperative or neoadjuvant chemotherapy into the treatment paradigm has shown significant benefits in terms of tumor downstaging, increased R0 resection rates, and improved overall survival.

The concept of perioperative chemotherapy was first validated in the pivotal MAGIC trial,[2] which demonstrated a survival advantage with the use of epirubicin, cisplatin, and 5-fluorouracil (ECF) compared to surgery alone. Subsequently, other regimens such as DCF (docetaxel, cisplatin, 5-FU) and FOLFOX (oxaliplatin, 5-FU, leucovorin) were explored, but their benefits were limited by their toxicity profiles or modest efficacy.

The FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) regimen has emerged as a superior alternative. The FLOT4-AIO trial[3] demonstrated that perioperative FLOT significantly improved overall survival (OS) (median OS 50 months vs 35 months) and pathological complete response (pCR) rates compared with ECF/ECX, with acceptable tolerability. These findings established FLOT as the standard of care for patients with resectable, locally advanced gastric or gastroesophageal junction adenocarcinoma.

Despite these encouraging results from randomized controlled trials, real-world data on the feasibility and outcomes of FLOT in diverse patient populations, particularly in low- and middle-income settings, remain limited. Differences in patient demographics, comorbidities, nutritional status, and access to supportive care can significantly influence treatment tolerance and survival outcomes. Therefore, evaluating the applicability of the FLOT regimen outside controlled trial environments is essential for understanding its true clinical impact.

This study aimed to assess the feasibility, safety, and clinical outcomes of perioperative FLOT chemotherapy in a real-world cohort of patients with resectable gastric adenocarcinoma treated at a tertiary care center.

Materials and Methods

Study Design and Population

This single-center retrospective observational study was conducted between April 2019 and April 2025 at a tertiary center. Data were collected from patients with resectable gastric adenocarcinoma who received perioperative FLOT chemotherapy as part of standard clinical practice.

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Eligible patients were aged 18–80 years with histologically confirmed gastric adenocarcinoma of clinical stage cT2 or higher and/or nodal involvement, according to the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor–Node–Metastasis (TNM) classification. Clinical staging was performed using contrast-enhanced computed tomography (CT), upper gastrointestinal endoscopy with biopsy, and/or 18F-FDG positron emission tomography (PET) scans.

Patients with clinical stage T1 disease, distant metastases, or nonadenocarcinoma histology were excluded from the study.

Chemotherapy Regimen

All patients received perioperative FLOT chemotherapy, consisting of the following:

- 5-fluorouracil (2600 mg/m^2).
- Leucovorin (200 mg/m^2).
- Oxaliplatin (85 mg/m^2).
- Docetaxel (50 mg/m^2).

These were administered intravenously on day 1 of each 14-day cycle. Treatment delays or dose modifications were permitted at the discretion of the treating oncologist, based on toxicity, patient tolerance, or drug availability.

Outcome Measures

Primary Outcomes

The feasibility of perioperative FLOT chemotherapy was defined as the completion of at least four cycles.

Pathological complete response was defined as the absence of viable tumor cells on histopathological examination after neoadjuvant chemotherapy.

Secondary Outcomes

Surgical outcomes, treatment adherence, and adverse events (AEs) were also analyzed. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Radiological response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Statistical Analysis

Demographic, clinical, and treatment-related variables were summarized using descriptive statistics. Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as medians with ranges. Statistical analysis was performed using the Jamovi software.

Results

Patient characteristics: Between April 2019 and April 2025, 44 patients received the neoadjuvant FLOT regimen. The patient characteristics are summarized in Table 1.

Twenty-seven patients (73%) were male, and 17 (27%) were female. The median age of the patients was 56 years (range, 26–71 years). The percentage of patients ≥56 years was 51%. Patients having comorbidities were 17 (37.7%), had comorbidities with a predominance of hypertension (20%) and diabetes (6%). 9 patients had hypertension (20%), 3 patients had type 2 diabetes (6%), and 3 patients had hypothyroidism (6%). One patient reported CAD with post-CABG status. One patient had CKD and was on medical management.

The most common clinical presentation was abdominal pain (48%) and weight loss (38%). Six patients reported recurrent vomiting (13%), four patients (8%) presented with gastric outlet obstruction, three patients had a history of melena (6%), two patients had dysphagia (4%), and one patient presented with incidental iron deficiency anemia (2%) (Table 2).

According to the Lauren classification, the histological type on diagnostic biopsy was diffuse-type adenocarcinoma noted in two patients (4%). The predominant histological grade was moderately differentiated adenocarcinoma, seen in 16 (51%) patients, with well differentiated histology in 3 (7%), poorly differentiated histology in 18 (29%), and 8 patients (18.2%) had signet ring cell histology. At the time of initial diagnosis, clinical stage T3–4 was reported in 87% (n = 29) of patients and nodal involvement in 80% (n = 41).

All patients were in good clinical condition, with an ECOG performance status (PS) of 0 or 1.

In the preoperative phase, 32 of 44 patients (64.4%) received at least four cycles of FLOT chemotherapy, regardless of dose reduction. Dose reduction or deintensification was performed in one patient (2%). Treatment delays occurred in two patients due to drug unavailability during the COVID period. The remaining 12 patients did not complete the entire treatment regimen.

Among the 32 patients who completed at least four FLOT cycles, 10 (24.4%) underwent surgical resection. Eight patients (22.2%) underwent total gastrectomy with D2 lymph node dissection (LND), while two patients underwent partial gastrectomy without LND. None of the patients achieved a pCR.

Among the 22 patients who did not undergo surgical intervention, nine experienced disease progression, six succumbed (4 due to nononcological causes and 2 as a result of febrile neutropenia with septic shock), and seven (11.1%) were lost to follow-up during the preoperative phase (2 due to symptom improvement, 1 due to apprehension regarding surgery, and 2 due to the prohibitive travel distances).

Table 1: Baseline characteristics

Characteristics	
Median age	56 years (26–71)
Gender	Male: 73%, Female: 27%
Comorbidities	37.7%
Hypertension (HTN)	20%
Diabetes	6%

Table 2: Symptoms at presentation

Symptoms	*Frequency (%)*
Abdominal pain	48
Weight loss	38
Recurrent vomiting	13
Gastric outlet obstruction	8

Among the cohort of 44 patients, 12 did not complete the four planned cycles of neoadjuvant FLOT therapy. Specifically, three patients underwent only one cycle, two patients completed two cycles, and seven patients received three cycles before becoming lost to follow-up. The reasons for this loss to follow-up were varied: symptom improvement (three patients), apprehension regarding surgery (two patients), fear of chemotherapy (three patients), preference for alternative or traditional medicine (one patient), and unspecified reasons for the remaining patients. Despite numerous attempts to contact these individuals through various communication channels, they remained unreachable (Fig. 1).

A total of 10 patients underwent adjuvant FLOT chemotherapy. Of these, six patients completed all four cycles, while two patients received two cycles, and two patients received one cycle. Among those who received fewer than four cycles of chemotherapy, one patient was lost to follow-up, and three patients experienced disease progression and subsequently received second-line CAPIRI chemotherapy.

Grade 3–4 adverse events (AEs) were observed in eight patients (18.1%). Cytopenias were the most frequently reported grade 3–4 AEs, with an incidence of 13.6%. Febrile neutropenia occurred in five patients, among whom two succumbed to progression to septic shock. Additionally, three patients required packed red blood cell (PRBC) transfusions following two cycles of chemotherapy. Intractable hiccups were documented in one patient, particularly during the initial two cycles of neoadjuvant FLOT chemotherapy.

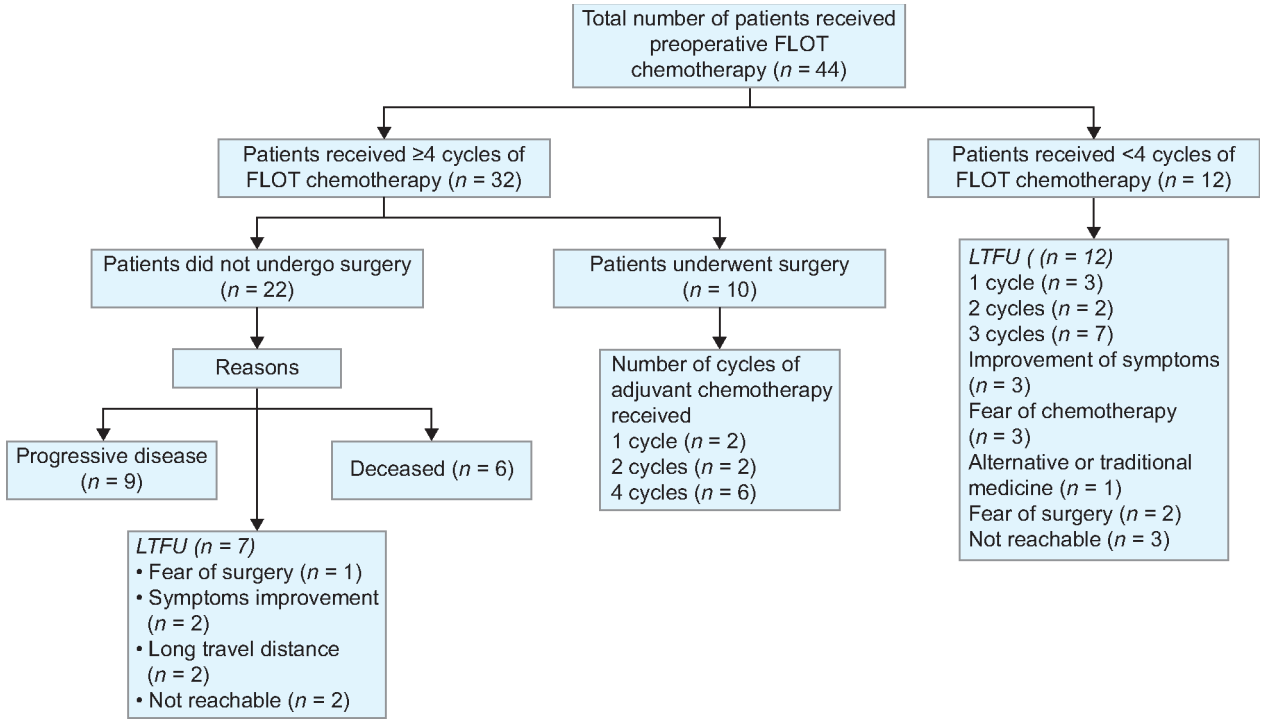

Fig. 1: Flow diagram of patient selection and treatment outcomes in patients receiving perioperative FLOT chemotherapy

Of the 44 patients, 20 (45.4%) were lost to follow-up. The primary reasons for this attrition were psychosocial factors, including fear of chemotherapy (n = 3) and fear of surgery (n = 2); socioeconomic factors, such as long travel distances (n = 2); and disease-related factors, such as improvement in symptoms (n = 1). Additionally, 20 patients could not be reached.

Discussion

This study aimed to assess the efficacy and safety of the neoadjuvant FLOT chemotherapy regimen in patients with locally advanced gastric cancer (GC), focusing on clinical outcomes, patient characteristics, surgical resection rates, and adverse events (AEs). Our findings are discussed in the context of published data on FLOT, particularly regarding patient demographics, chemotherapy adherence, surgical outcomes, and toxicity profiles.

The cohort consisted of 44 patients with a median age of 56 years, reflecting the typical age range of patients presenting with gastric cancer. A slight male predominance was observed, with 73% of patients being male, which is consistent with the established sex disparity in gastric cancer incidence. This sex distribution is commonly observed in Western and Asian populations, where men are more likely to be diagnosed with GC, particularly in advanced stages.[24]

In terms of comorbidities, 37.7% of the patients had at least one comorbidity, with hypertension (HTN) being the most common comorbidity (20%). These findings are consistent with other reports that suggest that cardiovascular disease is prevalent in patients with advanced gastric cancer.[5,6] The presence of comorbidities could complicate treatment strategies, especially in elderly patients, and may contribute to treatment delays or dose reductions, as was observed in 2% of our cohort.

The symptom profile in this cohort was also consistent with that typically seen in gastric cancer, with abdominal pain (48%) and weight loss (38%) being the most common presenting complaints. This is in line with the clinical presentation noted in other studies, where weight loss and abdominal discomfort were reported in the majority of patients with locally advanced GC.[7]

Histologically, moderately differentiated adenocarcinoma was the most common subtype (51%), followed by poorly differentiated adenocarcinoma (29%). This distribution aligns with the findings of large cohort studies, in which the majority of gastric cancers are classified as moderately or poorly differentiated.[8] Additionally, signet ring cell carcinoma, which is known for its poor prognosis, was observed in 18.2% of our patients, which is consistent with the expected incidence in gastric cancer cohorts.

At the time of diagnosis, the majority of patients (87%) were classified as having clinical stage T3–4 disease, and 80% had nodal involvement, underscoring the advanced nature of the disease at presentation. These findings reflect the late-stage diagnosis of GC, which is common because of nonspecific early symptoms and a lack of effective screening strategies.

In our cohort, 64.4% of the patients (32/44) received at least four cycles of FLOT chemotherapy. This adherence rate is comparable to that of the FLOT4 trial, in which over 60% of the patients completed the full course of neoadjuvant therapy. However, we observed a relatively high rate of progression or loss to follow-up during the preoperative phase, with nine patients progressing, six patients dying, and seven patients lost to follow-up. These figures highlight the challenges in managing high-risk populations with advanced disease, especially when combined with the socioeconomic and psychosocial barriers noted in our cohort.

Surgical resection was performed in 24.4% of the patients (10/32), which is lower than the 40–50% resection rates typically reported in large multicenter studies on neoadjuvant chemotherapy.[3] This discrepancy may be attributable to the high proportion of patients with metastatic disease discovered intraoperatively (two patients) or disease progression (seven patients) during treatment, highlighting the aggressive nature of advanced gastric cancer. In terms of resection type, eight patients underwent total gastrectomy, and two underwent partial gastrectomy, which aligns with typical surgical strategies based on tumor location and extent

of disease. Notably, no patient achieved a pathological complete response (ypT0), suggesting that although neoadjuvant FLOT therapy may reduce tumor burden, it does not guarantee a complete pathological response.

The safety profile in our cohort was consistent with the FLOT literature. The most commonly reported grade 3–4 adverse event (AE) was cytopenia (13.6%), which is a well-known dose-limiting toxicity of FLOT chemotherapy.[3,9] The need for blood transfusion in three patients and the occurrence of intractable hiccups in one patient, particularly during the first two cycles, were notable. The latter finding of hiccups is a rare but well-documented side effect of the FLOT regimen, and its occurrence may be more pronounced in the initial cycles of chemotherapy.[10]

Overall, the data from our cohort are in line with the findings from major studies, such as the FLOT4 trial, which demonstrated the efficacy of neoadjuvant FLOT chemotherapy in improving resectability in patients with locally advanced gastric cancer. However, the relatively low surgical resection rate and high rate of progression in our study suggest that while neoadjuvant FLOT is effective in downstaging tumors, not all patients achieve a sufficient tumor response to warrant surgery. This underlines the importance of refining patient selection and considering additional treatment modalities, including targeted therapies or immunotherapies, to improve the pathological completion rates.

Loss to follow-up (LTFU) represents a major barrier to optimal cancer care delivery, particularly in prolonged multimodal regimens, such as perioperative FLOT chemotherapy for gastric cancer. In this study, 45.4% of patients were lost to follow-up during the preoperative phase, despite initiating neoadjuvant chemotherapy. This high attrition rate adversely affected treatment completion, surgical resection rates, and overall clinical outcome assessments.

The causes of LTFU in this cohort were multifactorial, encompassing psychosocial, socioeconomic, disease-related, and healthcare system-related factors. Psychosocial causes included fear of surgery and chemotherapy, reflecting a limited understanding of disease prognosis and treatment intent. Symptom improvement following the initial chemotherapy cycles also contributed to discontinuation, suggesting a perceived resolution of the disease once the immediate symptoms subsided. Socioeconomic barriers, such as long travel distances, were additional contributors, reflecting the realities of treatment adherence in low- and middle-income countries. These findings align with prior studies identifying financial toxicity, geographical constraints, and limited health literacy as major determinants of nonadherence among oncology patients.[11,12]

Earlier reports on gastrointestinal malignancies have documented variable LTFU rates and follow-up completeness, with higher attrition in resource-limited settings.[13,14] The LTFU rate observed in the present study exceeds these figures, underlining the systemic challenges in maintaining continuity of care during perioperative chemotherapy. The long treatment duration, frequent hospital visits, and need for nutritional and psychosocial optimization may cumulatively contribute to patient fatigue and disengagement from care.

Loss to follow-up not only introduces attrition bias in outcome assessment but also has direct clinical implications. Patients who discontinue therapy prematurely are deprived of potential curative surgical interventions, which may negatively influence overall survival and disease control. Moreover, incomplete data regarding disease progression and treatment-related outcomes limit the generalizability of real-world evidence on FLOT efficacy. Therefore, addressing LTFU is essential for improving patient outcomes and the validity of clinical research.

Strategies to mitigate LTFU include implementing structured follow-up systems, patient navigation programs, and teleoncology models to maintain communication with patients from remote areas. Enhancing patient education regarding the importance of completing multimodal therapy, providing financial and travel assistance, and strengthening community-level cancer care networks may improve patient adherence. Incorporating psychosocial counseling and multidisciplinary support from oncologists, nurses, social workers, and psychologists can further alleviate fear and misinformation contributing to treatment discontinuation.

In summary, the high rate of LTFU observed in this study underscores the critical challenge in real-world gastric cancer management. Multifaceted interventions addressing patient, social, and systemic barriers are necessary to improve adherence, optimize treatment outcomes, and enhance the overall success of perioperative chemotherapy programs.

This study had several limitations. As this was a retrospective, single-center analysis with a small sample size, the findings may not be generalizable to broader populations. The high rate of loss to follow-up may have introduced attrition bias and limited the accurate assessment of survival and resection outcomes of the study.

Conclusion

Neoadjuvant FLOT chemotherapy remains the standard treatment for locally advanced gastric cancer with a potential for tumor downstaging. However, the lower-than-expected surgical resection rate and absence of pathological complete responses in our cohort highlight the aggressive nature of the disease and the need for improved treatment strategies to optimize patient outcomes.

Loss to follow-up was a key determinant of suboptimal outcomes, reflecting multifaceted psychosocial, economic, and systemic barriers to care. Addressing this requires a comprehensive, patient-centered approach that includes structured follow-up programs, tele-oncology services, financial and travel support, and improved patient education regarding treatment intent and benefits of treatment. By implementing such measures, healthcare systems can enhance adherence, reduce attrition, and ultimately improve patient outcomes and the success of treatment programs.

We propose that upfront surgery followed by adjuvant therapy may not be an inadequate treatment option for patients in this setting, particularly those who are likely to be noncompliant. Further prospective studies are required to substantiate this hypothesis.

Source of Support

Nil.

Conflict of Interest

None.

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ORIGINAL ARTICLE

An Attempt to Achieve Holistic Health by Improving Spiritual, Emotional, and Psychological Wellbeing: A Clinical Trial Using an Eastern Spirituality-based Intervention in Indian Context

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Abstract

Background and aims: Spirituality is an important fourth dimension of health. Spiritual wellbeing is a subconstruct of spirituality and an important contributor to overall wellbeing. Health cannot be conceived as "holistic" without including "spiritual wellbeing." The researchers attempt to look at the effects of an Eastern spirituality-based intervention on spiritual, emotional, and psychological wellbeing to achieve holistic health.

Methods: A total of 140 participants were randomized to attend either 6 "spirituality" sessions (1 session each week) or "usual care" pseudo sessions. The outcome parameters were measured pre- and postintervention. The spiritual wellbeing was measured by Spiritual Wellbeing Scale (SWBS) and WHO quality of life: spirituality, religiousness, and personal beliefs scale (WHOQOL-SRPB). Emotional wellbeing was measured by Depression, Anxiety, and Stress Scale (DASS-21), and psychological wellbeing by WHO-5 Wellbeing Scale. Repeated measures ANOVA tests were used for statistical analysis.

Results: The spirituality sessions improved the SWBS scores (treatment effect size: medium, $\eta p^2 = 0.1253$) and WHOQOL-SRPB scores (treatment effect size: small, $\eta p^2 = 0.04952$) significantly. In addition, DASS-21 scores: S stress (treatment effect size: medium, $\eta p^2 = 0.09784$), A anxiety (treatment effect size: medium, $\eta p^2 = 0.08542$), and D depression (treatment effect size: medium, $\eta p^2 = 0.0761$), and WHO-5 wellbeing scores (treatment effect size: medium, $\eta p^2 = 0.112$) also improved.

Conclusion: An Eastern spirituality-based intervention improved the spiritual, emotional, and psychological wellbeing of Indian participants. Addressing spiritual wellbeing will help one toward achieving the goal of "holistic" health. Future studies will help to corroborate the results.

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Introduction

World Health Organization (WHO) has recognized spirituality as the fourth dimension of health besides physical, mental, and social dimensions. Spirituality remains a complex, multidimensional (and somewhat controversial) construct. Spirituality differs from religion, which is "an organized system of beliefs, practices, rituals, and symbols designed to facilitate closeness to the sacred or transcendent."[1] Though religion and spirituality have often been used interchangeably in some literature, for our research work, spirituality is an entirely different and distinct entity. Spirituality can be defined as one's experience of connection with oneself, with others, with nature, and with the transcendent.[2] Spirituality remains a personal search for a purpose or meaning in life, peacefulness, harmony, and well-being.[3] Spirituality can be measured from 4 aspects: general spirituality, spiritual well-being, spiritual coping, and spiritual needs.[4] Spiritual well-being is a subconstruct in spirituality most relevant in health research. Spiritual well-being is functionally defined with a horizontal dimension that refers to a sense of purpose in life, peace, and life satisfaction, and a vertical dimension that refers to the sense of well-being in relation to a higher power.[5] Spiritual well-being might be affected by external stressors like illness and bereavement and can be improved by spiritual intervention.[6]

India is a country associated with spiritual traditions for thousands of years. Spiritual beliefs, values, and practices are important in the daily lives of millions of Indians. Most Indians have a natural inclination to seek support from spiritual connectedness and use it in personal crisis. Understanding a person's spiritual beliefs and practices, their relationship with health, and attempts of modification for better outcomes are important aspects of medical research. The Eastern spirituality practiced by Indians is an entirely different and distinct entity from its western counterpart. The connection between spirituality and health has not been scientifically explored for irrational, emotional, or political reasons, leading to a major research gap.[7] But health at present times cannot be conceived as holistic without including spiritual well-being, as it coordinates the physical, mental, and social dimensions of health.[8] Spirituality needs to be immediately incorporated in both research and clinical practice to promote health and well-being in Indian context.

Most scientific literature supports a positive relationship between spirituality and mental health, but the precise character of the relationship is yet to be known.[9] Unfortunately, in India, mental health specialists are mostly oblivious to spirituality in clinical practice, though many believe it has an important role in the lives of their patients.[10] Spiritual well-being was found to be consistently associated with the quality of life.[11] The effects of spirituality on different aspects of well-being (spiritual, emotional, and psychological) need to be explored, and a bio-psycho-socio-spiritual model of health needs to be brought into the current medical practice.

Spirituality should be measured as a unique, uncontaminated construct and not by indicators of mental health.[3] The instruments used to measure spiritual well-being like Spiritual Wellbeing Scale [SWBS (Ellison)] or WHO Quality of Life: Spiritual, Religiousness and Personal Beliefs (WHOQOL SRPB) are very distinct entities (different from mental well-being scales)

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appropriate in clinical settings for health research.[4] Previous research emphasizes the need to study spiritual well-being as a separate entity and design interventions for its improvement.[12] The present researchers are Indian physicians with a special interest in spirituality. This study can be considered an early attempt at community-level application of an Eastern spirituality-based educational program and see its effect on spiritual well-being (as well as emotional and psychological well-being) in the Indian general population. Previously, the researchers have tried this spiritual intervention only on a small group of Indian clinicians, studying its effect on specifically different outcome parameters (like psychological well-being and psycho-spiritual understanding).[13]

The objective of this research was to note any improvement in spiritual well-being postintervention in Indians. Along with this, its effects on stress, anxiety, and depression [emotional well-being (measured by Depression Anxiety Stress Scale: DASS 21)] and psychological well-being (measured by WHO 5 well-being scale) were noted. A hypothesis was formed that this intervention would improve the spiritual, emotional, and psychological well-being of the participants.

Methods

Settings and Design

This research was a randomized controlled prospective trial involving participants from the Indian general population. A medical center in West Bengal, India, collaborated with a meditation institute that acted as a community center to conduct the spirituality-based intervention. The study was conducted from July to December 2023. After taking institutional ethical clearance, the study was registered with Clinical Trial Registry of India (CTRI/2023/07/055/798).

Sample Size Calculation

Assuming a standard deviation (SD) difference of 1.14, the sample size was calculated for the expected mean difference in the spirituality well-being scale from limited available previous studies (e.g., by Nikfarjam et al.[14]) with a power of >85%, using repeated measures analysis of variance (RM-ANOVA) with a type I error (α) of < 5%. The calculated sample size came to 62 in each group, and the total sample size was 124. Hence, the study was initiated with 140 participants [calculating an attrition of 10% (124 + 12.6 = 136.6)].

Participant Selection

The researchers sent out messages on social media about a 6-session spirituality-based educational program. Those interested were requested to contact the study coordinators. A total of 140 participants were screened (based on inclusion and exclusion criteria), and written informed consent was obtained. The screened participants were further interviewed by a clinical psychologist to exclude any serious mental illness (if detected, referred to mental health specialists and excluded from the study), and finally 133 were randomized to 2 groups [see Fig. 1 (CONSORT flow diagram)].

Inclusion Criteria

1. Age between 18 and 65 years.
2. Suffering from no major physical illness.
3. Suffering from no major psychiatric illness (considering declaration of participants).
4. A resident of India.

Exclusion Criteria

1. Undergoing any psychological therapy or taking any psychiatric medicines.
2. Previous experience of attending any structured spirituality program.

Randomization

Post selection, participants were randomized to either group S (attending spirituality sessions) or group C (attending usual care pseudo sessions) using a random sequence of numbers. Using SPSS software random selection procedure, the sequence was produced. A total of 133 participants were randomized into the above groups (67 in group S and 66 in group C), and a total of 128 participants (65 in group S and 63 in group C) attended all the sessions and were included in the analysis (see Fig. 1). The participants were blinded to the type of intervention they would be receiving.

Intervention

The spiritual intervention consisted of 6 sessions (1 session each week), face-to-face, of nearly 1.5 hours duration (detailed in Table 1). The goal was to be conversant with core principles of Eastern spirituality (which conceptualizes human existence as potentially divine and the purpose of life as a union with the divinity), use the teachings for positive coping, and to achieve wellness. Positive virtues like acceptance, gratitude, and compassion were discussed

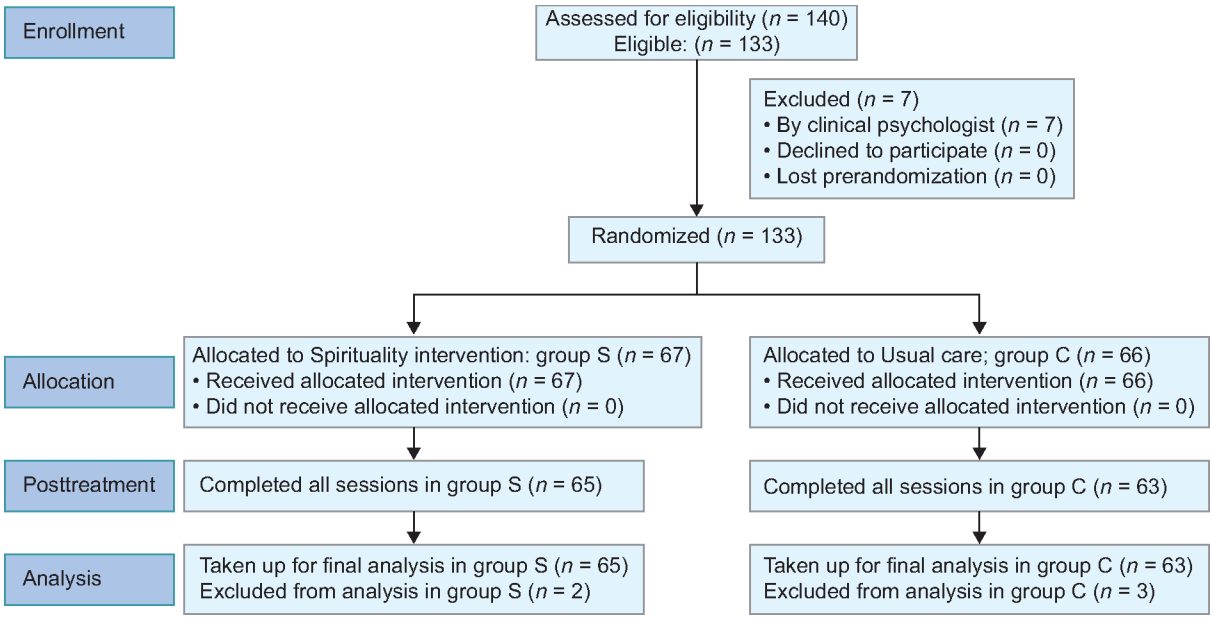

Fig. 1: CONSORT flow diagram of recruitment, progression, and completion of the study

Table 1: Overview on the 6-week Eastern spirituality-based educational program

Week	*Topic*	*Description*
1	Introduction	Facilitator gave group members an overview of the topics to be discussed in the program. Motivates the participants to understand that spirituality can be a helpful tool to inculcate "positivity" in daily life
2	Discussion on positive virtues in spirituality	Explanation of core concepts and virtues in spirituality like compassion, gratitude, and acceptance
3	Discussion on application of virtues and misconceptions in spirituality	Discussion on application of the virtues in modern life. Understanding the misconceptions and ritualistic constructs that prevail in the society resulting in "negative coping" and "emotional sufferings"
4	Discussion on emotional regulation and how to handle crisis	Explore positive spiritual strategies that can be used to handle crisis situations of life. Understanding how to use spirituality for "positive coping" in difficult situations
5	Discussion on connectedness to self and greater meaning of life	Explanation of the concept of connectedness to self and understanding a greater meaning in life by realizing this connectedness
6	Conclusion and sum-up	Facilitator revise all the topics covered and solicit feedback from group members

through a nonreligious, secular method. Participant activities included short formal talks, informal discussions, and meditations. The participants were encouraged to practice at home daily for 10 minutes of learned meditations (to achieve a calming effect). A physician well-versed with spirituality and meditation acted as a facilitator. The language of communication was simple English, but regional language was used in parts for understanding and doubt clarification. There were around 35 participants in a batch, and they maintained a daily practice log.

The group C participants attended self-care pseudo sessions conducted simultaneously on another day of the week. These placebo sessions were taken by the same facilitator of equal duration (excluding the core concepts of spirituality). In these sessions, different relaxation techniques were taught (to be practiced daily at home), informal discussions on coping with stress, and the importance of utilizing spare time for self-care were discussed. These sessions were not structured to qualify as active intervention, and participants of group C were later (after the specific study period) given the option to join the spirituality sessions.

Outcome Parameters

The demographic data (age, gender, and religious affiliation) were collected before the program. The outcome parameters were noted pre- and postprogram.

Spiritual well-being being a complex multidimensional construct, we have deliberately used 2 different scales to measure it.

1. The Spiritual Well-Being Scale (SWBS) consists of 20 items and estimates 2 dimensions of spiritual well-being.[15] One subscale consists of self-assessment of a person's relationship with a higher power, while the other measures one's sense of life purpose and satisfaction. Each item was calculated on a 6-point Likert scale. A total of 8 items were computed in a reverse direction, and the total scores range from 20 to 120, with a higher score reflecting greater spiritual well-being.
2. WHO Quality of Life–Spirituality, Religiousness and Personal Beliefs (WHOQOL-SRPB) is a 32-item questionnaire. It consists of 8 dimensions (4 items per dimension) and uses a 5-point Likert scale. This questionnaire was useful to people coming from many different cultures, spiritual or personal beliefs, and equally applicable to those with or without religious beliefs or following. Although based on an international consensus and among the most used spirituality scales, Moreira-Almeida and Koenig criticized it to be contaminated by indicators of coping strategies or positive mental health rather than spiritual well-being.[16]

Emotional well-being was measured by Depression Anxiety and Stress Scale–21 items (DASS 21): a set of 3 self-report scales (7 items each) estimate the emotional states of depression, anxiety, and stress. Each item is based on a 4-point rating scale and needs to be multiplied by 2 to calculate the final score.[17] Psychological well-being was assessed by World Health Organization Well-Being Index (WHO-5), a 5-item well-being scale.[18] Any adverse effects like exacerbation of stress or anxiety, or any experience of psychosis or hallucinations during the program was noted.

Statistical Analysis

The researcher was blinded to group allocations during data collection and analysis. Equality of variance was tested using Levene's test. Normality was tested using Shapiro–Wilk test. Unpaired *t*-test used for age and Chi-square (χ^2) test for sex parameters, respectively. The outcome parameters were analyzed using repeated measures ANOVA (RM ANOVA) (Bonferroni model). SPSS Statistics for Windows 7®, version 18.0.0 (Chicago, IL 60606-6412), GraphPad Prism® InStat version 5.0 (California 92037-3219), and Microsoft® Office Excel 2010 (Washington: Microsoft) were the statistical software used. Results were presented as mean (SD) and percentage format. $p < 0.05$ was considered statistically significant.

Results

The basic characteristics (age/sex distribution) were similar between group S and group C (Table 2), and religion-wise, all the participants were incidentally Hindus.

Regarding the spiritual well-being (Table 3), results of repeated measures ANOVA (RM-ANOVA) show a significant difference [F(1, 257) = 31.8506; p = 4.391e-8] between group S and C and [F(1, 257) = 36.8263; p = 4.605e-9] between pre- and postsession in Spiritual Well-Being Scale (SWBS). The treatment effect size was $\eta p^2 = 0.1253$ (medium). Statistically significant differences were observed between group and session comparison for WHO-SRPB [F(1, 257) = 17.3782; p = 0.0000419 and F(1, 257) = 13.3902; p = 0.0003069], and the treatment effect size was $\eta p^2 = 0.04952$ (small).

Regarding the emotional well-being (Table 3), statistically significant differences were also observed between group S and C and pre- and postsession comparison for DASS-S [F(1, 257) = 33.1340; p = 2.444e-8 and F(1, 257) = 27.8729; p = 2.759e-7], DASS-A [F(1, 257) = 22.2808; p = 0.000003874 and F(1, 257) = 24.0022; p = 0.000001704], and DASS-D [F(1, 257) = 32.6279; p = 3.078e-8 and F(1, 257) = 21.1679; p = 0.000006613]. The treatment effect size was $\eta p^2 = 0.09784$ for DASS-S, $\eta p^2 = 0.08542$ for DASS-A, and

Table 2: Representation of basic characteristics (age and sex) of study participants

	Group S (n = 67)	*Group C (n = 66)*	*(Groups S vs C)*
Age			Unpaired *t*-test
Mean years (SD)	46.07 (7.69)	46.02 (6.99)	$p = 0.9629$ $t = 0.0466$ df = 131, SE(d) = 1.275 95% CI = –2.46 to 2.58
Sex			Chi-square (χ^2) test
n (%)	Male = 19 (28.36%) Female = 48 (71.64%)	Male = 20 (30.30%) Female = 46 (69.70%)	$p = 0.805426$ $\chi^2 = 0.0607$ df = 1

In the above table, columns 2 and 3 show age and sex distribution for group S (case group) and group C (control group), respectively. Column 4 shows the *p*-value of unpaired *t*-test/χ^2 test comparison prior to the beginning of the session. *n* = number of participants in group, S = spirituality sessions group, C = usual care group, SD = standard deviation, df = degrees of freedom, SE(d) = standard error of difference between means, CI = confidence interval, *p* = *p*-value of the statistical test ($p < 0.05$ is significant)

Table 3: Representation of primary and secondary outcome variables attending "spiritual session" (group S) and "usual care" (group C) using RM-ANOVA

	Group S	*Group C*	*Comparison*	*Mean square (MS)*	*F-statistic (DF1, DF2)*	*p-value*	*Effect size (η^2)* *Treatment effect size (ηp^2)*
Primary outcome variable							
SWBS Mean (SD) (*n*)							
Presession	50.42 (8.92) (*n* = 67)	50.39 (8.77) (*n* = 66)	Between group S and group C	3219.8805	31.8506* (1,257)	4.391e-8**	$\eta^2 = 0.11$
Postsession	64.97 (11.43) (*n* = 65)	50.73 (8.14) (*n* = 63)	Between presession and postsession	3722.8979	36.8263* (1,257)	4.605e-9**	$\eta p^2 = 0.1253$ (medium)
WHO-SRPB Mean (SD) (n)							
Presession	64.73 (6.96) (*n* = 67)	64.18 (6.67) (*n* = 66)	Between group S and group C	857.1042	17.3782* (1,257)	0.0000419**	$\eta^2 = 0.047$
Postsession	70.98 (7.68) (*n* = 65)	64.19 (5.92) (*n* = 63)	Between presession and postsession	660.4129	13.3902* (1,257)	0.0003069**	$\eta p^2 = 0.04952$ (small)
Secondary outcome variables							
WHO-5 Mean (SD) (*n*)							
Presession	9.46 (2.29) (*n* = 67)	9.55 (1.96) (*n* = 66)	Between group S and group C	86.4563	17.8696* (1,257)	0.0000329**	$\eta^2 = 0.11$
Postsession	12.25 (2.40) (*n* = 65)	9.83 (1.68) (*n* = 63)	Between presession and postsession	156.8933	32.4283* (1,257)	3.372e-8**	$\eta p^2 = 0.112$ (medium)
DASS-S Mean (SD) (*n*)							
Presession	18.27 (3.62) (*n* = 67)	18.36 (3.46) (*n* = 66)	Between group S and group C	418.6348	33.1340* (1,257)	2.444e-8**	$\eta^2 = 0.088$
Postsession	13.51 (2.93) (*n* = 65)	18.56 (3.27) (*n* = 63)	Between presession and postsession	352.1637	27.8729* (1,257)	2.759e-7**	$\eta p^2 = 0.09784$ (medium)
DASS-A Mean (SD) (n)							
Presession	18.00 (3.76) (*n* = 67)	18.09 (3.18) (*n* = 66)	Between group S and group C	238.0001	22.2808* (1,257)	0.000003874**	$\eta^2 = 0.079$

Contd...

Table 3: *Contd...*

	Group S	*Group C*	*Comparison*	*Mean square (MS)*	*F-statistic (DF1, DF2)*	*p-value*	*Effect size (η^2) Treatment effect size (ηp^2)*
Postsession	14.20 (2.53) (*n* = 65)	17.98 (2.91) (*n* = 63)	Between presession and postsession	256.3875	24.0022* (1,257)	0.000001704**	ηp^2 = 0.08542 (medium)
DASS-D Mean (SD) (*n*)							
Presession	11.01 (2.42) (*n* = 67)	11.30 (2.28) (*n* = 66)	Between group S and group C	149.7388	32.6279* (1,257)	3.078e-8**	η^2 = 0.068
Postsession	8.57 (1.09) (*n* = 65)	11.35 (2.13) (*n* = 63)	Between presession and postsession	97.1453	21.1679* (1,257)	0.000006613**	ηp^2 = 0.0761 (medium)

In this table, column 1 enlists the outcome variables. Columns 2 and 3 describe the mean, standard deviation, and number for the case group (group S) and control group (group C), respectively, beside the rows depicting the corresponding sessions (i.e., presession or postsession). Column 4 describes the comparisons between groups and sessions using the RM-ANOVA. Column 5 shows intermediate calculations of mean squares. Columns 6, 7, and 8 describe the *F*-statistic, *p*-value, and effect size, respectively. RM-ANOVA = repeated measures analysis of variance, SWBS = spirituality wellbeing scale, WHO-SRPB = World Health Organization spirituality, religiousness, and personal beliefs, WHO-5 = World Health Organization 5 wellbeing index, DASS-S, A, D = depression anxiety stress scale (stress, anxiety, depression) scores, DF = degrees of freedom, SD = standard deviation, MS = mean square, η^2 = effect size of the difference of variance by RM-ANOVA, η_p^2 = treatment effect size, **F*-statistic is statistically significant, ***p* < 0.05 is statistically significant

ηp^2 = 0.0761 for DASS-D, respectively. All DASS-21 subgroup effect sizes were medium.

The psychological well-being measured by WHO-5 Well-Being Scale [F(1, 257) = 17.8696; *p* = 0.0000329 and F(1, 257) = 32.4283; *p* = 3.372e-8], and the treatment effect size was ηp^2 = 0.112 (medium), respectively. The outliers of the above test were done by Tukey fence with k = 1.5. The participants reported no adverse effects during the program.

Discussion

The results proved our hypothesis. The intervention improved the SWBS scores (treatment effect size medium: ηp^2 = 0.1253) and WHO-QOL SRPB scores (treatment effect size small: ηp^2 = 0.04952) significantly. In addition, the DASS 21 scores S stress (treatment effect size medium: ηp^2 = 0.09784), A anxiety (treatment effect size medium: ηp^2 = 0.08542), and D depression (treatment effect size medium: ηp^2 = 0.0761) also improved. The WHO 5 well-being scores (treatment effect size medium: ηp^2 = 0.112) were found to have changed for the better. So, the spirituality-based intervention had a positive impact not only on spiritual well-being but also on emotional and psychological well-being.

Our study results corroborate with those of previous studies from different parts of the world. A study from Indonesia found a significant improvement in spiritual well-being in gynecological cancer patients after receiving spiritual intervention,[19] similar to our study. A study from the USA found that higher levels of spirituality were associated with better levels of well-being (stronger associations among women than men).[20] A Polish study found that spirituality displayed a stronger relationship with psychological well-being,[21] like our study. An Iranian study also showed a group intervention to reduce anxiety and improve spiritual health.[14] Stress, anxiety, and depression scores decreased significantly by 41, 28, and 41%, respectively, in another Iranian study, similar to a decrease in DASS-21 scores in our study.[22] A meta-analysis reported an inverse relationship between spirituality and depression,[23] similar to our study.

After extensive search, studies in the Indian context remain minimal or absent. The researchers can find only 1 study in the Indian elderly rural woman where preexisting spiritual practices (no intervention was used) were found to significantly affect some indicators of health, quality of life, and well-being.[24]

Spirituality and health in the Indian context: WHO is keen on looking beyond the conventional health triangle and wants to incorporate the 4th dimension in health, that is, spirituality. Having a spiritual dimension in life does not mean escaping from reality or transcending to a divine bliss, but ways to handle life's difficulties by generating peace, joy, and happiness. An Indian study found that 65.65% of physicians in North India had a strong belief in the spiritual dimension of health.[25] At present times, Eastern spirituality has been demystified so that a common man can use the concepts and practices in day-to-day life to ensure optimum health.[26] By introducing an Eastern spirituality-based intervention within Indian community settings, this study can act as a foundation stone for further clinical research.

Eastern spirituality is a unique separate construct: unfortunately, the inference from studies in the Western world has less significance, as Eastern spirituality is distinctive to India and surrounding countries. Eastern spirituality is a complex entity that has been explored since ancient times in India. It sees human existence as interconnected and integrated into a greater universal existence. The universal self is the witness of everything happening and the substratum for the changing world of phenomena. A human life is conceptualized as the appearance in space-time perspective, and dying is its disappearance within this substratum. So everything only manifests in the unbroken wholeness or universal consciousness, and we can neither live nor die. A human being is not a separate individual but a psychosomatic apparatus (mind-body entity) through which the primal energy or universal consciousness brings about all happenings (or manifests itself).

Relevance of Eastern spirituality in Indian medical care: Medical sciences deal with diseases, pain, and sufferings of human beings. Many of these ailments cannot be satisfactorily addressed by medicines, therapies, or procedures. Eastern spirituality looks at stress, pain, and suffering as an inability to realize the oneness with the supreme existence. An individual remains worried about what might happen or what should be done in particular circumstances, leading to stress and anxiety. A person of spiritual wisdom remains open and impartial (he or she realizes that everything happens as per the cosmic law), so the question of stress or suffering does not arise. A disidentification from the sense of personal doership helps in better coping and brings in a sense of peace, tranquility, and harmony in life. Moreover, spirituality encourages the practicing of

positive virtues like love, gratitude, kindness, and compassion in daily life, which helps one to tide over the difficulties of life.

Using Eastern spirituality-based intervention for scientific research: Choosing an evidence-based spirituality-based intervention in the Indian context remains a daunting task due to the cultural and religious differences and lack of much published scientific literature. So, as an early attempt, the researchers selected a very basic intervention that was used in their previous study.[13] There has been no consensus about the content, efficacy, and usefulness of this program, and the scope for improvement will always be there with further research. The researchers are not in favor of the involvement of religious or spiritual teachers (like chaplains of the West) to impact well-being in a health context; rather, physicians or health workers with knowledge of spirituality may be regarded worthy of program delivery. The researchers are at least not aware of any high-quality scientifically structured instructor training module on Eastern spirituality available in the country.

Intermingling of spirituality and mental health or health in the Indian context: there may be a considerable overlap between spiritual well-being and psychological well-being (exact nature yet to be determined).[27] Our previous study found a spirituality program to improve mental well-being of Indian medical practitioners.[13] But some mental health specialists in India still believe spirituality (often confused as or with religion) acts against the science of mental health.[28] They mostly have a sole biological approach toward mental illness, ignoring the spiritual dimension.[10] The misunderstandings and misconceptions about religious concepts or beliefs may be responsible for even worsening mental health (when used in an unhealthy manner).[29] But a proper scientific understanding of the interrelation between spirituality and mental health will help one to understand the mechanism and outcome of many mental health problems better. This study did not attempt to explore the deep interconnection between spirituality and mental health in depth, but the effects of the spirituality-based intervention on stress, anxiety, depression, and psychological well-being will serve as a platform for further research.

Future Directions

There is no denying that medical research on spirituality can be problematic[30] if not understood properly or not dealt with sensitivity in Indian context. The community-level applications can open up vast possibilities for improving mental health, lifestyle diseases, and achieving holistic health. This research may instigate the development of more structured spirituality training programs, incorporation into curriculums, proper training of instructors or facilitators, and extensive ground-level spread in India. More high-quality research will be required for better understanding, refinement, modifications, and practical applications in both clinical and community settings.

Strengths

The main strengths of this study were a randomized controlled design, a considerable sample size, a scientific approach toward spirituality, community-level application of an Eastern spirituality-based intervention, and upholding the importance of spirituality in the overall well-being of a human individual.

Limitations

Being an early attempt, this study had several limitations. This research was a single-center study from the Eastern part of India, not representing the sociocultural religious diversity of the entire country. Only those participants who showed an intent to participate were included, and their spiritual inclination can be a potential bias. All participants were Hindus by religion, though the recruitment was open to all religious communities. In addition, the effects of various life circumstances, personality dimensions, and cross-cultural differences on spiritual well-being may not have been displayed in this research work. This study focuses on spiritual well-being, which remains a subconstruct of spirituality. The instruments for measurement of spiritual well-being are not free from criticism, and the wording of some items may not be appropriate. As follow-up data collection was not there, the long-term effects of the intervention were not known.

Despite these limitations, this present research remains a path-breaking one, taking care of spiritual well-being in the attainment of overall well-being by a ground-level application of intervention and paving the path of integration of spirituality with health sciences in the Indian context.

Conclusion

Spirituality is an important dimension of health, and spiritual well-being is an essential component in achieving holistic health. An Eastern spirituality-based intervention improved spiritual well-being as well as stress, anxiety, depression (emotional well-being), and psychological well-being. Future studies will be required to confirm these results.

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ORIGINAL ARTICLE

Acute Pancreatitis beyond Gallstones and Alcohol

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Abstract

Background: Acute pancreatitis (AP) is a potentially grave abdominal condition where the pancreas gets inflamed and is associated with variable regional and systemic involvement. The inflammatory state is usually characterized by acute abdominal pain with concomitant increase in serum pancreatic enzymes. Investigative workup includes serum amylase, lipase, liver function tests, triglycerides, serum calcium, and parathyroid hormone (PTH) assay; imaging includes ultrasonography, computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP), and/or endoscopic ultrasound in some patients.

Aim: To identify the etiology and frequency of nonalcoholic and nonbiliary causes of AP in a hospital scenario, and analyze the severity and outcome of the disease.

Materials and methods: A prospective, observational, hospital-based study was conducted on 150 consecutive AP patients in the Department of Gastroenterology at Yashoda Hospitals, Secunderabad, India. A total of 150 consenting patients who were hospitalized consecutively with AP were included, and subjects with chronic pancreatitis were excluded.

Results: Overall, 150 patients were included; 117 (72.9%) were men, and 37 (27.1%) women. Alcohol was the most common etiological factor noted in 54 (36%), followed by biliary tract disease 45 (30%), idiopathic 21 (14%), hypertriglyceridemia 7 (4.67%), endoscopic retrograde cholangiopancreatography (ERCP)-related 3 (2%), infection-related 5 (3%), hyperparathyroidism 3 (2%), and drug-induced 8 (5.33%). The most common presentation was abdominal pain (98.6%). Organ failure and mortality were low in the nonalcoholic/nonbiliary cause of pancreatitis.

Conclusion: AP in our study reports a significant number of nonalcoholic/nonbiliary causes. The current study showed that the mortality rate in nonalcoholic/nonbiliary cases was low. Despite low mortality in this group, there is a need to identify these causes and treat on an urgent basis for limiting the hospital stay.

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Introduction

One of the most frequent causes of acute abdominal pain seen in hospitals is acute pancreatitis (AP), which can have a range of clinical manifestations and consequences, from mild to severe multiorgan failure that can be potentially fatal. The treatment of severe AP and the clinical course of AP are not simple, as there is no specific therapy and there is uncertainty of pathogenesis and outcome.[1] As per the revised Atlanta classification, AP is diagnosed with abdominal pain, serum lipase (or amylase) activity that is at least three times higher than the upper limit of normal, and distinctive pancreatic abnormalities on contrast-enhanced computed tomography (CECT), magnetic resonance imaging, or transabdominal ultrasonography.[2]

A comprehensive summary of studies on AP worldwide over the previous 56 years suggested a consistent upward trend in the incidence of AP in numerous nations.[3] There is a need for multiple observational studies to evaluate the disease burden and etiology of AP in India. A relatively higher incidence of pancreatitis has been reported in the southern states of India.[4]

The severity levels for AP include mild (no organ failure and no local or systemic complications), moderate (transient organ failure of <48 hours' duration with or without local complications), severe and critical (infected pancreatic necrosis or persistent organ failure lasting longer than 48 hours, involving one or more organs).[2] The two distinct phases of AP include early phase, indicated by systemic inflammatory response syndrome (SIRS) and/or organ failure in the 1st week, while the late phase (lasting longer than 1 week) is indicated by local complications.[5]

The present study aims to identify the etiology, clinical features, and frequency of nonalcoholic and nonbiliary AP and analyze the severity and outcome in relation to the etiology involved.

Materials and Methods

Study Design

Single-center prospective observational study.

Sample Size

This study analyzed 150 consecutive, consenting patients of AP from the Department of Gastroenterology, Yashoda Hospitals, Secunderabad.

Study Site

This is a single-center study conducted at a tertiary care center, Yashoda Hospitals, Secunderabad.

Study Duration

This study was planned as a hospital-based prospective observational study and carried out from June 2021 to May 2022 in the Department of Gastroenterology, Yashoda Hospitals.

Inclusion Criteria

The study enrolled male and female participants between 18 and 80 years of age who had a confirmed diagnosis of AP established through clinical, radiological, and biochemical evaluation. A clinical examination was performed for every patient in a routine manner. Patients were enrolled only after providing written and informed consent.

Exclusion Criteria

The study excluded patients such as cases of recurrent AP, chronic pancreatitis, pregnant and lactating women, AP patients with malignancy, <18 years of age, and patients not consenting for the study.

Statistical Analysis

The data of categorical values were represented by proportions, and continuous variables were represented as mean ± standard deviation. Statistical analyses were conducted using IBM SPSS Statistics, version 29 for Windows. An alpha value of <0.05 (two-tailed) was considered statistically significant. The Chi-squared test was used to assess the

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association of categorical data (gender and age-group of AP, gender and etiology of alcoholic AP, and gender and etiology of gallstone-related AP). The linear correlation between serum amylase and serum lipase levels in AP cases was measured using Pearson correlation coefficient (*r*). One-way analysis of variance (ANOVA) was employed to compare the means of C-reactive protein (CRP), hematocrit (HCT), serum calcium, and serum parathyroid hormone (PTH) levels among mild, moderate, and severe AP.

Results

The study comprised a total of 150 patients, of which men had a greater (74.33%) incidence of AP than women (25.7%). The age distribution included 21–80 years, with a mean age of 42.5 years. The maximum percentage of AP was reported in the group of 31–50 years of age, and the least was recorded in <21 years of age in both males and females, which denotes statistical significance ($p = 0.342$) (Table 1).

Gender and etiology of alcoholic- and biliary-related AP were statistically significantly associated ($p = 0.001$). Out of the 150 participants, alcohol was the most common cause of AP 54 (36%), followed by biliary disease 45 (30%), idiopathic 21 (14%), hypertriglyceridemia 7 (4.6%), hyperparathyroidism 3 (2%), drug-induced 8 (5.33%), infectious conditions 5 (3.33%), postendoscopic retrograde cholangiopancreatography (post-ERCP) 3 (2%), and pancreatic divisum 2 (1.33%). Alcohol was the prime factor for AP in men, whereas in women, biliary tract-related conditions had a major role. Results also show that 95 cases (63.3%) did not have any noticeable comorbidities, and the remaining 55 cases reported various comorbidities, like diabetes mellitus (11), systemic hypertension (14), diabetes mellitus plus systemic hypertension (18), and other comorbidities (12), such as bronchial asthma, coronary artery disease, rheumatoid arthritis, metabolic dysfunction-associated steatotic liver disease (MASLD), hypothyroidism, ulcerative colitis, psoriasis, and postatrial septal defect (post-ASD) closure (Table 2).

Patients' clinical presentation was mostly with abdominal pain 147 (98.6%), followed by abdominal distension 57 (38%), vomiting 48 (32%), pleural effusion 12 (8.6%), fever 42 (28%), and jaundice 5 (3.3%) (Fig. 1). As per the diagnostic criteria of the revised Atlanta classification, 129 and 21 cases were diagnosed

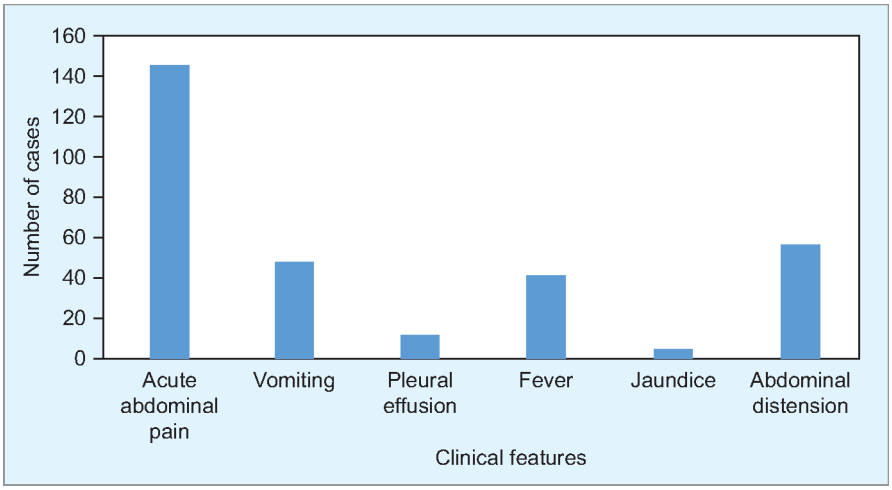

Fig. 1: Clinical features of studied patients

Table 1: Age and gender distribution of AP

Age-group (years)	*Male N = 113*		*Female N = 37*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
<21	7	6.2	1	2.7	8	5.3
21–30	16	14.2	4	10.8	20	13.3
31–40	34	30.1	8	21.6	42	28
41–50	25	22.1	6	16.2	31	20.7
51–60	17	15	10	27	27	18
61–70	8	7.1	6	16.2	14	9.3
71–80	6	5.3	2	5.4	8	5.3

%, percentage of cases; *N*, number of cases

Table 2: Etiological profile of AP

Etiology	*Male*	*Female*	*DM*	*HTN*	*DM + HTN*	*Other comorbidities*
	N (%)	*N (%)*	*N*	*N*	*N*	*N*
Alcohol	51 (34)	3 (2)	2	4	7	2
Biliary-related	15 (10)	30 (20)	4	4	4	3
Idiopathic	14 (9.33)	7 (5)	–	1	3	2
Hypertriglyceridemia	6 (4)	1 (1)	5	1	1	–
Hyperparathyroidism	1 (0.67)	2 (1)	–	–	–	–
Drug-induced	4 (2.27)	4 (3)	–	1	1	3
Infectious	3 (2)	2 (1)	–	2	1	1
Post-ERCP	2 (1.33)	1 (1)	–	–	–	–
Pancreatic divisum	1 (0.67)	1 (1)	–	–	–	1
Hereditary	2 (1.33)	0 (0)	–	1	1	–
Total	99 (66)	51 (34)	11	14	18	12

%, percentage; DM, diabetes mellitus; HTN, systemic hypertension; *N*, frequency of cases

Table 3: Clinical types of AP and modified CTSI of patients

Types of AP	*Modified CT severity index*		
	Mild	*Moderate*	*Severe*
Interstitial edematous pancreatitis	101	28	Nil
Necrotizing pancreatitis	Nil	6	15

Table 4: CRP, HCT, calcium, and PTH in AP

	CRP mg/L		*HCT %*		*Calcium mg%*		*PTH pg/mL*	
	N	*Mean ± SD*	*N*	*Mean ± SD*	*N*	*Mean ± SD*	*N*	*Mean ± SD*
Mild	101	21.87 ± 6.225	101	42.52 ± 3.654	101	8.0 ± 1.34	101	87.9 ± 98.2
Moderate	34	27.71 ± 6.891	34	44.56 ± 2.798	34	7.6 ± 0.89	34	51.4 ± 17.4
Severe	15	40.67 ± 11.690	15	51.13 ± 2.774	15	7.1 ± 0.73	15	56.0 ± 12.0
Total	150	25.07 ± 9.076	150	43.85 ± 4.250	150	7.8 ± 1.2	150	76.2 ± 82.7

as interstitial edematous pancreatitis and necrotizing pancreatitis, respectively (Table 3).

Acute pancreatitis is subgrouped as mild, moderate, and severe. It was observed that out of the 150 cases, 67.3% of the patients were categorized as mild, 22.6% moderate, and 15 (10%) severe AP. Results show that there are no statistically significant differences ($p = 0.06$) of serum calcium level among the mild, moderate, and severe groups of AP. However, there is a statistically significant difference ($p = 0.05$) in the mean levels of the serum PTH (lower values in more severe pancreatitis) between mild and moderate AP. Results also show that the mean difference of CRP and HCT between mild, moderate, and severe AP is significant ($p = 0.03$) (Table 4). Higher values of CRP and HCT suggested a more severe disease pattern.

Discussion

Our study reports a higher incidence of AP in males. In the past, there has been evidence that suggests excessive alcohol consumption as the etiology of both acute and chronic pancreatitis.[6] In the current study, the next common cause was biliary tract disease. Alcohol and gallstone/biliary-related conditions have been identified as common etiological variables for AP, recurring AP, and alcohol as the cause of chronic pancreatitis in various Indian publications.[7,8]

Our study showed that one-fifth of the biliary-related cases were positive for biliary sludge rather than gallstones among those with biliary-related AP. In fact, AP linked to biliary sludge would be classified as idiopathic if biliary sludge is underrated. Women experience a higher incidence of gallstone-related AP, which may cause a significant increase in mortality and morbidity.[9] According to our research, women are more likely to experience AP associated with gallstones, while men experience alcoholic AP. In a Chinese study, 35–65% of cases of AP occurred due to acute biliary pancreatitis (ABP), which had 5–20% mortality.[10]

According to a prospective observational study done in a hospital in Lucknow, India, 2.5% of cases had hypertriglyceridemia as the etiological cause of AP.[11] In the current study, 4.67% of AP is attributed to hypertriglyceridemia as the cause of AP. In a different study from Chennai, India, hypertriglyceridemia was not found among the 70 patients with AP.[12] It is important to remember that not every case of severe hypertriglyceridemia results in AP.[13]

The most common drug incriminated in our study was azathioprine (0.1–0.5% of cases of pancreatitis were due to drugs), and most of these cases had mild to moderate pancreatitis.[14] Our study showed drug-induced AP in 5.33% of cases. The majority of studies carried out in India with smaller sample sizes ($n < 100$) revealed a lower incidence of drug-induced AP.[15]

The underlying pathogenic cause of hyperparathyroidism-induced pancreatitis is hypercalcemia, which is due to hypersecretion of PTH. Primary or secondary hyperparathyroidism (PHPT) may be linked to either acute or chronic pancreatitis.[16] In the present study, three cases were due to parathyroid adenoma causing hyperparathyroidism. Population studies on hyperparathyroidism showed that only 1.5% of PHPT patients experienced AP.[17] AP as a post-ERCP complication has been documented in 2% of our study group.

Conclusion

Biliary disease and alcohol are the main etiologies of AP. However, the current study reports a significant number of nonbiliary/nonalcoholic causes. The morbidity and mortality in this group of nonbiliary/nonalcoholic causes seem to be low. A proper identification of these causes definitely improves the outcome of patients. Various modalities to treat these patients could be insulin infusion, plasmapheresis for hypertriglyceridemia, evaluation for parathyroid adenoma, and early identification of a drug incriminated in the cause of pancreatitis. Hence, there is a need to recognize these causes of AP and treat on an emergency basis for limiting the hospital stay.

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ORIGINAL ARTICLE

Comparison of qSOFA Score and NEWS2 Score in Sepsis Patients Admitted in Emergency Department and ICU as Prognostic Markers of Patient Outcome

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Abstract

Background: Sepsis causes high short-term mortality in emergency and ICU settings. Quick sequential organ failure assessment (qSOFA) and national early warning score 2 (NEWS2) are bedside tools for early risk stratification, yet comparative evidence remains limited.

Objectives: To compare qSOFA and NEWS2 for predicting 7-day and 28-day mortality and length of stay in adult sepsis patients.

Methods: This prospective observational study was conducted over 1 year (March 2024–February 2025) at a tertiary care center in northern India. A total of 874 patients aged 18–65 years admitted with sepsis were enrolled. On-admission qSOFA and NEWS2 scores were recorded. Outcomes included 7-day, 28-day mortality and length of hospital stay.

Results: Among 874 patients, NEWS2 showed higher sensitivity than qSOFA for 7-day (63.1% vs 35.1%) and 28-day mortality (64.1% vs 37.3%), with comparable specificity (~86%). Area under receiver operating characteristic curve (AUROC) values favored NEWS2 for 7-day (0.627 vs 0.606) and 28-day mortality (0.629 vs 0.609).

Conclusion: In adults with sepsis, the NEWS2 score showed higher sensitivity and marginally better prognostic accuracy than qSOFA for predicting short-term mortality and hospital stay. NEWS2 may therefore serve as a more reliable bedside tool for early identification of high-risk patients in emergency and ICU settings.

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Introduction

Sepsis is a dysregulated host response to infection that can progress to septic shock and multiorgan dysfunction.[1–4] Despite advances, it continues to cause major global mortality. Globally, sepsis remains a significant public health concern, with an estimated 48.9 million new cases and 11 million related deaths in 2020—nearly 20% of all global deaths.[5] India alone reported about 11 million cases in 2017, with roughly 3 million fatalities.[6] Despite advances in management, in-hospital mortality remains 25–30%, reaching 58% in septic shock.[7] Continuous assessment of vital parameters—mean arterial pressure, respiratory rate, oxygen saturation, mental status, and body temperature—is critical for early detection and management.[8] These parameters form the basis of several early-warning systems that guide timely intervention. Among them, the quick sequential organ failure assessment (qSOFA) is a bedside tool that identifies patients with suspected infection who are at higher risk for poor outcomes outside the ICU. It consists of three variables: respiratory rate ≥22/min, systolic BP ≤100 mm Hg, and altered mental status (GCS < 15), each assigned one point. A qSOFA score ≥2 is associated with increased mortality and prolonged ICU stay, making it useful for triage and prognostication.[9–12] Similarly, the national early warning score 2 (NEWS2), developed by the Royal College of Physicians, is a standardized scoring system incorporating respiration rate, oxygen saturation, systolic BP, heart rate, consciousness level, temperature, and supplemental oxygen requirement.[13] It is increasingly adopted for its practicality and sensitivity in detecting clinical deterioration. Given the variability in prognostic performance, the present study compared qSOFA and NEWS2 scores in predicting outcomes among sepsis patients admitted to the emergency department and ICU. To test this hypothesis, a prospective observational study was conducted at a tertiary care center in North India, and the methodology is described below.

Methods

This prospective observational study was conducted at a tertiary-care center in North India from March 2024 to February 2025. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Inclusion Criteria

Adults aged 18–65 years admitted to the medicine emergency or ICU with a diagnosis of sepsis, septic shock, or organ dysfunction were enrolled according to the surviving sepsis-3 criteria.[1] Sepsis was defined as suspected infection with an increase in SOFA score ≥ 2. Septic shock was defined as persistent hypotension requiring vasopressor support to maintain mean arterial pressure ≥65 mm Hg with serum lactate >2 mmol/L despite adequate fluid resuscitation. Organ dysfunction included reduced platelet count, elevated serum bilirubin, deranged renal function, altered Glasgow Coma Scale score, hypotension or vasopressor requirement, or any acute change in total SOFA ≥ 2 points consequent to infection.

Exclusion Criteria

Patients younger than 18 or older than 65 years, those with recent surgery, trauma, or burns, known cardiac illness, pregnancy, malnutrition, malignancy, or organ transplantation, and patients unwilling to participate were excluded.

Data Collection

For every enrolled patient, demographic data, detailed clinical history, and examination findings were recorded. qSOFA parameters—respiratory rate ≥22/min, systolic blood pressure ≤100 mm Hg, and altered mental status (Glasgow Coma Scale <15)—and NEWS2 parameters—respiratory rate, oxygen saturation, use of supplemental oxygen, systolic blood pressure, heart rate,

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temperature, and level of consciousness—were documented on admission. Laboratory investigations included complete blood count, renal and liver function tests, serum electrolytes, C-reactive protein, and procalcitonin. All patients were treated in accordance with surviving sepsis guidelines. Follow-up continued until discharge or death to determine 7-day and 28-day outcomes and total hospital stay.

Sample Size

The sample size was calculated using the formula: $n = (Z_1-\alpha/2)^2 \times p \times q/d^2$, where p was 35.12% and $q = 64.88\%$ with $d = 4\%$. Based on this, the required sample size was 870, and 874 patients were finally included, using the prevalence from a previous study.[14]

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using SPSS and GraphPad Prism 5. Descriptive statistics (mean, SD, percentages) were calculated. Because qSOFA (0–3) and NEWS2 (0–20) operate on different scales, direct comparison of mean values between the two was not performed. Each score was analyzed independently for association with outcomes. Chi-square and ANOVA-F tests were applied where appropriate. Receiver-operating-characteristic (ROC) analysis with area-under-curve (AUROC) values, sensitivity, specificity, and coefficient of variation were computed with 95% confidence intervals. A p-value < 0.05 was considered statistically significant.

Results

A total of 874 patients with sepsis were enrolled. Of these, 476 (54.5%) were males, and 398 (45.5%) were females. Most patients were aged 51–65 years (39.3%), followed by 31–50 years (31.4%) and 18–30 years (29.3%). Patients with a qSOFA score of 0–1 (n = 539) had favorable outcomes, with 242 discharged and 49 expired within 7 days, while at 28 days, 411 were discharged and 77 expired. The number of patients still hospitalized was 249 at 7 days and 52 at 28 days, indicating shorter hospital stays and better survival in those with lower scores. In contrast, patients with qSOFA scores of 2–3 (n = 334) showed poorer outcomes, with only 55 discharged and 47 expired within 7 days, and 196 discharged and 73 expired by 28 days. Hospitalization was prolonged in this group, with 232 patients admitted beyond 7 days and 65 at 28 days, confirming a clear association between higher qSOFA scores, increased mortality, and extended hospital stay.

Patients with a NEWS2 score of 0–4 (n = 290) had the best prognosis, with 184 discharged and 14 expired within 7 days, and 254 discharged and 21 expired at 28 days. The hospital stay in this group was short, with 92 patients admitted at 7 days and 15 at 28 days. Those with scores of 5–6 (n = 154) showed intermediate outcomes, with 33 discharged and 23 expired within 7 days, and 89 discharged and 40 expired by 28 days; 94 and 25 patients remained hospitalized at 7 and 28 days, respectively. Patients with scores of 7–20 (n = 430) had the worst outcomes, with 80 discharged and 59 expired within 7 days, and 264 discharged and 89 expired at 28 days. Hospital stay was longest in this group, with 291 patients hospitalized at 7 days and 77 at 28 days. This difference was statistically significant (p < 0.001) (Table 1).

National early warning score 2 demonstrated higher sensitivity than qSOFA for both 7-day (63.1% vs 35.1%) and 28-day mortality (64.1% vs 37.3%). Specificity was also marginally better for NEWS2 compared to qSOFA in both timeframes. This finding represents the central result of the study, emphasizing the superior ability of NEWS2 to identify high-risk sepsis patients early. Additionally, NEWS2 showed a lower coefficient of variation (55.1%) compared to qSOFA (72.4%), indicating greater consistency (Table 2).

Receiver operating characteristic (ROC) curve analysis showed that NEWS2 consistently outperformed qSOFA across all measured outcomes. For predicting 7-day mortality, the AUROC was 0.627 for NEWS2 versus 0.606 for qSOFA. Similarly, for 28-day mortality, NEWS2 had an AUROC of 0.629 compared to 0.609 for qSOFA (Table 3).

When analyzing the 7-day length of hospital stay prediction, NEWS2 again demonstrated slightly higher AUROC values than qSOFA (0.677 vs 0.671) in the overall patient group. A similar trend was observed among a group of sepsis patients, predicting 28-day length of hospital stay, where NEWS2 achieved an AUROC of 0.638 compared to 0.626 for qSOFA (Table 3). ROC analysis showed that NEWS2 consistently yielded higher AUROC values than qSOFA across all measured outcomes. Although the differences were modest, NEWS2 demonstrated greater consistency (lower coefficient of variation) and higher sensitivity while maintaining specificity, supporting its role as a more reliable prognostic tool for sepsis outcomes.

Discussion

A slight male predominance was observed (54.5%), a pattern consistent with findings by studies that associated this trend with greater exposure to risk factors such as smoking, alcohol use, and comorbidities among males.[14] Similarly, studies reported a male majority in their sepsis cohorts, with an even higher representation (around 60%).[15] Age-wise distribution revealed that mortality increased

Table 2: Diagnostic performance of qSOFA and NEWS2 for mortality

Category	*qSOFA (%)*	*NEWS2 (%)*
Sensitivity (7-day)	35.1	63.1
Specificity (7-day)	85.4	87.5
Sensitivity (28-day)	37.3	64.1
Specificity (28-day)	84.5	86.6
Coefficient of variation	72.4	55.1

Table 1: Association of qSOFA and NEWS2 with 7-day and 28-day outcomes

Sepsis score	*Score range (n)*	*7-day outcome*			*28-day outcome*			*p-value**
		Discharged (n)	*Expired (n)*	*Hospital stay (n)*	*Discharged (n)*	*Expired (n)*	*Hospital stay (n)*	
qSOFA	0–1 (539)	242	49	249	411	77	52	<0.001
	2–3 (334)	55	47	232	196	73	65	
NEWS2	0–4 (290)	184	14	92	254	21	15	
	5–6 (154)	33	23	94	89	40	25	
	7–20 (430)	80	59	291	264	89	77	

*p-value is between outcomes comparing qSOFA and NEWS2

Table 3: AUROC comparison of qSOFA and NEWS2 for outcomes

Outcome	*Score*	*AUROC (95% CI)*	*p-value*
7-day mortality	qSOFA	0.606 (0.546–0.665)	<0.001
	NEWS2	0.627 (0.570–0.684)	
28-day mortality	qSOFA	0.609 (0.561–0.656)	<0.001
	NEWS2	0.629 (0.583–0.675)	
7-day length of stay	qSOFA	0.671 (0.634–0.707)	<0.001
	NEWS2	0.677 (0.641–0.714)	
28-day length of stay	qSOFA	0.626 (0.589–0.663)	<0.001
	NEWS2	0.638 (0.601–0.675)	

progressively with advancing age. Patients aged 51–65 years exhibited the highest rates of prolonged hospitalization and mortality at both 7 and 28 days. These results mirrored the observations of previous studies, which reported significantly higher mortality in patients over 60 years.[14,15] Other studies also documented increased deaths among those aged >65 years, and some noted up to 70% mortality in elderly ICU patients.[16,17] Further research demonstrated a similar age-related mortality trend, supporting the assertion that age is an independent predictor of poor outcomes in sepsis.[18] When evaluating qSOFA scores, 61.6% of patients had scores of 0–1 at admission, and 38.2% had scores of 2–3. By day 7, early discharge was more frequent among those with low qSOFA scores, whereas patients with higher scores experienced prolonged hospital stays and comparable mortality. At day 28, mortality was modestly higher among the qSOFA ≥2 group. These findings were aligned with studies that reported a 53.6% mortality in qSOFA ≥2 patients.[14] Other research found increased mortality and longer hospitalization in patients with high qSOFA scores.[15] The relatively lower mortality observed in our cohort may reflect earlier intervention strategies or different baseline characteristics. The prognostic trend extended to NEWS2 scores as well.

Patients with scores ≥7 had significantly higher mortality and longer hospital stays at both 7-day and 28-day follow-ups. This aligned with studies that found a 56% mortality in NEWS2 ≥7 patients and demonstrated NEWS2's strong correlation with ICU admission and organ dysfunction.[14,15] Additional studies reported an AUC of 0.686 for NEWS2 in predicting mortality, consistent with our findings.[16] Further research documented a 62% mortality in ICU patients with NEWS2 ≥7 and showed that NEWS2 was more sensitive than qSOFA in early mortality prediction.[17] ROC analysis for 7-day mortality showed that qSOFA had an AUC of 0.606 and NEWS2 had a slightly higher AUC of 0.627. While both reached statistical significance ($p < 0.001$), their predictive strength was modest. For 7-day hospital stay prediction, qSOFA had an AUC of 0.671 and NEWS2 showed a slightly better AUC of 0.677. For 28-day hospital stay prediction, qSOFA had an AUC of 0.626 and NEWS2 showed a slightly better AUC of 0.638. This small difference nonetheless favored NEWS2, consistent with previous reports citing its superior sensitivity.[18] Similar trends were seen at the 28-day endpoint. NEWS2 maintained a marginally better AUC than qSOFA (0.638 vs 0.626 for length of stay; 0.629 vs 0.609 for mortality) reinforcing its reliability. These findings paralleled the results of previous studies, which demonstrated higher AUC values for NEWS2 (0.74) compared to qSOFA (0.66) with greater sensitivity and comparable specificity.[18]

Sensitivity and specificity assessments in our study further supported these trends. At day 7, NEWS2 showed a sensitivity of 63.1% versus 35.1% for qSOFA with both having similar specificity (~85%). At day 28, NEWS2 again had higher sensitivity (64.1%) than qSOFA (37.3%), with specificity remaining high for both. These values highlighted that although both scores reliably ruled out low-risk patients, NEWS2 was superior in identifying high-risk individuals, particularly in early phases. The performance metrics observed in our cohort were comparable to those reported by other studies, which noted higher sensitivity and AUC for NEWS2 than for qSOFA.[14] Similar findings also reported a higher AUC for NEWS2 (0.80) compared to qSOFA (0.70), while others echoed this superiority with consistent sensitivity and AUC trends.[15,17] The ANOVA F-scores at day 7 (qSOFA: 85.609; NEWS2: 88.425) and day 28 (qSOFA: 29.395; NEWS2: 31.296) confirmed statistically significant differences across outcome categories. The coefficient of variation (CV) was lower for NEWS2 (55.1%) than for qSOFA (72.4%), reflecting more stable score distribution and consistent prognostic reliability. The origin of NEWS2 as a standardized score from the Royal College of Physicians lends further support to its utility in structured emergency care.[13] Previous research demonstrated NEWS's ability to discriminate high-risk patients requiring ICU care, which is reaffirmed by our findings and by subsequent validation studies.[9,18]

In summary, the findings of our study supported the conclusion that while both qSOFA and NEWS2 are valuable for early risk stratification in sepsis, NEWS2 consistently demonstrated higher sensitivity, marginally better discriminatory power (via AUC), and more robust statistical behavior across various outcome measures. These results endorse the application of NEWS2 as a more effective early warning score in emergency and ICU settings, particularly when timely triage and intervention are essential. Given the limited evidence from Indian studies assessing the predictive accuracy of NEWS2 versus qSOFA in sepsis patients admitted to emergency and intensive care units, there is a pressing need for well-designed, multicentric trials involving larger sample sizes.

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ORIGINAL ARTICLE

Effectiveness of Simulation Training on Students' Confidence and Competence in Performing Basic Life Support

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Abstract

Background: Basic life support (BLS) is a critical skill for healthcare professionals. Traditional teaching approaches may not sufficiently ensure retention or practical proficiency. Simulation-based training offers a dynamic learning environment with opportunities for practice and feedback.

Objectives: This study aimed to assess the effectiveness of simulation-based BLS training in improving (1) competence and (2) confidence among undergraduate medical students.

Materials and methods: A quasi-experimental pre/posttest design was employed with two parallel groups (simulation vs traditional lecture-based instruction). Sixty undergraduate medical students were recruited and randomly assigned. Competence was assessed using an objective structured clinical examination (OSCE)-based performance checklist. Confidence was measured via a validated Likert-scale questionnaire. Pre- and post-training evaluations were conducted.

Results: Simulation-trained students demonstrated significantly higher posttest competence scores ($p < 0.05$) and reported increased confidence ($p < 0.05$) compared to the control group. Within-group comparisons also showed significant improvement from pre- to posttest in both metrics for the simulation group.

Conclusion: Simulation-based training significantly enhances students' competence and confidence in performing BLS. These findings support its integration into medical curricula to foster critical life-saving skills.

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Introduction

Basic life support (BLS) is an essential clinical competency for all healthcare professionals, forming the foundation of emergency response in cases of cardiac arrest, respiratory failure, and other life-threatening situations. Early recognition and prompt initiation of BLS significantly improve patient outcomes and survival rates. Therefore, ensuring that healthcare students are both competent and confident in performing BLS is a crucial component of medical and nursing education.

Traditionally, BLS training has relied heavily on didactic lectures and static demonstrations. While these methods can convey theoretical knowledge, they often fall short in promoting the hands-on proficiency and rapid decision-making required during real-life emergencies. In contrast, simulation-based education—particularly high-fidelity simulation—has emerged as a transformative pedagogical approach. It allows learners to engage in realistic clinical scenarios in a controlled, risk-free environment where they can repeatedly practice skills, receive immediate feedback, and reflect on their performance.[1,2]

High-fidelity simulators replicate real patient responses, providing immersive experiences that enhance psychomotor learning, critical thinking, and teamwork.[3] Studies have consistently shown that simulation-based BLS training results in better skill acquisition, greater retention over time, and improved performance under pressure when compared to traditional training modalities.[4,5] Moreover, simulation fosters a learner-centered environment that can enhance motivation, self-efficacy, and engagement.

Despite its increasing use, there remains a need for more robust evidence on the dual impact of simulation-based BLS training—specifically its effectiveness in improving both competence (objective demonstration of skills) and confidence (learner self-perception and assurance in applying those skills). This is particularly relevant for undergraduate healthcare students, who may have limited clinical exposure and require structured, experiential learning opportunities to develop readiness for emergencies.

Therefore, the present study was undertaken to evaluate the effectiveness of simulation-based training in enhancing students' competence in performing BLS and to assess the impact of simulation training on students' self-reported confidence in performing BLS.

This research tried to explore the following questions: "Does simulation-based training improve students' practical competence and increase their confidence in performing BLS?"

Materials and Methods

The study was conducted within a dedicated simulation laboratory (SMART Lab) at a tertiary teaching institute in Andhra Pradesh. It employed a quasi-experimental, pre/posttest design with two distinct groups: a simulation-intervention group and a control group.

Undergraduate medical students who have not received any prior BLS certification within the preceding 12 months and are currently in their clinical years of study were eligible and included in this study after giving informed consent. A convenience sampling method was utilized for participant recruitment. A total of 60 students were included in the study, and they were divided randomly into two groups of 30 students each group.

- *Control group*: Received traditional lecture-based BLS instruction, adhering to American Heart Association (AHA) guidelines.
- *Simulation group*: Participated in high-fidelity BLS simulation training, which included hands-on practice sessions followed by structured debriefing sessions.

Data were collected at two time points: preintervention (pretest) and postintervention (posttest).

Competence: BLS competence was objectively evaluated using an objective structured clinical examination (OSCE)

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performance checklist. The maximum achievable score on this checklist was 20, and it was developed based on established AHA guidelines.[6]

Confidence: Participants' self-reported confidence in performing BLS was assessed using a validated self-report questionnaire. This questionnaire utilized a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree) and was adapted from previously published BLS training studies.[7,8]

In the pretest phase, all enrolled participants completed the confidence questionnaire and performed a standardized BLS scenario to establish baseline competence. During the intervention phase, participants received the assigned training specific to their group (either lecture-based for the control group or simulation-based for the simulation group). Immediately following the intervention, both competence and confidence were reassessed using the same instruments and standardized BLS scenario as in the pretest.

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants. Confidentiality and anonymity were maintained throughout the study. Participation was voluntary, and participants were free to withdraw at any stage without prejudice. The benefit of the intervention was also assured to be extended to the other group.

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean and standard deviation (SD) for continuous variables. For within-group comparisons, a paired *t*-test. Between-group differences were assessed using an independent *t*-test. A *p*-value of < 0.05 was considered statistically significant.

Results

The study was conducted with 30 students in each blinded group. Statistically significant improvements were observed in both self-reported confidence and competence following the respective interventions.

Confidence Scores

In the control group (lecture-based), the mean confidence score increased from 2.8 ± 0.5 to 3.2 ± 0.6 (mean difference: +0.4; $p = 0.00047$). The simulation-based group demonstrated a marked improvement from 2.9 ± 0.4 to 4.4 ± 0.5 (mean difference: +1.5; $p < 0.000000000003$). Between-group comparison of posttest confidence scores revealed a statistically significant difference favoring the simulation group (4.4 ± 0.5 vs 3.2 ± 0.6; mean difference: +1.2; $p < 0.000000001$), highlighting the superior effect of simulation-based training in enhancing learner confidence (Table 1).

Competence Scores

Both groups also demonstrated gains in posttest assessment scores, although the improvement was more substantial in the simulation group. The control group improved from 10.2 ± 1.9 to 12.1 ± 2.0 (mean difference: + 1.9; $p = 0.08$), which was not statistically significant. In contrast, the simulation group showed a significant increase from 10.1 ± 2.0 to 16.3 ± 1.7 (mean difference: + 6.2; $p < 0.001$). Between-group comparison of posttest scores further demonstrated a significant advantage in favor of the simulation group (16.3 ± 1.7 vs 12.1 ± 2.0; mean difference: + 4.2; $p < 0.001$) (Table 2).

These findings affirm that simulation-based training is a highly effective pedagogical approach for enhancing both clinical confidence and competence in BLS among undergraduate medical students. The structured, immersive nature of simulation—characterized by repetitive hands-on practice, real-time feedback, and experiential learning—contributed to significantly higher postintervention OSCE scores, reinforcing its utility in preparing learners for high-stakes emergencies.

Discussion

The findings of the present study are in alignment with previously published literature,[1,4,5] reinforcing the efficacy of high-fidelity simulation in enhancing both psychomotor performance and learner self-confidence in BLS training. Unlike traditional didactic methods, simulation allows learners to engage in active, hands-on practice within a safe and controlled environment that closely mimics real-life clinical scenarios. This experiential learning approach not only facilitates the acquisition of technical skills but also improves decision-making under pressure, a critical component in emergency response.

Aqel and Ahmad[7] reported significant improvement in CPR performance and confidence levels among nursing students following simulation-based instruction, while Roh et al.[8] similarly observed superior outcomes in knowledge retention, procedural accuracy, and team communication. These findings collectively underscore

Table 1: Comparison of confidence scores

Group	*Pretest confidence*	*Posttest confidence*	*Mean difference*	*p-value*
Control (lecture)	2.8 ± 0.5	3.2 ± 0.6	+ 0.4	0.00047
Simulation-based	2.9 ± 0.4	4.4 ± 0.5	+ 1.5	< 0.000000000003
Between groups	–	Sim: 4.4 ± 0.5 Ctrl: 3.2 ± 0.6	+ 1.2	< 0.000000001

Ctrl, control group; Sim, simulation group

Table 2: Comparison of competence scores

Group	*Assessment*	*Mean score ± SD*	*Mean difference*	*p-value*
Control	Pretest	10.2 ± 1.9	+ 1.9	0.08
	Posttest	12.1 ± 2.0		
Simulation	Pretest	10.1 ± 2.0	+ 6.2	< 0.001
	Posttest	16.3 ± 1.7		
Between groups	Posttest	Sim: 16.3 ± 1.7 Ctrl: 12.1 ± 2.0	+ 4.2	< 0.001

Ctrl, control group; Sim, simulation group

the value of simulation as an instructional strategy that addresses both cognitive and affective learning domains, which are often inadequately targeted in conventional lecture-based formats.

Moreover, simulation allows for repeated practice, immediate feedback, and structured debriefing, all of which are essential for the reinforcement of skills and correction of errors. Given the time-sensitive and high-stakes nature of BLS, such immersive training modalities are particularly relevant for equipping students with the competence and confidence necessary to perform effectively during actual resuscitation events. Therefore, the integration of high-fidelity simulation into medical and nursing curricula should be viewed not merely as an enhancement but as an essential component of BLS training.

Conclusion

Simulation-based BLS training was found to significantly enhance both confidence and competence among students. These findings support its wider incorporation into health professional curricula to improve preparedness for life-saving interventions.

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ORIGINAL ARTICLE

Factors Contributing to COVID-19 Mortality In-hospital and after Discharge: Results of an Ambivalent Cohort Study from a Tribal District of Kerala, India

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Abstract

Introduction: The morbidity and mortality burden of the COVID-19 pandemic was high in socioeconomically deprived areas. Identifying the factors associated with in-hospital mortality in such settings will help physicians prioritize the scarce resources for the more needy individuals.

Objective: To study the demographic, clinical, and biochemical factors associated with in-hospital mortality in COVID-19 patients in Wayanad, Kerala, India. We also report the incidence of post-COVID symptoms and the mortality rate in the survivors of COVID-19 pneumonia.

Materials and methods: The study design was a record-based retrospective cohort, and the study participants were 402 patients admitted with moderate to severe COVID-19 at the secondary care hospital of Wayanad, Kerala, India, during late 2020 and early 2021. In-hospital mortality was the major outcome variable, and we expressed the mortality risk in terms of relative risks (RRs). Factors associated with the same were assessed using Chi-square, Fisher's exact tests, and *t*-tests depending upon the type of exposure variable. Dose-response relationships were assessed using Chi-square for trend. A subgroup of consented survivors ($n = 156$) was followed to study the post-COVID symptoms and mortality rate outside the hospital. We constructed binary logistic models to find out the independent predictors of mortality.

Results: The patient group ($n = 402$) was composed of individuals aged 18–95 years, and two-thirds ($n = 258$) were men. The in-hospital mortality rate was 17.7%. The risk of mortality increased with age, multimorbidity, and extent of hypoxia, peripheral oxygen saturation/fraction of inspired oxygen [SpO_2/FiO_2 (SF)] ratio, D-dimer, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), serum creatinine, and blood urea. The case fatality rate (CFR) had a dose-response relationship with the number of comorbidities. Out of the individual comorbidities analyzed, systemic arterial hypertension [RR = 1.5 (1.16–1.83)], cancer [RR = 4.7 (1.38–15.6)], and neurological disorders [RR = 5.8 (1.6–21.16)] were significantly associated with mortality in the hospital. According to the binary logistic regression analysis, age, hypoxia at the time of admission, intensive care unit (ICU) admission, serum creatinine, and SF ratio were the significant predictors of mortality. Most of the patients (73%) complained of some symptoms during follow-up. Easy fatigability and tiredness were the most common post-COVID symptoms, followed by exertional breathlessness, myalgia, decreased sleep, weight loss, and cough.

Conclusion: The physician should prioritize patients with multimorbidity and markers of organ involvement to save lives in resource-poor settings during pandemics and large infectious disease outbreaks affecting the community. The early diagnosis and management of comorbidities should be included in pandemic or outbreak preparedness to reduce morbidity and mortality.

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Introduction

The global impact of COVID-19 has been profound, with significant loss of life and considerable social and economic upheaval. The impact of the pandemic was not equal for every health system. Limited infrastructure and human resources posed significant obstacles to the health systems of the global south.[1,2] Mitigation strategies of the pandemic were multifaceted. Public health activities, including vaccinations, reduced the death toll of the surging infection. Saving the lives of patients admitted with COVID-19 pneumonia is the last opportunity on the ladder of the preventive and therapeutic activity spectrum. Large numbers of ill patients will come to hospitals at the time of any pandemic, and the lessons learned at hospitals while treating those patients are an important learning to build resilience against impending outbreaks of infectious diseases and future pandemics. There is significant overlap among factors contributing to mortality and clinical features of near-miss deaths among most infectious diseases, as many of the infections act through common immunological cascades, including cytokine storm and organ involvement.[3]

The physicians working in the setting where the present study was conducted faced significant challenges in managing their patients in terms of infrastructure, diagnostics, and therapeutics. The government of Kerala brought the treatment of COVID-19 under universal health coverage, which reduced the out-of-pocket expenditure significantly.[4] The government published updated evidence-based treatment guidelines and ensured the supply of essential diagnostic mechanisms and therapeutic agents.[5] Strong public health measures prevented the COVID-19 caseload from overwhelming the capacities of the state throughout the pandemic.[6] However, Wayanad is one of the most backward districts of the state; it is deprived socially as well as in terms of health system amenities. It is the only district in Kerala categorized as an "aspirational district," and a significant proportion of the population is tribal.[7] The mountainous terrain and remote areas make accessing healthcare facilities difficult in the Wayanad district. It is important to

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understand the challenges and the resilience the system faced, specifically in the Wayanad district, and this learning will help in preparing for future pandemics and will be useful for places with similar struggles. It is always a priority to document the pandemic impact in terms of morbidity and mortality in such deprived settings and to identify the priority patients in the clinical setting.

The current study evaluates the demographic, clinical, and biochemical factors contributing to in-hospital COVID-19 mortality of patients admitted at a COVID hospital in Wayanad, Kerala, India. We also report the features of long COVID syndrome and the 1-year mortality rate in survivors of COVID-19 pneumonia in a subgroup of patients.

Materials and Methods

This study was conducted in two phases. The first phase was the analysis of a record-based retrospective cohort of COVID-19 patients who were admitted to the secondary care hospital (Government District Hospital), Mananthavady, Wayanad, Kerala, India. Patients with RT-PCR/TrueNAAT/CBNAAT-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and features of COVID pneumonia aged 18 years or more were included. The patients were admitted between July 1, 2020, and February 28, 2021. The second phase was a follow-up study on discharged patients during March to April 2022.

Data collection from hospital records was done using a validated structured questionnaire. For the first part of the study, which was record-based, data were collected from 402 COVID-19-confirmed patients who were admitted to the hospital during the study period. According to Kerala State's COVID treatment protocol, asymptomatic and mildly symptomatic patients were managed at their homes or COVID first-line treatment centers in the community. As our cohort of patients was enrolled from a COVID hospital, they were suffering from moderate to severe symptoms of COVID pneumonia or had some vulnerabilities for complications as assessed by the treating physician. Data regarding the sociodemographic characteristics, comorbidities, clinical profile, including the need for oxygen support, intensive care unit (ICU) admission, vitals, laboratory investigations at the time of admission, treatment given, and the outcome in terms of hospitalization and in-hospital mortality were recorded for most of the patients. A team of clinicians, epidemiologists, and biostatisticians compiled and reviewed the data.

For the follow-up, a telephonic interview was conducted using a pretested semi-structured questionnaire to gather information from willing participants who could be reached through the information they provided in the hospital record at the time of admission. From 38% of patients from the initial cohort (156/402) who consented to telephonic interviews and were followed up after discharge, information regarding demography, symptoms, comorbidities after discharge, reinfection, vaccination, addictions, and mortality after discharge was documented. The calls were connected to the subjects hospitalized earlier or to a close relative who answered the call.

A COVID-19 death was defined as per the World Health Organization (WHO) as the major outcome variable, which is death resulting from a clinically compatible illness in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease without a period of complete recovery between illness and death.

The data were entered in Microsoft Excel and analyzed using the Statistical Package for Social Science (SPSS version 27). Continuous variables such as age, temperature, blood pressure, oxygen saturation level, lab indices, and duration of ICU admission were expressed as mean (SD) or median (IQR), and frequency and percentage for categorical variables like gender, socioeconomic status, occupation, addictive habits, comorbidity status, symptomatology, treatment, and presence of coinfection. We used the Chi-square or Fisher's exact test to evaluate the univariable analysis. Chi-square for trend was used to compare differences in mortality in different groups, and the Mann–Whitney *U* test was used to compare the difference in scores. Imputation was done using the expectation maximization (EM) method for quantitative variables whose data were incomplete, and those with <10% of missing data were included in the analysis. The relevant variables, along with the ones that showed a significant association, were included for binary logistic regression.

The Institutional Ethics Committee (IEC) approved the study (GMCKKD/RP 2024/IEC/37) dated February 16, 2024.

Results

The patient group (n = 402) consisted of 258 (64.2%) men. The mean (SD) age of the patients was 62.1 (14.7), ranging from 18 to 95 years. The major symptoms at the time of admission included breathlessness 78.8% (n = 317), fever 50.2% (n = 202), and cough 45% (n = 181). Most patients [77.1% (310/402)] had at least one known comorbidity. The most frequent comorbidities were diabetes mellitus [n = 192 (47.8%)], systemic arterial hypertension [n = 180 (44.7%)], and coronary artery disease (CAD) [n = 73 (18.1%)]. Most patients [316 (78.6%)] required ICU admission. The duration of ICU stay was between 1 day and 38 days, with a median (IQR) of 7 (4.5–11) days. The most common reasons for ICU admission were desaturation and hypoxia, breathlessness, prolonged cough, and uncontrolled fever. The number of patients who needed ventilator support was 45 (11.1%), among them 40 patients (88.8%) received noninvasive ventilation. Most of the patients [353 (87.8%)] required HFNC/O_2 support.

The in-hospital mortality rate experienced by the cohort is 17.7% (n = 71). The case fatality rate (CFR) among men was 17.4% (45/258), while among women it was 18.1% (26/144). Among ICU-admitted patients, the CFR was 22.1% (70/316). The risk of mortality increased with age, multimorbidity, and the extent of hypoxia on admission and among ICU-admitted patients. The SpO_2/FiO_2 (SF) ratio, D-dimer, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), serum creatinine, and blood urea exhibited a dose-response gradient with the mortality risk (Table 1). The mortality risk was higher in those with elevated serum ferritin levels, although the relationship was not statistically significant.

The CFR has a dose-response relationship with the number of comorbidities. Odds ratios showed an increasing trend, with seven times the odds of mortality in multimorbidity with two existing diseases compared to people without any reported comorbidities (Chi-square for linear trend p-value <0.001). Of the individual comorbidities analyzed, only systemic arterial hypertension [relative risk (RR) = 1.5 (1.16–1.83)], cancer [RR = 2.97 (1.54–5.73)], and neurological disorders [RR = 3.31 (1.77–6.18)] were significantly associated with mortality in the hospital (Table 2).

We didn't observe a significantly different symptomatology in the expired group compared to the survivors at the time of presentation (Table 3). The major symptoms at the time of admission were breathlessness (85.7 vs 89.8%), fever (57.1 vs 56.7%), and cough (49.2 vs 51.4%) in both groups. Chest skiagrams of all the patients showed evidence of pleural effusion, alveolar opacities, and ground-glass appearance. The median (IQR) radiographic assessment of lung edema (RALE) score of the 197 patients was 16 (9–24), which was higher in patients who expired [25 (20–34)] compared to the survivors [14 (8–21)], $p < 0.0001$. Regarding medications, steroids

Table 1: Patient characteristics at the time of admission and their association with in-hospital mortality

Variable	*Categories*	*Total n = 402*	*Dead (CFR) n = 71*	*OR*	*Chi-square for linear trend p-value*
Age (in years)	<40	29 (7.2%)	1 (3.4%)	Ref = 1	<0.001
	40–49	46 (11.4%)	1 (2.2%)	0.62	
	50–59	85 (21.1%)	8 (9.4%)	2.91	
	60–69	107 (26.6%)	18 (16.8%)	5.66	
	70 and above	135 (33.6%)	43 (31.9%)	13.09	
Comorbidity	No comorbidity	92 (22.9%)	4 (4.3%)	Ref = 1	<0.001
	Single comorbidity	100 (24.9%)	13 (13%)	3.28	
	Multimorbidity—two	95 (23.6%)	23 (24.2%)	7.02	
	Multimorbidity—three	69 (17.2%)	14 (20.3%)	5.6	
	Multimorbidity—four and more	46 (11.4)	17 (36.9%)	12.9	
Hypoxia at admission	No hypoxia (>94)	151 (37.6%)	14 (19.7%)	Ref = 1	<0.001
	Mild (93–94)	79 (19.7%)	11 (15.5%)	1.27	
	Moderate (90–92)	77 (19.2%)	8 (11.3%)	0.91	
	Severe (<90)	95 (23.6%)	38 (53.5%)	5.24	
Oxygen support while in hospital	No	47 (11.7%)	5 (7%)	Ref = 1	0.179
	Yes	355 (88.3%)	66 (93%)	1.92	
ICU admission	Yes	316 (78.6%)	70 (98.6%)	Ref = 1	<0.001
	No	86 (21.3%)	1 (1.4%)	24.18 (3.30–176)	
SF ratio *n* = 350	>315	118 (29.4%)	2 (2.8%)	Ref = 1	<0.001
	≤315	232 (57.7%)	61 (85.9%)	20.69	
D-dimer *n* = 402	<5	383 (95.3%)	62 (16.2%)	Ref = 1	0.002*
	≥5	19 (4.7%)	9 (47.3%)	0.21 (0.08–0.55)	
SGOT *n* = 402	<40	344 (85.6%)	61 (85.9%)	Ref = 1	0.023*
	40–120	51 (12.7%)	6 (11.8%)	0.62	
	>120	7 (1.7%)	4 (57.1%)	6.19	
SGPT *n* = 402	<40	211 (52.5%)	36 (17.1%)	Ref = 1	0.011*
	40–120	174 (43.3%)	27 (15.5%)	0.89	
	>120	17 (4.2%)	8 (47.1%)	4.32	
Serum creatinine *n* = 402	<2	343 (85.3%)	46 (13.4%)	Ref = 1	<0.001*
	≥2	59 (14.6%)	25 (42.3)	0.211 (0.11–0.38)	
Blood urea *n* = 402	<40	241 (60%)	21 (29.6%)	Ref = 1	<0.001*
	≥40	161 (40.0%)	50 (31.0%)	0.21 (0.12–0.37)	
Serum ferritin *n* = 358	≥1000	56 (15.6%)	15 (26.8%)	Ref = 1	0.058
	<1000	302 (84.4%)	49 (16.2%)	0.52 (0.27–1.03)	

* Corresponds to *p*-value of fisher's exact test

were administered to 333 (82.8%) patients, anticoagulants to 314 (78.1%), remdesivir to 93 (23.1%), other antivirals to 215 (53.4%), hydroxychloroquine (HCQ) to 125 (31.1%), and azithromycin to 233 (58%) patients. We didn't compare the mortality rates between people who received medication because such medications were given to patients with severe disease and the groups were not comparable.

Binary logistic regression was done to find out the determinants of mortality for COVID-19 patients admitted to the hospital. Factors that were significant at a 5% level were included in the model. The dependent variables were age, presence of comorbidity, hypoxia, SF ratio, ICU admission, D-dimer, serum creatinine, blood urea, hypertension, heart condition, neurological disorder, and cancer, and nonsignificant variables like SGPT and SGOT. The model was found to be significant at *p*-value <0.001, and the Hosmer and Lemeshow Chi-square goodness-of-fit test illustrates *p*-value >0.05 (0.781), indicating

Table 2: Known comorbidities and risk of mortality

Comorbidity *n = 402*	*Expired* *n = 71*	*Survived* *n = 331*	*RR (95% CI)*	*p-value*
Diabetes mellitus, *n* = 192 (47.8)	38 (53.5%)	154 (46.5%)	1.1 (0.8–1.4)	0.26
Hypertension, *n* = 180 (44.7)	43 (60.6%)	137 (41.4%)	1.5 (1.16–1.83)	0.001
CAD, *n* = 73 (18.1)	15 (21.1%)	58 (17.5%)	1.2 (0.72–2.00)	0.46
COPD, *n* = 67 (16.6)	14 (19.7%)	53 (16%)	1.23 (0.72–2.09)	0.44
CKD, *n* = 31 (7.7)	9 (12.7%)	22 (6.6%)	1.74 (0.96–3.15)	0.084
DLP, *n* = 14 (3.4)	1 (1.4%)	13 (3.9%)	0.36 (0.04–2.69)	0.48*
Cancer, *n* = 10 (2.4)	5 (7%)	5 (1.5%)	2.97 (1.54–5.73)	0.018*
Neurological diseases, *n* = 9 (2.2)	5 (7%)	4 (1.2%)	3.31 (1.77–6.18)	0.011*
CLD, *n* = 6 (1.4)	3 (0.9%)	3 (0.9%)	2.91 (1.27–6.67)	0.071*
Other lung condition, *n* = 3 (0.7)	2 (2.8%)	1 (0.3%)	3.86 (1.68–8.83)	0.082*
Musculoskeletal disorders, *n* = 4 (0.9)	2 (2.8%)	2 (0.6%)	2.88 (1.06–7.86)	0.145*

* Corresponds to *p*-value of fisher's exact test

Table 3: Symptoms at the time of admission and risk of mortality

Symptoms *n = 356*	*Expired* *n = 63*	*Survived* *n = 293*	*RR (95% CI)*	*p-value*
Breathlessness	54 (85.7%)	263 (89.8%)	0.95 (0.85–1.06)	0.402
Cough	31 (49.2%)	150 (51.4%)	0.96 (0.73–1.26)	0.777
Fever	36 (57.1%)	166 (56.7%)	1 (0.79–1.27)	0.94
Diarrhea	3 (4.8%)	20 (6.8%)	0.69 (0.21–2.27)	0.55
Tiredness	29 (46%)	101 (34.5%)	1.3 (0.97–1.82)	0.067
Body ache	9 (14.3%)	52 (17.7%)	0.80 (0.41–1.54)	0.51
Sore throat	4 (6.3%)	31 (10.6%)	0.60 (0.21–1.63)	0.31

Table 4: Post-COVID symptoms at the time of follow-up

Reported post-COVID symptom	*Total* *n = 156*	*Reported post-COVID symptom*	*Total* *n = 156*
Easy fatigability and tiredness	49 (31.4)	Wheezing	7 (4.5)
Exertional breathlessness	41 (26.2)	Palpitation	6 (3.8)
Myalgia	25 (16)	Chest pain	5 (3.2)
Decreased sleep	22 (14.1)	Stroke	4 (2.6)
Weight loss	19 (12.2)	DVT	4 (2.6)
Cough	18 (11.5)	MI	4 (2.6)
Hair loss	11 (7.1)	Constipation	3 (1.9)
Lack of concentration	11 (7.1)	Nightmare	3 (1.9)
Deficit of memory	11 (7.1)	Rash	4 (2.6)
Headache	10 (6.4)	Loss of bladder control	3 (1.9)
Anxiety	7 (4.5)	Pedal edema	2 (1.3)
Depressed mood	7 (4.5)		

a good fit for the model. The model could explain 51.2% of the determinants of mortality (Nagelkerke's R^2 = 0.512). The significant predictors of in-hospital mortality were age ($p < 0.001$), hypoxia at the time of admission ($p < 0.001$), ICU admission ($p = 0.015$), serum creatinine ($p = 0.028$), and SF ratio ($p = 0.026$).

Result of Follow-up Data (*n* = 156)

Out of the participants who were followed up, the majority were males, 109 (69.8%). The mean age was 59.4 ± 14.1 years, ranging from 18–87 years. Most of the patients [73% (114/156)] complained of some symptoms at the time of follow-up (Table 4), and 23 (14.7%) reported hospitalization after discharge. Easy fatigability and tiredness were the most common symptoms, followed by exertional breathlessness, myalgia, decreased sleep, weight loss, and cough. About 53 (34%) patients suffered from some symptoms, dominated by easy fatigability, tiredness, exertional dyspnea, and cough, even after 1 year of follow-up. A significant association was found between gender and post-COVID symptoms (RR = 0.59 (0.37–0.94), *p*-value = 0.029). Females were at lower risk of having post-COVID symptoms (Table 5).

A number of 13 patients had a history of reinfection after discharge, and the median duration of reinfection was 12 months after the previous infection. Only three (1.9%) were immunized against COVID at the time of initial hospitalization, but most of them, 143 (91.6%), got vaccinated after the event. At the time of follow-up, the majority of them received two doses [79.4% (124/143)], 9.6% (15/143) received three doses, and 2.5% (4/143) received one dose of vaccination. Most of them were immunized with Covishield (adenovirus vector vaccine), 121 (84.6%); Covaxin (whole-virion inactivated vaccine), 20 (14%); one person with

Table 5: Factors associated with the reporting of post-COVID symptoms

Variables	*Categories*	*Post-COVID symptoms n = 156*		*Total*	*RR (95% CI)*	*p-value*
		Yes n = 114	*No n = 42*			
Gender	Female	29 (61.7)	18 (38.3)	47	0.59 (0.37–0.94)	0.029
	Male	85 (78)	24 (22)	109		
Hospitalization after discharge	Yes	22 (95.7)	1 (4.3)	23	8.1 (1.1–58.2)	0.037
	No	92 (69.2)	41 (30.8)	133		
Reinfection with COVID	Yes	10 (76.9)	3 (23.1)	13	1.23 (0.35–4.24)	0.74
	No	104 (72.7)	39 (27.3)	143		
Vaccination at the time of follow-up	Yes	104 (74.2)	39 (27.8)	143	0.98 (0.88–1.08)	0.73
	No	10 (62.5)	3 (18.7)	13		
Smoking *n* = 133	Yes	6 (75)	2 (25)	8	1.33 (0.28–6.34)	0.71
	No	86 (68.8)	39 (31.2)	125		
Alcohol consumption *n* = 148	Yes	7 (70)	3 (30)	10	0.92 (0.25–3.40)	0.906
	No	99 (71.7)	39 (28.3)	138		
Vaccinated at the time of hospitalization *n* = 144	Yes	3 (100)	0	3	Not calculated because of empty cell in the table	
	No	100 (70.9)	41 (29.1)	141		

Table 6: Factors associated to mortality at the time of follow-up

Variables	*Categories*	*Expired n = 15*	*Alive n = 141*	*Total n = 156*	*RR (95% CI)*	*p-value*
Sex	Female	2 (4.3)	45 (95.7)	47	0.41 (0.11–1.55)	0.192
	Male	13 (11.9)	96 (88.1)	96		
Post-COVID symptoms	Yes	13 (11.4)	101 (88.6)	114	1.2 (0.96–1.51)	0.09
	No	2 (4.8)	40 (95.2)	42		
Hospitalization after discharge	Yes	11 (47.8)	12 (52.2)	25	8.61 (4.62–16.03)	1.08
	No	4 (3)	129 (52.2)	133		
Reinfection	Yes	0 (0)	13 (100)	13	Not calculated because of empty cell in the table	
	No	15 (10.5)	128 (89.5)	143		
Vaccination	Yes	5 (3.5)	138 (96.5)	143	0.34 (0.16–0.69)	0.003
	No	10 (62.5)	3 (18.5)	16		
Smoking	Yes	3 (37.5)	5 (62.5)	8	6.05 (1.64–22.25)	0.006
	No	9 (7.2)	116 (92.8)	125		
Alcohol consumption	Yes	1 (10)	9 (90)	10	1.15 (0.15–8.40)	0.887
	No	12 (8.7)	126 (91.3)	138		
Vaccinated at the time of hospitalization *n* = 144	Yes	1 (33.3)	2 (66.7)	3	4.3 (0.41–44.64)	0.221
	No	14 (9.9)	1 27 (90.1)	141		

Pfizer (COVID mRNA vaccine); and one person with both Covishield and Covaxin.

On follow-up, 9.6% (15/156) had expired. Out of the 15 patients who had expired, the diagnoses were cancer, CAD, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), cerebrovascular accident (CVA), heart disease, pneumonia, and post-COVID complications. The median (IQR) duration from discharge to death was 30 (6.5–135) days. A significant association was found between vaccination status (positive) and smoking status (negative) with mortality at the time of follow-up (Table 6).

Discussion

One out of six patients in our cohort succumbed to death during hospitalization. It is very difficult to compare the mortality rates between different hospital settings. The mortality rate can vary between hospitals based on the clinical severity of patients admitted and the resources available at each hospital to save lives. The general in-hospital mortality rate of COVID-19 in the United States during the initial phase of the pandemic was 11–19%.[8] The hospital where we conducted the analysis was one of the apex hospitals in the backward tribal districts and reports a comparable in-hospital mortality rate. Most of the patients included in our cohort have severe SARS-CoV-2 infections, as indicated by the fact that three-fourths of the cohort needed ICU care. However, our data suggested that most patients received steroids and anticoagulants to support their lives, and antivirals were also tried on compassionate grounds as instructed by the state treatment guideline.[5] Like other settings, in our patients, the risk of death increased with age, comorbidity, and the extent of hypoxia.[9–12]

Comorbidities and multimorbidity as risk factors for death in COVID-19 have been

extensively studied.[10,11,13] In our study, the CFR exhibited a dose-response relationship with the number of comorbidities. In addition to malignancies, systemic hypertension was also associated with an increased likelihood of death. The presence of malignancy is a significant risk factor for mortality due to severe SARS-CoV-2 infection in hospitals.[9] However, the high prevalence of hypertension renders it a factor with a greater population-attributable risk. A meta-analysis involving over 0.5 million individuals from 23 observational studies across five countries revealed that systemic hypertension was the most significant contributor to mortality during the pandemic.[14] The study posits that systemic hypertension indirectly contributed to the elevated rates of COVID-19 mortality among elderly and morbid populations.[14] Lung involvement was evident in the chest X-rays of all patients, with those who expired showing a significantly higher average RALE score compared to the survivor group. The RALE score serves as a reliable predictor of oxygenation and clinical outcomes for patients with acute respiratory distress syndrome (ARDS). A higher RALE score correlated with lower partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) and poorer survival,[15] a finding consistent for COVID-19-associated lung injury.[16] We identified SpO_2/FiO_2 as a risk factor for COVID mortality as reported in other literature.[17] The SF ratio, or SpO_2/FiO_2, is a noninvasive surrogate for the PaO_2/FiO_2 (P/F) ratio, utilized to assess oxygenation in patients, particularly those with ARDS, and can be helpful in identifying more severe disease and prioritizing transportation and ICU admission in resource-limited settings.

We found that indicators of coagulopathy and organ involvement, such as markers like D-dimer, SGOT, SGPT, serum creatinine, and blood urea, exhibited a dose-response gradient with the risk of mortality. Elevated D-dimer values not only predicted the clinical outcomes of severe COVID-19 infections but also have prognostic significance during the recovery phase of the disease.[18] Liver and kidney involvement were also important predictors of COVID-19 mortality. Both organ injury, as a complication of the clinical severity of SARS-CoV-2 infection, and preexisting chronic diseases contributed to the risk.[19,20] The serological markers of hepatic and renal injury were the most commonly used prognostic factors for recovery from severe infection in hospital settings during the pandemic.[19,20] However, our multiple logistic regression model predicted that the age of the patient, hypoxia at the time of admission, serum creatinine, and ICU admission were the predictors of mortality, accounting for potential confounders. Among these factors, ICU admission serves as a surrogate measure for many clinical and biochemical markers, as the physician bases the decision about ICU admission on clinical judgment and biochemical markers of severity.

We conducted the follow-up study after 1 year of discharge, but we could include only a subgroup of patients in the study. The analysis revealed a 10% additional mortality in the cohort. Still, it is likely to be an underestimation of 1-year mortality outside the hospital because of selection bias, as the relatives of the deceased individuals may be less likely to answer our follow-up calls. However, combining both the data together, at least 25% of patients with severe COVID pneumonia admitted to the COVID hospital might have died either in the hospital or within 1 year of their hospitalization. Only a limited number of studies have analyzed COVID-19 mortality inside and outside of the hospital together. One-year mortality among patients admitted to 60 Spanish ICUs was 14% for noninvasively ventilated patients and 40% for patients who received mechanical ventilation.[21]

One-third of our patients (34%) reported symptoms even after a year following the infection. A systematic review and meta-analysis on the persistence of long COVID after 1 year reported high prevalence rates for persistent symptoms—fatigue/weakness (28%), dyspnea (18%), arthromyalgia (26%), depression (23%), anxiety (22%), memory loss (19%), concentration difficulties (18%), and insomnia (12%).[22] Our patients reported easy fatigability and tiredness as the most common symptoms during the follow-up period, followed by exertional breathlessness, myalgia, decreased sleep, weight loss, and cough. The syndrome complexes are very similar to another study conducted in the southern part of Kerala, India.[23] Easy fatigability is the most commonly reported symptom of long COVID in both severe and nonsevere infections of SARS-CoV-2.[24] Contrary to the reported literature, in our study, men are more prone to the development of post-COVID syndrome.[25]

We noticed that the presence of vaccines was negligible among the patients who were admitted with severe COVID manifestations. Still, almost all of them received the jab after being discharged from the hospital. COVID vaccines taken even after the infection and severe disease manifestation seem to offer significant protection from death. Smoking was found to be a risk factor for mortality among those who survived severe COVID-19 pneumonia. Vaccination against the disease delivers its protection from the progression of the infection to severity and prevention of mortality during the course of the illness.[26] If vaccination was a protective factor, tobacco smoking was a risk for every complication of SARS-CoV-2 infection. Smoking not only reduces lung health, but it is also thought to increase the likelihood of severe infection through extensive expression of angiotensin-converting enzyme 2 (ACE2) receptors in the respiratory passages.[27,28] A major strength of our paper is that we combined the follow-up data with the hospital data for our analysis. There are only a few reports from the deprived districts in India, where the mortality burden of the pandemic may be high because of the scarcity of resources. However, we could only include 39% of the initial cohort in the follow-up part of the study.

Conclusion

The COVID-19 was the only devastating pandemic that the current clinicians witnessed. It is essential to understand the major challenges the health system faced while navigating these difficulties. In this article, we present how a district with geographical and health-related challenges confronted the COVID-19 pandemic with the facilities available at a secondary care level. What did we physicians learn from this pandemic, and specifically from our study? Multimorbidity and age were two factors that increased mortality and morbidity, including ICU stays. This study also showed that, along with malignancies, systemic hypertension was found to be associated with a higher risk of death in patients with COVID-19 infection. We know there was a complete disruption in treating all other medical conditions during the early part of the pandemic. To prepare for future pandemics, we must focus on managing all multiple long-term conditions, specifically on the management and control of hypertension, as it is often undervalued by those diagnosed, with symptoms typically absent until target organ damage occurs. This study also provided follow-up data of hospitalized patients and emphasized the need for regular follow-up.

Ethics

Received IEC approval from the Institutional Ethics Committee, Government Medical College, Kozhikode, Ref. no. GMCKKD/RP 2024/IEC/37 dated February 16, 2024.

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ORIGINAL ARTICLE

A Study on Electrocardiography Echocardiography and Cardiac Biomarkers in Aluminium Phosphide Poisoning and Their Prognostic Correlation

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Abstract

Background: Aluminum phosphide (AlP) poisoning is a medical emergency with an alarmingly high mortality rate, primarily due to its rapid cardiotoxic effects.

Objective: To identify and evaluate key prognostic indicators—clinical, electrocardiographic, echocardiographic, and biochemical—in patients with AlP poisoning.

Materials and methods: A cross-sectional observational study was conducted on 100 patients with confirmed AlP ingestion. ECG changes, cardiac biomarkers (troponin-I, CPK-MB, LDH, and CPK-NAC), 2D echocardiography findings, and acid-base disturbances were analyzed in relation to survival outcomes.

Results: ECG abnormalities and decreased ejection fraction were significantly associated with mortality. Elevated cardiac biomarkers and profound acidosis were strong independent predictors of poor prognosis.

Conclusion: AlP poisoning causes critical cardiovascular compromise. Early identification of high-risk patients may guide aggressive intervention and resource allocation in intensive care settings.

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Introduction

Aluminum phosphide (AlP) poisoning represents one of the most fatal toxicological emergencies encountered in clinical practice, particularly in countries such as India, where the compound is widely used and poorly regulated.[1] Once ingested, AlP reacts rapidly with water and gastric acid to release phosphine (PH_3) gas, a potent mitochondrial poison.[2] Phosphine inhibits cytochrome c oxidase, disrupts the electron transport chain, reduces ATP production, and triggers a cascade of oxidative stress and cellular injury.[3] These biochemical disruptions predominantly affect vital organs with high metabolic demand, such as the heart, brain, and liver.[4]

Among the complications, cardiotoxicity remains the most prominent and prognostically significant. The majority of AlP poisoning-related deaths are attributed to refractory hypotension, cardiac arrhythmias, and severe myocardial depression.[5] Electrocardiographic changes such as ST-T wave abnormalities, conduction defects, tachyarrhythmias, and QT prolongation are frequently reported.[6] Additionally, echocardiographic findings such as global hypokinesia and reduced ejection fraction provide structural evidence of myocardial compromise.[7] Elevated cardiac biomarkers—troponin-I, CPK-MB, CPK-NAC, and LDH—further confirm the extent of myocardial damage.[8]

Despite these well-documented effects, timely identification of patients at greatest risk of death remains a clinical challenge. Early and accurate risk stratification can significantly influence management decisions, resource allocation, and potentially patient outcomes.[9] This study aims to evaluate the prognostic significance of these clinical and biochemical markers in patients with AlP poisoning. By doing so, the study seeks to contribute to both improved clinical outcomes and rational use of intensive care resources in this high-fatality poisoning scenario.[11]

Materials and Methods

This cross-sectional observational study was carried out in the Department of Medicine, Government Medical College, Kota, and affiliated hospitals over a 12-month period. Ethical clearance was obtained, and written informed consent was secured from all participants or their legally authorized representatives.

The study enrolled 100 patients above 18 years of age who presented with a clear history of AlP ingestion. Patients with preexisting structural or ischemic heart disease, congenital heart disease, or mixed poisoning were excluded. The objective was to assess parameters predictive of mortality and develop a practical nomogram model.

Each patient underwent detailed clinical evaluation on admission, including assessment of vitals, level of consciousness, oxygen saturation, and systemic examination. ECG was performed on admission and repeated every 24 hours or earlier if deterioration occurred. Electrocardiographic findings such as QT interval, ST-T changes, arrhythmias, or conduction defects were documented.

All patients underwent 2D echocardiography (using Wipro GE Vivid T8, 3S probe) within the first 24 hours of admission. Key echocardiographic parameters assessed included left ventricular ejection fraction (LVEF), global hypokinesia, regional wall motion abnormalities, and septal motion. Cardiac biomarkers—troponin-I, CPK-MB, CPK-NAC, and LDH—were analyzed at baseline and repeated every 24–48 hours depending on clinical status.

Laboratory tests included arterial blood gas (ABG), serum electrolytes, renal and liver function tests, and complete blood count. Patients were closely monitored for survival outcomes and duration of hospitalization.

Statistical analysis included multivariate logistic regression to identify independent predictors of mortality. This study emphasized the prognostic utility of early cardiac assessment and metabolic profiling in predicting clinical outcomes in AlP poisoning cases.

Results

This study analyzed 100 patients to assess prognostic indicators in AlP poisoning, with special emphasis on cardiac involvement. Correlation between specific ECG abnormalities and mortality in patients

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with AlP poisoning showed that, in those with atrial fibrillation and heart block, the mortality rate was 100%, indicating a strong association between these arrhythmias and fatal outcomes ($p = 0.008$). ST-T changes were the most prevalent abnormality, observed in 36 patients, with a high mortality rate of 72.2% ($p = 0.001$). Both ST elevation and ST depression were associated with significantly increased mortality ($p = 0.001$). These results emphasize that certain ECG abnormalities, especially atrial fibrillation, heart block, and ST-T changes, serve as strong prognostic indicators in AlP poisoning. The findings highlight the utility of ECG as a noninvasive, rapid bedside tool for early prognostication in AlP poisoning. The presence of malignant arrhythmias such as atrial fibrillation and heart block should immediately raise concern for poor prognosis and necessitate intensive monitoring. The statistically significant *p*-values reinforce the clinical relevance of ECG patterns in predicting patient outcomes and guiding the level of care required (Table 1).

A significant correlation between echocardiographic findings and patient outcomes in AlP poisoning was noted. Of the 60 patients evaluated, all 12 individuals with normal echocardiography findings survived (100%), strongly suggesting that normal cardiac function is a reliable predictor of survival. In contrast, global hypokinesia was present in 40 patients, with a mortality rate of 50%, indicating moderate prognostic risk. Most notably, decreased ejection fraction (EF) was observed in 45 patients, among whom 66.6% succumbed to the poisoning, establishing it as a powerful predictor of poor prognosis. The statistical significance of these findings ($p < 0.001$) confirms that echocardiographic abnormalities, particularly reduced EF, are closely linked to mortality. These results affirm the role of echocardiography as a noninvasive, rapid, and critical bedside tool for early prognostication in AlP poisoning. Identifying global hypokinesia and impaired EF early can aid clinicians in initiating aggressive supportive measures. This strengthens the case for routine echocardiographic evaluation in all moderate to severe cases of AlP poisoning. Integrating echo parameters into triage protocols may ultimately help reduce preventable deaths in resource-limited settings (Table 2).

A strong association was noted between elevated cardiac biomarkers and poor outcomes in patients with AlP poisoning. Among the 26 patients with positive troponin-I levels, 84.6% died, establishing troponin-I as a critical prognostic indicator ($p < 0.001$). Similarly, elevated CPK-MB and CPK-NAC levels were associated with 87.5 and 89.3% mortality rates, respectively, reinforcing their role in predicting myocardial injury severity. LDH, though a nonspecific marker, also showed a 90% mortality rate in positive cases, further confirming widespread cellular damage. The *p*-values for all markers were statistically significant (<0.001), underscoring their prognostic reliability. This reinforces the concept that myocardial damage, as evidenced by biochemical markers, plays a central role in AlP-related mortality (Table 3).

Multivariate analysis identified several independent predictors of mortality in AlP poisoning, emphasizing the critical role of both cardiac and systemic parameters. Cardiac biomarkers demonstrated the highest odds of predicting death, with positive CPK-NAC (OR 4.34), CPK-MB (OR 2.11), and troponin-I (OR 0.31) showing strong associations with fatal outcomes

Table 1: Correlation between specific ECG abnormalities and mortality ($n = 60$)

ECG abnormality	*Survived*		*Died*		*p-value*
	No.	*%*	*No.*	*%*	
Sinus tachycardia ($n = 24$)	16	66.7%	8	33.3%	0.045*
Sinus bradycardia ($n = 12$)	6	50%	6	50%	0.834
Atrial fibrillation ($n = 4$)	0	0%	4	100%	0.008*
VPCs ($n = 10$)	4	40%	6	60%	0.122
Heart block ($n = 4$)	0	0%	4	100%	0.008*
ST-T changes ($n = 36$)	10	27.8%	26	72.2%	0.001*
ST elevation ($n = 22$)	6	27.3%	16	72.7%	0.001
ST depression ($n = 14$)	4	28.6%	10	71.4%	0.001
BBB ($n = 8$)	2	25.0%	6	75.0%	0.038
QT prolongation ($n = 15$) (QTc)	12	80%	3	20%	0.001

*Indicates statistical significance $p < 0.05$

Table 2: Correlation between echocardiographic findings and outcome ($n = 60$)

Echo findings	*Survived*		*Died*		*p-value*
	No.	*%*	*No.*	*%*	
Normal ($n = 12$)	12	100%	0	0%	<0.001*
Global hypokinesia ($n = 40$)	20	50%	20	50%	
Decreased EF ($n = 45$)	15	33.3%	30	66.6%	

*Indicates statistical significance $p < 0.05$

Table 3: Correlation between cardiac biomarker and outcome ($n = 100$)

Markers	*Survived*		*Died*		*p-value*
	No.	*%*	*No.*	*%*	
Positive trop-I ($n = 26$)	4	15.4%	22	84.6%	<0.001*
Positive CPK-MB ($n = 32$)	4	12.5%	28	87.5%	<0.001*
Positive CPK-NAC ($n = 28$)	3	10.7%	25	89.3%	<0.001*
Positive LDH ($n = 30$)	3	10.0%	27	90.0%	<0.001*

*Indicates statistical significance $p < 0.05$

Table 4: Multivariate analysis of factors predicting mortality in aluminum phosphide poisoning ($n = 100$)

Factor	*Odds ratio*	*95% CI*	*p-value*
Abnormal ECG	6.44	2.42–17.15	<0.001*
Positive troponin-I	20.31	6.20–66.54	<0.001*
Positive CPK-MB	22.11	7.23–73.34	<0.001*
Positive CPK-NAC	24.34	5.02–72.45	<0.001*
Positive LDH	16.78	3.02–32.43	<0.001*
Abnormal PaO_2	9.03	3.65–22.34	<0.001*
Abnormal pH	4.89	2.01–11.88	<0.001*
Global hypokinesia	8.42	3.12–22.71	<0.001*
Decreased ejection fraction	18.67	4.86–71.72	<0.001*

*Indicates statistical significance $p < 0.05$

($p < 0.001$). Echocardiographic abnormalities, including decreased ejection fraction (OR 8.67) and global hypokinesia (OR 0.42), were also significant indicators of mortality, reinforcing the role of myocardial dysfunction in prognosis. Additional predictors included abnormal PaO_2 (OR 0.03), abnormal ECG (OR 0.44), and acid-base disturbances, particularly abnormal pH (OR 0.89). The high statistical significance ($p < 0.001$ for all) highlights the reliability of these factors in early risk stratification. This analysis supports the development of a practical, multiparameter prognostic model for early identification of high-risk patients, facilitating timely and aggressive therapeutic interventions in AlP poisoning (Table 4).

Discussion

Aluminum phosphide poisoning is notorious for its high case fatality rate and rapid clinical deterioration. This study aimed to identify reliable prognostic indicators for mortality through multivariate analysis. Findings from our 100-patient cohort underscore the critical role of cardiac dysfunction, oxygenation parameters, and acid-base balance in determining patient outcomes.

Among cardiac biomarkers, troponin-I, CPK-MB, CPK-NAC, and LDH were significantly elevated in nonsurvivors, with odds ratios ranging from 16.78 to 24.34. Troponin-I, in particular, demonstrated strong prognostic value, with 84.6% mortality in troponin-positive patients. Soltaninejad et al.[5] and Kalawat et al.[7] previously reported similar associations, highlighting the myocardial injury mechanism through mitochondrial disruption and oxidative stress caused by phosphine gas.

Electrocardiographic abnormalities were present in 60% of patients, with ST-T changes being the most frequent (60%), followed by sinus tachycardia and bradycardia. Specific abnormalities such as atrial fibrillation and heart block were associated with 100% mortality. These findings are consistent with those by Siddique et al.[12] and Singh et al.[8] and underscore the importance of ECG as a rapid and accessible tool for mortality risk stratification.

The most critical echocardiographic predictors were global hypokinesia and reduced ejection fraction. Mortality was 66.6% among those with reduced EF and 50% among those with hypokinesia, while all patients with normal echocardiograms survived. Elgazzar et al. and Sheta et al.[11] also emphasized the prognostic importance of these echocardiographic findings in their respective cohorts. Given that echocardiography is noninvasive and widely available, its utility as a bedside predictor is invaluable in the emergency setting.

Multivariate logistic regression identified 6 independent predictors of mortality: positive troponin-I (OR = 20.31), reduced EF (OR = 18.67), abnormal PaO_2 (OR = 9.03), global hypokinesia (OR = 8.42), abnormal ECG (OR = 6.44), and abnormal pH (OR = 4.89). These factors formed the foundation for the proposed risk prediction nomogram.

The interplay between acid-base imbalance and cardiac function was also evident. A strong association was found between low pH, low bicarbonate levels, and the presence of ECG abnormalities. These findings reinforce the understanding that metabolic acidosis not only reflects severity but also exacerbates myocardial dysfunction. Vikhe et al.[13] and Farzaneh et al.[9] also validated bicarbonate and pH as predictive tools in their analyses.

Our findings converge with those of Elgazzar et al.,[14] who also reported that global left ventricular hypokinesia, ECG abnormalities, and low oxygen saturation were independent predictors of mortality. While we did not assess the SOFA score, the identified variables overlap significantly with components of SOFA and other critical care scoring systems, supporting their integration into emergency protocols.

In summary, this study emphasizes the role of early and comprehensive cardiac evaluation in the prognostication of AlP poisoning. The use of accessible tools—ECG, echocardiography, cardiac biomarkers, and ABG—enables effective risk stratification. Our nomogram approach allows clinicians to anticipate adverse outcomes and tailor management strategies accordingly. Future work should focus on external validation and refining this tool for broader clinical use.

Conclusion

Our study demonstrates that certain clinical, biochemical, electrocardiographic, and echocardiographic parameters can serve as reliable prognostic indicators in AlP poisoning. Notably, positive troponin-I, reduced ejection fraction, abnormal ECG findings, low PaO_2, global hypokinesia, and acid-base disturbances were identified as independent predictors of mortality on multivariate analysis. The findings support the development of a practical, bedside prognostic tool that can guide clinicians in triaging patients for intensive monitoring and interventions.

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ORIGINAL ARTICLE

Assessment of WHO Core Drug Use Indicators in a Government Teaching Hospital of Assam: Evidence from Prescription Audit Data

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Abstract

Background: With the rise of irrational drug prescriptions, leading to polypharmacy, increased health care costs, drug interactions, and risks of adverse drug reactions, irrational antibiotic prescribing, overuse of injections, and hospitalization, it has become important to monitor drug use patterns.

Materials and methods: With the objective to assess the drug use indicators of a government teaching hospital of Assam using WHO Core Drug Use Indicators, 700 prescriptions from OPDs of various specialties were assessed prospectively from the hospital dispensary and details of core drug use indicators were noted and analyzed for each in a proforma as per WHO recommendation on investigating drug use in health care facilities. Descriptive statistics were used thereafter to express the results.

Results: The WHO core prescribing indicators analysis revealed that the average number of drugs per encounter was 3.6. The percentage of drugs prescribed by generic name was 37%, with only 6% being injectable drugs; however, 39.14% of prescriptions included one or more antibiotics. Only 37% of the drugs prescribed were from the NLEM.

Conclusion: This study highlights that only prescriptions involving injectable drugs were in accordance with WHO recommendations, while the other parameters exceeded the WHO-recommended values.

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Introduction

With the rise of irrational drug prescriptions, leading to polypharmacy, increased health care costs, drug interactions, and risks of adverse drug reactions, irrational antibiotic prescribing, overuse of injections, and hospitalization, it has become important to monitor drug use patterns. Polypharmacy, inappropriate use of antimicrobials, overuse of injections, and failure to prescribe as per clinical guidelines shall be labeled as irrational use of medicines.[1] The drug utilization pattern can be reliably assessed by the World Health Organization (WHO) core prescribing indicators, which is a highly standardized tool to identify the drug use problem areas and alert physicians to rational prescribing.[2]

Interventions to promote rational use of medicines are: framing appropriate policies on medication use, use of clinical guidelines, adaptation of National List of Essential Medicines, incorporating committees for drug use in respective hospitals, initiating of case-based pharmacotherapy modules in undergraduate curriculum, continuing medical education as an essential component for licensure renewal, supervision, timely audit of prescriptions and feedback to the physicians, use of Drug Information Centers (DIC) for prescribing and public education, refraining from financial incentives, adhering to guided regulations and sufficient government expenses to ensure round-the-clock availability of medications and health care providers.[3]

As part of the monthly prescription audit for the hospital, this study aims to analyze the trends in drug prescribing patterns in a tertiary teaching hospital in Assam, adopting the WHO-core prescribing indicators.

Materials and Methods

A cross-sectional study was carried out in the dispensary of a teaching government hospital. 700 prescriptions were analyzed (WHO "How to investigate drug use in health facilities"[2] document advocates minimum 600 prescriptions) using simple random sampling for the WHO core prescribing indicators in the process of routine monthly prescription audits for the hospital. The investigator visited the hospital dispensary every day for a month and collected digital photographs of the prescriptions, irrespective of the department and diagnosis, after the prescribed drugs were dispensed.

The WHO guidelines and methodology[2] were followed as mentioned in the document to ensure data reliability. Data was collected and recorded in a data collection form, designed to contain the parameters for evaluation, excluding details of patient identifiers. Completeness of the prescriptions was also assessed along with the core prescribing indicators, which include patient identifiers (Name, Age, Sex, Address, Religion), physician identifier (name/signature), instructions (review, follow-up advice), and dose regimen.

All the values were recorded and analyzed using Microsoft Excel. Data are presented using descriptive statistics, including means, frequencies, and percentages.

Results

A total of 700 outpatient prescriptions were assessed. On analyzing the dosage regimes, the total drugs prescribed were found to be 2,521, of which only 1,080 drugs were available in the hospital dispensary (1.54 drugs per prescription were available). Hence, 42.8% of drugs were actually dispensed, and the remaining 57.2% of prescription drugs either had to be bought from pharmacies or, if expensive, they might be skipped by the poor who cannot afford them, thereby leading to incomplete treatment.

The WHO prescribing indicators of the 700 analyzed prescriptions are listed in Table 1.

Parts of the prescription containing patient particulars (Name, Age, Sex, Date of consultation, OPD registration number, Address, Religion) were printed at the ticket-dispensing counter and hence were 100% present in all prescriptions.

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Table 1: WHO prescribing indicators

Core prescribing indicators	*Value*	*WHO optimal values*
Average number of medicines per encounter	3.6 drugs per prescription	1.6–1.8
Percentage of prescriptions with generic name	37%	100%
Percentage of drugs prescribed from essential medicines list	45.3%	100%
Percentage of encounters with an injection prescribed	6%	13.4–24.1%
Percentage of encounters with one or more antibiotics	39.14%	20–26.8%

Table 2: Clinical examination details

Variables	*Percentage (%) mentioned*
Brief history/chief complaints of the patient	39.5
Salient features of clinical examination	32.5
Presumptive/definitive diagnosis	36.8
Any history of allergy to food/medication mentioned?	0

Table 3: Completeness of prescription

Variables	*Percentage (%) mentioned*
Percentage of prescriptions having medicines prescribed in generic name	37
Percentage of prescriptions having medicine schedules/doses written	95.5
Duration of treatment written	96.4
Date of next visit/review written	70.8
Follow-up advice and precautions (do's and don'ts) mentioned	24.5

However, to maintain the privacy of the study participants and the confidentiality of their personal information, the data were excluded from the data collection format. Out of all, 58 pediatric prescriptions were encountered, and weight was mentioned for only 46 of them (79.3%). Handwriting was legible in 82.1% of prescriptions, with 7.42% of them lacking a legible doctor's signature/name.

Clinical examination details of the patient mentioned are listed in Table 2. The completeness of the prescription concerning the dosage regimen is mentioned in Table 3. Routine investigations were prescribed to 43.8% of the patients. 36.2% of prescriptions included at least one Vitamin, tonic, or enzyme.

Discussion

In this study, the WHO core prescribing indicators and completeness of prescriptions were assessed. Our observations were compared to studies conducted by Priyadarsini et al.,[4] Meenakshi et al.,[5] Özdamar et al.,[6] Karki et al.,[7] and Asmamaw et al.[8] (Table 4) for different parts of the world.

Our study has the highest record for the number of drugs per prescription amongst all other studies compared with,[4–8] although the availability of drugs was not at par. In our study, although only 37% of prescriptions had generic name drugs prescribed, the lowest percentage of 0 (zero) and the highest 87.5% was observed in other studies,[4,6] respectively. Also, in this study, only 39.14% of the prescriptions had drugs being prescribed from the ELM, which is much lower than the WHO standard value (100%). Whereas, a highest of 88% and a lowest of 17.5% was seen with other studies,[4,5] respectively. Generic drug prescribing helps decrease the cost of treatment burden for the patients, as most of them are available in the hospital dispensary free of cost, as per the NLEM. Hence, physicians should be motivated to prescribe generic drugs from the ELM.

Although our study had 45.3% of OPD prescriptions with an antibiotic (greater than the WHO optimal value), it is still less than those compared to other studies.[4,8] This finding may be due to a lack of prescribing practice as per the standard treatment guidelines.[9] Rational antibiotic prescribing can be achieved by adapting and implementing diagnostic and treatment guidelines for the hospital.

In the current study, the percentage of encounters with an injection was 6%, which is well below the WHO optimal value of 13.4–24.1%. This finding is consistent with the studies conducted by Priyadarsini et al.,[4] Meenakshi et al.,[5] Özdamar et al.,[6] Karki et al.,[7] and Asmamaw et al.[8] The probable reason for the lower prevalence of injections could be the availability of cheaper, noninvasive, and less expensive oral medications over the parenteral route. Moreover, patients visiting outpatient services are more compliant with oral medicines until it is a regular and easily administered injection (such as tetanus toxoid, antirabies vaccine, etc.).

All the sampled prescriptions in this study (700 prescriptions) were complete with the patient identifier data (100%) as a "Scan and Share" method, using ABHA ID to generate the OPD prescriptions for all departments. It is a convenient, faster, and accurate method used. Similar was the finding for studies conducted by Meenakshi et al.,[5] Singh et al.,[10] and Mercy et al.,[11] pertaining to printed details of the patient. Whereas, audits of handwritten prescriptions were usually found to be incomplete for the patient's details.[12]

The clinical examination details were mostly incomplete upon analysis in this study, and a similar finding was observed in other studies.[10] This could be due to hectic OPDs with heavy patient loads, where the doctors prefer verbal communication rather than noting the details. Prescriptions were also found to be incomplete regarding medication dose, schedule, duration of treatment, dos and don'ts, review, follow-up advice, and precautions. Such omissions were also seen in other studies[8,10] at various rates, which can lead to therapeutic failure, antibiotic resistance, drug reactions, incorrect intake of dose, incorrect duration of treatment, and omission of dose. Enrollment into the prescribing skills course designed for Indian medical graduates, sensitization of clinicians on both legal and ethical aspects of completeness of prescriptions, and discussion and dissemination of prescription audit data to all clinicians can help boost the writing of proper and complete prescriptions in daily practice.

The illegible handwriting of doctors has been infamous for ages.[13] In this study, 17.9% of the prescriptions had illegible handwriting, which was in accordance with the study by Singh et al.[10] This could lead to adverse drug reactions, medication errors, and even wrong dispensing of the drugs by the pharmacist. Contrary to this, in a study conducted by Meenakshi et al.,[5] 97.8% of prescriptions were written legibly. Also, 7.42% of the prescriptions in our study lacked a legible doctor's signature. Meanwhile, in the study by Singh et al.[10] and Meenakshi et al.,[5] the

Table 4: Comparison of the WHO prescribing indicators with other studies

Prescribing indicators	*Our study*	*Priyadharshini et al.*[4]	*Meenakshi et al.*[5]	*Özdamar et al.*[6]	*Karki et al.*[7]	*Asmamaw et al.*[8]
Average no. of drugs per encounter	3.6	2.5	2.38	2.9	2.6	1.83
Percentage of drugs prescribed by generic name	37%	87.5%	55.4%	0	41.4%	65.3%
Percentage of encounters with an antibiotic	39.14%	62.5%	7.3%	2.6%	11.7%	63.8%
Percentage of encounters with an injection	6%	0	10.5%	10.7%	3.8%	11.5%
Percentage of drugs prescribed from ELM	45.3%	17.5%	88%	33.8%	34.3%	78.9%

value is even higher, with 34.2% and 20.3% of prescriptions having illegible signatures, respectively. This value was highest in a study conducted by Asmamaw et al.,[8] where 94% of prescriptions had a prescriber's signature. These details of the prescribing doctor are important to validate the authenticity of the prescriptions. No (zero) prescriptions from our OPD had doctor's registration numbers mentioned, while just 3.3% and 46.77% mentions were seen in other studies, respectively.[10,11]

Routine investigations were ordered in 43.8% of our prescriptions, while 63.87% of investigations were ordered in the study conducted by Mercy and Antony.[11] This study provides constructive feedback to the hospital administration on implementing strategies and establishing guidelines for prescribing more generic drugs and appropriate antibiotics as per clinical guidelines. Further, the need for more legible and complete prescriptions still stands. Moreover, with continued regular prescription audits, the drug use pattern and behavior shall improve. It is also recommended that the hospital dispensary keep stocks of NLEM medicines updated and make them available for the patients at all times, which shall not only reduce the cost burden on the patients but also encourage physicians to prescribe from the NLEM for both OPD and IPD patients.

Inability to assess the indicators for patient-care and complementary drug use are the limitations of the study. However, the prospective design helps collect data directly from the patients and prevents data duplication as well.

Conclusion

For cost-effective health care and to provide sustainability to improve patient outcomes, WHO advocates the "Responsible use of Medicines," which indicates that appropriate use of medicines for optimum benefit to the patients can be achieved by aligning existing resources and healthcare facilities with the stakeholders.[14] Regular audits of the OPD prescriptions have now provided insightful observation reports and continuing medical education on rational prescriptions, with adherence to clinical protocols and therefore improving and ensuring the quality of healthcare.

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ORIGINAL ARTICLE

A Clinical Profile of Transverse Myelitis with Special Reference to Outcomes: A 5-Year Retrospective Study

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Abstract

Introduction: Transverse myelitis (TM), a rare inflammatory condition affecting the spinal cord, presents with a rapid onset of bilateral motor and sensory symptoms with or without bladder/bowel and sexual dysfunction. Recent studies are attempting to identify its improvement, worsening, or conversion to multiple sclerosis, and the factors that determine these outcomes. The present study aims to assess the immediate and long-term outcomes of TM and to determine the factors associated with them.

Materials and methods: The study involved a retrospective review of hospital records of 30 patients diagnosed with TM between 2018 and 2022, followed by a telephonic interview to assess their present outcomes.

Results: Median age of the patients was 40 years [Interquartile range (IQR) = 30–48.5], with 53% males. About 76.7% had longitudinally extensive transverse myelitis (LETM). Onset was acute in 63.3%. Half (50%) of the patients had paraparesis. MRI spine showed involvement of the long segment in 65.5% and the short segment in 24.1%. At the end of treatment, 43.3% patients improved partially, and 16.7% improved completely. At follow-up, nearly 30% of the respondents reported complete recovery, while 8.3% reported worsening. One patient (3.33%), with an acute onset of TM, quadriparesis, bowel involvement, sexual dysfunction, and long spinal segment involvement, converted to multiple sclerosis at follow-up. 25% of patients with initial partial improvement showed complete improvement at follow-up.

Conclusions: Acute onset LETM cases can potentially convert to multiple sclerosis. Patients who show early improvement, whether partial or complete, have higher chances of complete recovery at follow-up.

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Introduction

Transverse myelitis (TM), a relatively rare disease characterized by inflammation of the spinal cord involving its length as well as width, presents with a rapid onset of bilateral weakness of the limbs and sensory deficit with or without bladder/bowel/ sexual dysfunction.[1,2] Its etiology may be classified as infectious/postinfectious, autoimmune, and idiopathic.[3] Its clinical manifestations depend primarily on the location of the lesion and the severity of involvement of the spinal cord.[4] Its treatment includes intravenous steroids or immunoglobulins, plasmapheresis, monoclonal antibodies, rehabilitation, and supportive care.[5] Despite this, its outcomes differ from person to person and depend on the etiology, site, and severity of spinal cord involvement. and the time of initiation and nature of the treatment. The present study aims to assess the immediate and long-term outcomes of TM and to determine the factors that influence these outcomes.

Selection Criteria

- Presentation of symptoms and signs of acute noncompressive myelopathy.
- Evolution of symptoms for no more than 4 weeks, sustained for at least 48 hours, and maximum peak reached in more than 4 hours.
- No evidence of symptoms or signs suggestive of cranial involvement.[6]
- Absence of any other chronic neurodegenerative disorders.

Materials and Methods

Study Design

Retrospective analytical follow-up study.

Study Site

Apollo Hospitals, Chennai, Tamil Nadu.

Study Subjects

Patients diagnosed with TM between 2018 and 2022.

Sample Size

Hospital records of patients diagnosed with TM between 2018 and 2022 were reviewed. A total of 30 patients who met the selection criteria were enrolled in the study.

Data Collection

The case sheets of the 30 patients with TM were retrieved from the medical records department. A semistructured questionnaire format was used to collect the data on their clinical history, diagnosis, and immunological and radiological findings. A telephonic follow-up interview was done to obtain details of their present status. The initial modified Rankin Score (mRS) scores at the time of presentation were estimated based on the documented history and examination. The outcome of each patient at the time of discharge is recorded as the "initial" outcome. Final mRS scores, as well as "final" outcomes or "outcome at follow-up," were estimated based on their responses to the telephonic interviews.

Statistical Analysis

Data were managed, cleaned, coded, and analyzed using Microsoft Excel 2010 and SPSS version 21.0. Continuous variables are described in the form of Median and interquartile ranges (IQR). Categorical variables are described in the form of frequencies and proportions. The outcomes were compared with respect to various dependent and independent variables to understand the effects of each variable on the initial outcomes and outcomes at follow-up.

Results

The median age of the patients was 40.5 years (IQR = 30.5–48.75 years), and males and females were almost equally involved, with a slight male predominance (16/30, 53.33%), with a sex ratio of 8 males per 7 females (1.14) (Table 1).

Sensory involvement was noted in 24/30 (80%) of subjects. Pain and temperature involvement was seen in 22/24 (91.67%); among these, it was most common (12/24, 50%), and only 2/24 (8.3%) had vibration and proprioception involvement. Involvement

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of both pain and temperature, as well as vibration and proprioception, was seen in 10/24 (41.67%). Paresis of varied severity was seen in 21/30 (70%) subjects, among which paraparesis was most common (16/21, 76.2%), followed by Brown-Sequard-like partial weakness (i.e., unilateral partial loss of power in upper and lower limbs) seen in 3/21 (14.3%) and quadriparesis seen in 2/21 (9.5%). Complete paralysis ("plegias") was seen in 9/30 (30%), including paraplegia in 8/9 (88.9%) and Brown-Sequard-like complete weakness (i.e., unilateral complete loss of power in upper and lower limbs) in 1/9 (11.1%).

Bowel involvement was seen in 22/30 (73.33%), and bladder involvement was seen in 21/30 (70%) subjects. Visual symptoms were noted in 3/30 (10%) subjects, including two subjects with monocular and one subject with binocular involvement.

MRI was done in 29/30 subjects, wherein involvement of the spinal cord long segment, i.e., *>3 vertebral segments*, was seen in the majority of the subjects (19/29, 65.5%), followed by spinal cord short segment, i.e., ≤3 vertebral segments, in (7/29, 24.1%). Only three subjects (10.3%) showed involvement of the brain and spinal cord long segment on MRI. Hence, based on the nature of spinal cord and brain involvement identified by MRI, longitudinally extensive transverse myelitis (LETM) was the predominant diagnosis among the subjects (22/29, 75.86%).

Radiologically, the most common site of lesion was thoracic in 15/29 (51.73%), followed by cervical in 6/29 (20.68%). In comparison, 4/29 (13.79%) showed cervical and thoracic cord involvement, one (3.45%) subject had thoracic and lumbar involvement, two (6.90%) had extensive involvement from thoracic to conus, and one (3.45%) subject had extensive involvement from cervical to lumbar region (Fig. 1).

A contrast study, along with MRI, was done on 26 subjects. Normal findings (no enhancement) were documented in 17/26 (65.4%), whereas enhancement was reported in 9/26 (34.6%). Three out of these 9 subjects (33.3%) showed leptomeningeal enhancement; among them, one subject had autoimmune etiology with positive antihistone antibodies, and the other two subjects had parainfectious etiology. One out of the 9 subjects (11.1%) with contrast enhancement was positive for antinuclear antibodies (ANA).

Cerebrospinal fluid (CSF) analysis was done in 23/30 (76.67%) subjects, among which 4/23 (17.4%) had abnormal CSF cell counts (> 10 cells/dL, with no polymorphonuclear cells) and 11/23 (47.8%) had raised CSF proteins (> 45 mg/dL).

The findings of various serological investigations are documented in Table 2.

Table 1: Baseline characteristics of Transverse myelitis cases

Characteristics	*Frequencies (proportions)*
Median age [IQR]	40.5 years [30.5–48.75 years]
Gender	
Males	16/30 (53.3%)
Females	14/30 (46.7%)
Onset	
Acute (<1 week)	19/30 (63.3%)
Subacute (1 – 4 weeks)	11/30 (36.7%)
Weakness	
Paresis	21/30 (70%)
Paraparesis	16/30 (53.3%)
Quadriparesis	2/30 (6.7%)
Brown-Sequard-like	3/30 (10%)
Plegia	9/30 (30%)
Paraplegia	8/30 (26.7%)
Brown-Sequard-like	1/30 (3.3%)
Bowel involvement	
Present	22/30 (73.3%)
Absent	8/30 (26.7%)
Bladder involvement	
Present	21/30 (70%)
Absent	9/30 (30%)
Visual symptoms	
Present	3/30 (10%)
Absent	27/30 (90%)
CSF Analysis	Done in 23/30, Not done in 7/30
CSF cell counts:	
Normal	19/23 (82.6%)
Abnormal	4/23 (17.4%)
CSF proteins	
Normal	12/23 (52.2%)
Abnormal	11/23 (47.8%)
MRI findings	
Not done in	1/30
Spinal cord Long segment	19/29 (65.5%)
Spinal cord Short segment	7/29 (24.1%)
Brain + spinal cord long segment	3/29 (10.3%)

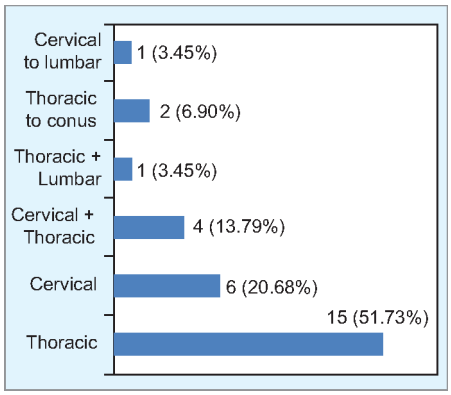

Fig. 1: Distribution of Transverse myelitis cases based on site of lesion (*n* = 29)

Table 2: Findings of serological investigations of transverse myelitis cases

Investigations	*Frequencies (proportions)*
Serological investigations done	11/30 (36.7%)
Positive serological reports	5/11 (45.4%)
SSA Antibodies	1
Anti-histone Antibodies	1
CENP + ANA Antibodies	1
ANA antibodies alone	2
The MOG antibody test was done in	20/30 (66.7%)
Positive in	1/20 (5%)

Table 3: Comparison of baseline characteristics and clinical presentations based on early outcomes (*n*, row%)

Early outcomes (n = 30)	*Completely improved (5, 16.67%)*	*Partially improved (13, 43.33%)*	*No change (12, 40%)*
Median age (in years)	36	33	46
IQR	32–41	29–50	36–47.25
Onset			
Acute (19, 63.33%)	4 (21.0%)	8 (42.1%)	7 (36.9%)
Subacute (11, 36.67%)	1 (0.9%)	5 (45.45%)	5 (45.45%)
Gender			
Male (16, 53.33%)	3 (18.75%)	6 (37.5%)	7 (43.75%)
Female (14, 46.67%)	2 (14.3%)	7 (50%)	5 (35.7%)
MRI findings (*n* = 29)			
SSTM (7, 24.14%)	3 (42.8%)	2 (28.6%)	2 (28.6%)
LETM (22, 75.86%)	2 (9.1%)	11 (45.45%)	10 (45.45%)
Weakness			
Paresis (21, 70%)			
Para (16, 53.33%)	2 (12.5%)	8 (50%)	6 (37.5%)
Quadri (2, 6.67%)	2 (100%)	0 (0%)	0 (0%)
One-sided (3, 10%)*	1 (33.33%)	1 (33.33%)	1 (33.33%)
Plegia (9, 30%)			
Para (8, 26.67%)	0 (0%)	3 (37.5%)	5 (62.5%)
One-sided (1, 3.33%)	0 (0%)	1(100%)	0(0%)

*One-sided (Brown-Sequard-like), unilateral complete loss of power in upper and lower limbs

Myelin oligodendrocyte glycoprotein (MOG) antibody test was done for 20 subjects, and 1/20 (5%) showed positive results. Aquaporin antibodies were tested in 22 subjects, but were negative in all. Fourteen subjects were tested for oligoclonal bands (OCB) in CSF, and only one was positive. Serological investigations were done for connective tissue disorders in 11/30 (36.67%), and 5/11 (45.4%) were positive for antibodies, with 1 in each (CENP + ANA, SSA, and antihistone), and ANA antibodies alone were positive in 2/22 (9.09%).

Distribution according to the etiological classification of TM showed that idiopathic TM was most common (15/30, 53%), followed by postinfectious (7/30, 23.33%). 2/30 (6.7%) had COVID-19 infection, while 5/30 (16.7%) had various systemic autoimmune conditions [Including SLE (3), SJS (1), and CREST syndrome (1)]. Onset was acute, i.e., developing over a few hours to 1 week, in nearly two-thirds (19/30, 63.33%), while the remaining (11/30, 36.67%) had subacute onset, i.e., developing over 1 to 4 weeks.

Treatment was given in a stepwise manner, starting with IV methylprednisolone.

Twenty-nine of 30 (96.67%) subjects, viz., 25/29 (86.2%) received 1000 mg for 5 days and 4/29 (13.8%) received 500 mg of methylprednisolone for 5 days, while one subject received 40 mg of oral prednisolone from the start of treatment. Oral Prednisolone was continued in all of them in tapering doses for the next 15 days. Those who did not show sufficient improvement with steroids were treated with rituximab (6/30, 20%), intravenous immunoglobulins (5/30, 16.67%), or plasmapheresis (3/30, 10%) (Table 3).

The early outcomes at the time of discharge showed that 18/30 (60%) had improved, 5 (27.8%) completely, and 13 (72.2%) partially, while 12 (40%) showed no immediate improvement. During the period of hospitalization, complications were documented in 14/30 (46.7%). The most common complications noted were Urinary tract infections in 7/14 (50%), bedsores in 4/14 (28.6%), steroid-related complications in 3/14 (21.4%), and others, including contractures in 2 (6.67%) and deep vein thrombosis in 1 (3.33%) (Table 4).

During the telephonic follow-up, 25 out of 30 patients were only able to be contacted, and one out of them had died due to the existing comorbid condition of liver failure and multiple organ dysfunction syndrome (MODS). Data from the follow-up interviews showed that 15/24 (62.5%) subjects improved, with 8/24 (33.33%) showing partial improvement and 7/24 (29.16%) showing complete improvement, while 5/24 (20.83%) showed no change. However, two subjects (8.33%) reported worsening of the symptoms. Two subjects developed new symptoms, i.e., Guillain–Barré syndrome and multiple sclerosis, respectively (Table 5).

The initial modified Rankin Score (mRS) of the subjects at the time of their presentation was deduced from the history and examination. However, the final mRS could be assessed for only 24/30 subjects via the telephonic follow-up interview, as five subjects were lost to follow-up and one died due to liver failure. Analysis of mRS scores showed a reduction in the median score from four (IQR = 4–5) at baseline to one (IQR = 0–2) at follow-up. The mRS score improved completely in 9/24 (37.5%) and partially in 12/24 (50%) subjects, while 3/24 (12.5%) showed no change. The number of subjects with bowel and bladder involvement who showed improvement was 8 and 10, respectively.

Three subjects had shown brain and spinal cord long-segment involvement on MRI. Among them, one patient had died. One had completely improved. One subject showed no improvement. Three subjects (10%) had visual symptoms at admission; among them, 2 (66.7%) had monocular involvement and 1 (33.3%) had binocular involvement. All three cases were LETM type with an acute onset of TM. Although one of them showed complete initial improvement, the other two showed no improvement.

The subjects with LETM alone had higher partial improvement initially as well as at follow-up, i.e., 47.4% and 37.5%, respectively. In comparison, short segment transverse myelitis (SSTM) patients have made a high proportion of patients with complete improvement initially as well as at follow-up, i.e., 42.8% and 66.6%, respectively. In contrast to SSTM, LETM subjects had shown worsening (2/18, 11.1%) or development of new symptoms (2/18, 11.1%).

There were 10 subjects with a duration of >4 years between the onset of symptoms and follow-up. Among them, 5/10 cases were lost to follow-up, 1 died, 2/10 developed new symptoms, and 2 showed complete improvement. 4/7 subjects with <1 year duration since onset showed no improvement, 2/7 remained partially improved, while 1/7 showed complete improvement.

Partial improvement was highest among subjects with paraparesis, i.e., 8/16 (50%) at initial assessment and 5/13 (38.4%) at follow-up. Both subjects with quadriparesis had complete initial improvement, but at the time of follow-up, one of them developed new symptoms. The single patient with "Brown-Sequard-like complete weakness" initially showed partial improvement but later worsened by the time of follow-up.

Changes in mRS scores across subjects with different antibodies are depicted in Table 6.

There was one subject with positive oligoclonal bands in CSF alone, and this subject showed partial improvement at follow-up.

Three subjects had extensive involvement of the spine, i.e., from cervical to lumbar in 1 and thoracic to conus in 2 subjects. Although they showed initial partial improvement, one subject had worsened at follow-up, one remained partially improved, and one was lost to follow-up. The subjects with short-segment involvement showed high mRS improvement as compared to long-segment involvement (Table 7).

Analysis of the distribution of outcomes at follow-up, based on the initial outcomes, showed that most subjects with initial partial improvement maintained partial improvement (50%) and complete improvement (25%). One patient with complete initial improvement had developed new symptoms (Table 8).

Discussion

While no significant difference in outcome was observed between patients with acute and subacute onset TM, the small sample size at follow-up precludes definitive conclusions. However, Simone et al.[7] identified rapid onset with complete paraplegia and spinal shock as potential predictors of poor prognosis.

Among patients presenting with TM, paraparesis is the most prevalent symptom. Notably, 81.8% of individuals with paraparesis demonstrate improvement. However, the extent of improvement is inversely proportional to the severity of initial weakness, regardless of presentation pattern (paraparesis, quadriparesis, Brown-Séquard syndrome). This observation aligns with the findings of Defresne et al.[8] who identified paraplegia as a significant predictor of unfavorable prognosis.

Consistent with previous findings by Harzheim et al.[9] demonstrating thoracic spinal cord involvement as the predominant pattern in acute TM, our study identified thoracic cord lesions as the most frequent localization. Notably, 83.33% of patients with isolated thoracic involvement had a positive mRS score, suggesting improvement. Moreover, complete recovery was observed in patients with both isolated cervical lesions and those with extensive lesions encompassing both the cervical and thoracic regions.

Among patients with LETM, 75% demonstrated clinical improvement, whereas 83.3% of those with SSTM did. Interestingly, one LETM patient with two relapses was subsequently diagnosed with clinically defined multiple sclerosis. Notably, CSF cell counts and protein values did not reveal any significant correlation with clinical outcomes.

The median initial mRS score of the subjects was 4 (IQR = 4–5), and it reduced to 1 (IQR = 0–1) at final follow-up. The mRS scores improved in 20/24 (83.3%) subjects, while 3 subjects (12.5%) showed no change. Bowel dysfunction and bladder dysfunction were improved in 38% and 47% of patients, respectively. The higher the initial Rankin score, the poorer the long-term outcome.[10] All subjects underwent a systematic therapeutic approach, commencing with intravenous methylprednisolone. Subsequent to inadequate response to intravenous steroids, subjects underwent additional treatment modalities including plasmapheresis, intravenous immunoglobulins, and rituximab. Evaluation of immediately documented outcomes at discharge revealed a noteworthy recovery rate: 60% of subjects showed improvement (43.3% partial recovery and 16.7% complete recovery). This contrasted with the findings of Chinnappan et al.,[11] where a mere 33% of subjects demonstrated recovery with limited or no residual effects.

In the current investigation, two subjects were identified with COVID-19. Both subjects underwent intravenous methylprednisolone

S. No.	mRS score before	mRS score present	mRS difference	Outcome
1	5	2	3	Improved
2	4	1	3	Improved
3	5	2	3	Improved
4	2	1	1	Improved
5	5	5	0	No change
6	5	5	0	No change
7	4	0	4	Improved
8	5	0	5	Improved
9	4	1	3	Improved
10	2	0	2	Improved
11	2	0	2	Improved
12	4	0	4	Improved
13	3	1	2	improved
14	4	1	3	Improved
15	3	1	2	Improved
16	2	1	1	Improved
17	4	3	1	improved
18	1	0	1	Improved
19	4	1	3	Improved
20	2	1	1	Improved
21	4	3	1	Improved
22	5	LTF	N/A	N/A
23	5	LTF	N/A	N/A
24	5	0	5	Improved
25	4	0	4	Improved
26	5	LTF	N/A	N/A
27	5	6	N/A	DEATH
28	4	LTF	N/A	N/A
29	4	LTF	N/A	N/A
30	5	5	0	No change

Table 4: Comparison of baseline characteristics and clinical presentations based on various late outcomes (*n*, row%)

Late outcome (n = 24)	*Completely improved (7, 23.33%)*	*Partially improved (8, 26.67%)*	*No change (5, 16.67%)*	*Worsened (2, 6.67%)*	*New symptoms (2, 6.67%)*
Onset					
Acute (15, 62.5%)	4/15 (26.68%)	5/15 (33.33%)	2/15 (13.33%)	2/15 (13.33%)	2/15 (13.33%)
Subacute (9, 37.5%)	3/9 (33.33%)	3/9 (33.33%)	3/9 (33.33%)	0/9 (0%)	0/9 (0%)
Gender					
Male (12, 50%)	3/12 (25%)	6/12 (50%)	1/12 (8.33%)	1/12 (8.33%)	1/12 (8.33%)
Female (12, 50%)	4/12 (33.33%)	2/12 (16.67%)	4/12 (33.33%)	1/12 (8.33%)	1/12 (8.33%)
MRI findings (*n* = 23)*					
SSTM (6, 26.08%)	4/6 (66.66%)	1/6 (16.67%)	1/6 (16.67%)	0/6 (0%)	0/6 (0%)
LETM (16, 69.56%)	3/16 (18.75%)	6/16 (37.5%)	3/16 (18.75%)	2/16 (12.5%)	2/16 (12.5%)
LETM + Brain demyelination (1, 4.34%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)
Weakness					
Paresis (18, 75%)					
Para (13, 54.16%)	4/13	5/13	2/13	1/13	1/13
Quadri (2, 8.33%)	1/2	0/2	0/2	0/2	1/2
One-sided (3, 12.5%)	2/3	0/3	1/3	0/3	0/3
Plegia (6, 25%)					
Para (5, 20.83%)	0/5	3/5	2/5	0/5	0/5
One-sided (1, 4.16%)	0/1	0/1	0/1	1/1	0/1
Infection					
None (16, 66.67%)	5/16 (31.25%)	4/16 (25%)	3/16(18.75%)	2/16 (12.5%)	2/16 (12.5%)
Postinfectious (6,25%)	2/6 (33.33%)	3/6 (50%)	1/6 (16.67%)	0/6 (0%)	0/6 (0%)
COVID-19 (2, 8.33%)	0/2 (0%)	1/2 (50%)	1/2 (50%)	0/2 (0%)	0/2 (0%)
CSF cell count (*n* = 20)					
Normal (17, 85%)	4/17 (23.5%)	8/17 (47.1%)	4/17(23.5%)	1/17 (5.9%)	0/17 (0%)
Abnormal (3, 15%)	2/3 (66.7%)	0/3 (0%)	1/3(33.3%)	0/3 (0%)	0/3 (0%)
CSF protein (*n* = 20)					
Normal (10, 50%)	3/10 (30%)	4/10 (40%)	2/10 (20%)	1/10 (10%)	0/10 (0%)
Raised (10, 50%)	3/10 (30%)	4/10 (40%)	3/10 (30%)	0/10 (0%)	0/10 (0%)

*MRI was not done in one subject who was found to be partially improved at follow-up; One-sided (brown-Sequard-like), unilateral complete loss of power in upper and lower limbs

Table 5 : Comparison of baseline characteristics and clinical presentations based on status of improvement at follow-up (*n*, row%)

Status of improvement at follow-up	*Improved (15, 62.5%)*	*Not improved (5, 16.67%)*
Onset (*n* = 20)		
Acute (11, 55%)	9/11 (81.81%)	2/11 (18.18%)
Subacute (9, 45%)	6/9 (66.67%)	3/9 (33.33%)
Gender (*n* = 20)		
Male (10, 50%)	9/10 (90%)	1/10 (10%)
Female (10, 50%)	6/10 (60%)	4/10 (40%)
MRI findings (*n* = 19)*		
SSTM (6, 31.57%)	5/6 (83.33%)	1/6 (16.67%)
LETM (12, 63.15%)	9/12 (75%)	3/12 (25%)
LETM + Brain demyelination (1, 5.26%)	0/1 (0%)	1/1 (100%)
Weakness (*n* = 20)		
Paresis (15, 75%)		
Para (11, 55%)	9/11 (81.8%)	2/11 (18.2%)
Quadri (1, 5%)	1/1 (100%)	0/1 (0%)
One-sided (3, 15%)	2/3 (66.67%)	1/3 (33.33%)
Plegia (5, 25%)		
Para (5, 25%)	3/5 (60%)	2/5 (40%)
Infection (*n* = 20)		
None (12, 60%)	9/12 (75%)	3/12(%)
Postinfectious (6, 30%)	5/6 (83.33%)	1/6 (16.67%)
COVID-19 (2, 10%)	1/2 (50%)	1/2 (50%)
CSF cell count (*n* = 19)		
Normal (16, 84.2%)	12/16 (75%)	4/16 (25%)
Abnormal (3, 15.8%)	2/3 (66.67%)	1/3 (33.33%)
CSF protein (*n* = 19)		
Normal (9, 47.4%)	7/9 (77.77%)	2/9 (22.23%)
Raised (10, 52.6%)	7/10 (70%)	3/10 (30%)

*MRI was not done in one subject who was found to be improved at follow-up

Table 6: Comparison of initial and final mRS scores in subjects with various antibodies

Positive serology	*Initial mRS*	*Final mRS*	*mRS change*
CENP-b+ANA Antibodies	4	1	Partially improved
SSA antibodies	5	5	Not improved
Anti-histone antibodies	5	2	Partially improved
ANA antibodies (a*)	4	1	Partially improved
ANA antibodies (b*)	4	0	Completely improved
MOG antibodies	3	1	Partially improved

*The two subjects positive for ANA antibodies are addressed as "a" and "b" in this table

Table 7: Comparison of initial and final mRS scores based on site of spinal lesion (n = 23)

Site of lesion in the spinal cord	*mRS improved (20)*	*mRS not improved (3)*
Cervical (5)	5 (100%)	0
Thoracic (12)	10 (83.33%)	2 (16.67%)
Cervical and thoracic (4)	4 (100%)	0
Thoracic to lumbar (2)	1 (50%)	1 (50%)

The subject in whom an MRI was not done also showed an mRS score improvement

Table 8: Initial outcomes versus outcomes at follow-up

Outcome at follow-up	*Completely improved (7, 28.16%)*	*Partially improved (8, 33.33%)*	*No change from initial outcome (5, 20.83%)*	*Worsened (2, 8.33%)*	*New symptoms (2, 8.33%)*
Initial outcome					
Partially improved (12)	3 (25%)	6 (50%)	1 (8.3%)	1 (8.3%)	1 (8.3%)
Completely improved (5)	4 (80%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)
No change (7)	0 (0%)	2 (28.6%)	4 (57.1%)	1 (14.3%)	0 (0%)

Lost to follow-up = 5, death =1

administration at a dosage of 1000 mg. The initial presentation of the first subject was characterized by partial improvement, which persisted during follow-up. Conversely, the second subject showed no initial improvement but demonstrated partial improvement on subsequent assessment. Unfortunately, the absence of COVID-19 cerebrospinal fluid polymerase chain reaction (CSF PCR) testing precluded establishing a definitive link between COVID-19 spinal infection and TM.

Studies conducted by Doi et al.,[12] Chow et al.,[13] and Gudlavalleti et al.[2] have reported cases of acute-onset TM associated with COVID-19, presenting with sensory loss, diminished muscle strength, hyperreflexia, and involvement of bowel and bladder function. Importantly, these manifestations were identified as post-infectious and post-vaccination sequelae of COVID-19, and notably, they exhibited favorable responses to intravenous steroid therapy.

An examination of the trajectory of outcomes during the final follow-up, contingent upon the initial outcomes, revealed that 46.2% of participants exhibiting initial partial improvement maintained a status quo, while 23% experienced complete resolution. Conversely, 20% of those initially demonstrating complete improvement manifested new symptoms at the final follow-up. Notably, among the cohort of 12 subjects who displayed no initial improvement, 33.3% exhibited a persistently unaltered condition, 16.7% demonstrated partial improvement, and 8.3% experienced a deterioration in symptoms.

The majority of individuals diagnosed with idiopathic TM typically undergo at least partial recovery, a restorative process typically commencing within a span of one to three months. Continued improvement is observed through the implementation of exercise and rehabilitation therapy, with the potential for recovery extending over several years. Notably, Defresne et al.[8] reported that around 40% of patients sustained some level of disability despite the recovery process.

Conclusion

Acute onset LETM cases can potentially convert to Multiple Sclerosis. Patients who show early improvement, whether partial or complete, have higher chances of complete recovery at follow-up.

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API Announcement

Elections of API, ICP and PRF

(Full details circular No. 1 & 2/2026)

Election for Governing Body of API, Board of PRF and Faculty Council of ICP are announced for the following posts:

Governing Body of API:
President-Elect: One; Vice President: Two (One VP for 3 years & One VP for 1 year); Hon. General Secretary: One; Elected Members: Six and Hilly Zone (Himachal Pradesh, Uttarakhand, Jammu & Kashmir) – one for 2 years (2027–2028)

Board of PRF:
Director-Elect: One; and Board Members: Three (Out of these three members, one post will be reserved for a female candidate).
- Separate nominations must be submitted for each post.

Faculty Council of ICP:
Dean-Elect: One; Vice Dean: One; and Elected Members: Six posts (Out of these six posts of Faculty Council Members, one post shall be reserved for a female candidate).

Eligibility Criteria to contest election for the Governing Body of API posts:
A) **President-Elect:** To contest for the post of President-Elect, the candidate should be a life member of API for at least 12 years and have completed at least 3 full terms of 3 years each in any elected position in the Governing Body.
B) **Vice President:** To contest for the post of Vice President, the candidate should be a life member of API for at least 9 years and should have completed at least two full terms of 3 years in any elected position in the Governing Body.
C) **Hon. General Secretary:** To contest for the Post of Hon. General Secretary, the candidate should be a life member of API for at least 6 years and should have completed at least one continuous full term of 3 years in any elected position in the Governing Body.
D) **Governing Body Member/Zonal Member:** To contest for all other elected positions, continuous membership of the Association of at least 3 years is mandatory.

Eligibility Criteria to contest election for the Board of PRF posts:
A) **Director-Elect:** A member of API for at least 10 years with research experience and have 10 research publications in peer-reviewed indexed journals.
B) **Board Member:** A Member of API for at least 10 years with research experience and having 5 research publications in peer-reviewed indexed journals.
- *Note*: The members contesting for the PRF election must attach copies of the Research Papers as mentioned above; this is mandatory.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. (Nomination form is available on the website). The nominations for API/PRF posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them. The candidate must sign a declaration signifying his/her willingness to stand for election and serve on the Governing Body, if elected, & affirming his/her commitment to abide by all rules and regulations and to uphold the society's constitution throughout the election process and their subsequent term of office.

Eligibility Criteria to contest election for election to ICP posts:
A) **Dean-Elect:** i. A member of API for at least 15 years, and
ii. A Founder Fellow or a Fellow of the College of 7 years standing, and
iii. Any person who has held the position of President/Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for two terms.
B) **Vice Dean:** i. A member of API for at least 12 years, and
ii. A Founder Fellow or a Fellow of the College of 5 years standing, and
iii. Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ or one full term member of the Faculty Council.
C) **Elected Members:** A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 years standing.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. (Nomination form is available on the website). The nominations for ICP posts shall be proposed by one valid Founder Fellow/Fellow and seconded by another valid Founder Fellow/Fellow of ICP and duly signed by them. The candidate must sign a declaration signifying his/her willingness to stand for election and serve on the Faculty Council, if elected, & affirming his/her commitment to abide by all rules and regulations and to uphold the society's constitution throughout the election process and their subsequent term of office.

General Guidelines:
A) A member shall not contest simultaneously for more than one post (i.e., President-Elect, Vice-President, Hon. Treasurer; Member of the Governing Body/Zonal Member; Dean-Elect; Vice Dean and Elected Members of Faculty Council; and Director-Elect and Board Members of PRF). Post means not only an office-bearer but also a member of the Governing Body of API or Faculty Council of ICP or Board of PRF.
B) Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 1st June 2026, 5 pm (31st May 2026 falling on Sunday). For every post on the Governing Body/Faculty Council/Board of PRF, the nomination must be accompanied by a Demand Draft (Payable at Mumbai) ONLY of Rs. 7,500/- + 1,350/- (GST) i.e. Total Rs. 8,850/- (Rupees eight thousand eight hundred & fifty only). The Nomination fee is NON-REFUNDABLE. For Nomination, no cheque/Net Banking will be accepted.
C) Canvassing in any form is strictly not allowed. Any contestant who is found to be canvassing will be disqualified as per the provisions of the constitution of API/ICP/PRF.
D) All the contestants are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be placed on the API website. Excess bio-data beyond the first two hundred words shall be deleted.
E) The contestant will have to sign the declaration that the particulars submitted by him/her in the nomination form are true & correct. And he/she will abide by all rules and regulations and uphold the society's constitution throughout the election process and their subsequent term of office.
F) The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for approval.
G) For full information regarding elections eligibility, schedule of elections, and any other information please visit the website: apiindia.org

IMPORTANT DATES FOR ELECTION SCHEDULE

Last date to receive the nomination at API Office:	1st June 2026, 5 pm
Last date for withdrawal:	10th June 2026, 5 pm
Last date to receive ballot papers at API Office:	31st August 2026, 5 pm
Counting of ballots:	6th September 2026, 9 am
Declaration of Election Results:	6th September 2026, 4 pm

Dr. Puneet Saxena
Hon. General Secretary

ORIGINAL ARTICLE

Examination and Validation of Neutrophil–Lymphocyte Ratio as a Perioperative Risk Assessment Biomarker in Major Noncardiac Surgical Patients: An Observational Cross-sectional Study

Shalini Nangalia[1], Sugata Dasgupta[2], Arpita Choudhury[3*], Karan Kumar Pathak[4]

Received: 11 January 2025; *Accepted:* 18 February 2026

Abstract

Background and aims: Neutrophil–lymphocyte ratio (NLR) can predict prognosis of disease in patients suffering from cerebrovascular accidents, ischemic heart disease, infectious diseases, sepsis, etc., that can cause increased postoperative morbidity and prolonged stay in hospital. So, NLR can be a potential preoperative risk assessment and stratification biomarker. Our study aims to estimate any correlation between preoperative NLR and coexisting medical and surgical disease and to validate NLR against American Society of Anesthesiologists Physical Status (ASA PS) Classification System, Revised Cardiac Risk Index (RCRI), Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score, and Gupta's postoperative respiratory failure risk in Indian patients.

Materials and methods: This observational, cross-sectional study was conducted in the preanesthesia check-up clinic. Information regarding sociodemographic profile, primary surgical disease, hematological investigations, that is, complete blood count, neutrophil count, lymphocyte count, NLR, and coexistent medical disease was collected, and ASA PS, RCRI, ARISCAT score, and Gupta's postoperative respiratory failure risk were calculated for each study subject. Data were analyzed using standard statistical tests.

Results: Age, congestive cardiac failure, smoking, malignancy, and beta blockers usage were associated with elevated NLR. NLR was found to have a significant relationship with anesthesia risk indices: ASA PS, RCRI, ARISCAT, and Gupta's postoperative respiratory failure risk.

Conclusion: Significant association has been observed between increased NLR and occurrence of systemic illness. NLR also has a significant association with ASA PS Classification System, RCRI, ARISCAT score, and Gupta's postoperative respiratory failure risk. So, NLR may serve as a valuable biomarker in preoperative risk stratification.

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Introduction

Patients undergoing major noncardiac surgery face a higher risk of adverse events.[1] Preoperative prediction of the severity of systemic illness and identifying the patients at a higher risk are important to plan safe intraoperative and postoperative care.[2] The use of risk stratification indices, like the American Society of Anesthesiologists Physical Status (ASA PS) classification system[3] as the sole risk stratification score, may not accurately predict the inflammatory processes underlying a patient's comorbid condition, and may not be appropriate for assessment and stratification of preoperative risk.[3] Considering the above facts, biomarkers may be used in preoperative risk stratification along with the perioperative risk stratification indices.

Neutrophil–lymphocyte ratio (NLR) has emerged as a novel marker in the prognostication and management of COVID-19.[4] NLR is an easily available ratio that can be calculated from routine preoperative complete blood count (CBC). As this study was conceived during full-blown COVID times, when we were trying our best to use resources judiciously everywhere, we planned to import this easily obtainable marker from COVID-19 to the perioperative scenario and see how this could be useful here. This is the concept behind conducting this study. So, we set out to investigate the normal levels and distribution of preoperative NLR to determine the frequency of patients who had an increased NLR among noncardiac surgical patients. Examination of the link between NLR and coexisting medical and primary surgical disease, and validation of NLR against the widely applied preoperative risk estimation tools, that is, ASA PS classification system,[3] Revised Cardiac Risk Index (RCRI),[5] Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score,[6] and Gupta's postoperative respiratory failure risk[7] in Indian patients were also aims of this study.

Materials and Methods

This observational, analytical, cross-sectional study was executed in the preanesthesia check-up (PAC) clinic of a tertiary care center from January 2021 to August 2022, in compliance with the Institutional Ethics Committee guidelines. Patients attending pre-anesthesia check-up clinics, aged 18 and above, planned for elective major noncardiac surgeries were enrolled in this study after getting their written informed consent.

The sample size of this cross-sectional study was calculated taking the assumption of sample size used in the previous study by Venkatraghavan et al.[8]

Here, sample size $(n) = Z(1 - \alpha/2)^2 pq/d^2$, where the confidence interval is assumed to be conventionally 95%, therefore, $\alpha = 0.05$ and $Z(1 - \alpha/2) = 1.96$ (2-sided test with a significance level of 0.05), p is the expected proportion in a population-based study. A prevalence of 26.6% was noted in the study by Venkatraghavan et al.,[8] thus $p = 0.266$ is taken in this study, q is $(1 - p) = 0.734$, and d is absolute precision, which is taken as 10% in this study. After applying the formula, n derived = 300. Considering 10% nonresponse or incomplete data, final sample size is calculated to be $n = 330$. Therefore, the final sample size on which the study was performed is $n = 330$.

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Patient's demographic data, primary surgical disease, hematological investigations (CBC, neutrophil count, lymphocyte count, NLR), coexistent medical disease, anesthesia risk indices, that is, ASA PS, RCRI, ARISCAT score, Gupta's postoperative respiratory failure were collected.

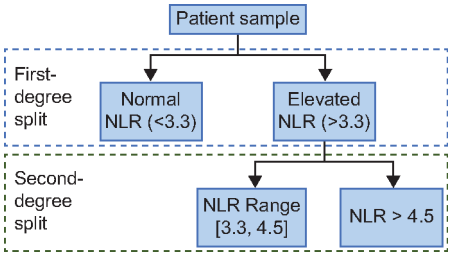

Fig. 1: Distribution of NLR in the study population

Data were entered into a Microsoft Excel spreadsheet and subsequently analyzed statistically by Python statistical analysis tool (version 3.9.6, Python.org). Data had been summarized as mean and standard deviation (SD) for numerical/continuous variables, and for categorical variables, data were expressed as count and percentages. For multivariate and univariate regression analysis, an NLR value of >3.3 and >4.5, respectively, have been found in prior research to be predictive of an increased risk of major adverse cardiovascular events (MACEs) in postsurgical as well as asymptomatic populations.[8–10] So, patients were classified as having normal or high NLR based on 2 defined cutoff values.[8] A *p*-value of <0.25 (*p*-value < 0.25) in univariate analysis served as the criterion for including the potential variables in the multivariate analysis. To identify independent determinants of a higher NLR, multiple logistic regressions were carried out.[8]

During the analysis of the collected data, the data was segregated based on the threshold value of NLR > 3.3, and a thorough data exploration, comparison, and hypothesis testing were performed to check for variables' significance and correlation. Now, to check what factors are responsible for increased risk in patients with elevated NLR, a second-degree dichotomous comparison was made taking the threshold of 3.3 ≤ NLR < 4.5 and NLR > 4.5 during multivariate and univariate regression analysis (Fig. 1). To choose the potential predictors for the multivariate model, a screening was performed using univariate analysis, and the criterion for inclusion was set at $p < 0.25$. To identify independent determinants of a higher NLR, multiple logistic regressions were carried out. A *p*-value of <0.05 was the criterion for statistical significance (*p*-value < 0.05).

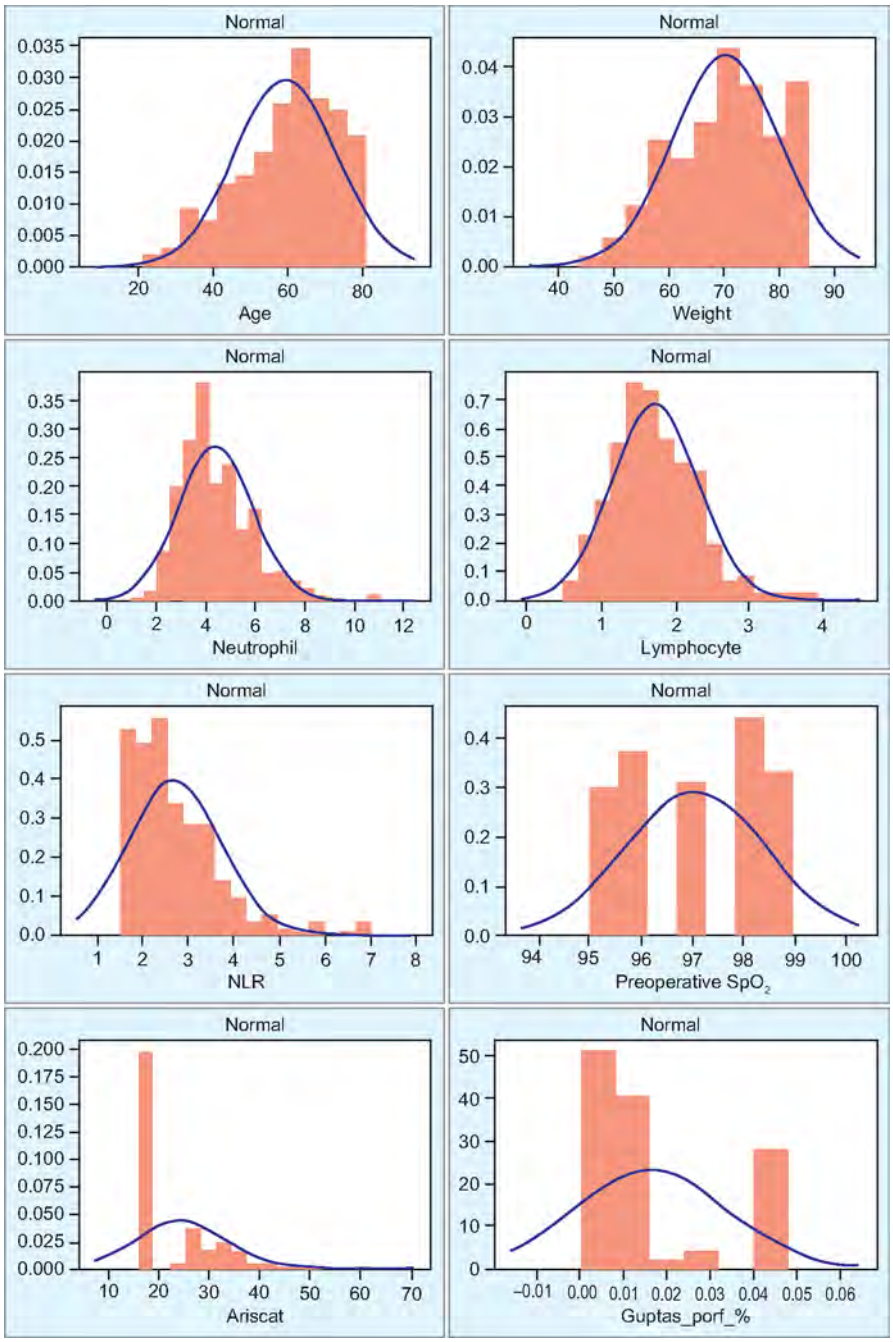

Fig. 2: Distributions of continuous variables

Results

From Table 1, it can be observed that in the present study, mean age (± SD) of the participants is 60 years (±13.5), weight 70.3 kg (±9.5), NLR 2.7 (±1). Continuous variables were also checked for skewness by checking the distribution of each of the variables.

Upon looking at the distribution in Figure 2, all the continuous variables follow a normal distribution except for NLR with a median of 2.5, GUPTA score with a median of 1.02, and ARISCAT with a median of 19.

In Table 2, we compared the distribution of each categorical variable with elevated NLR values. The test is used in conjunction with the goodness-of-fit test to assess whether 2 categorical variables are independent of one another or whether they are connected. The condition of elevated NLR was considered as NLR > 3.3; therefore, NLR > 3.3 were labeled as 1 and NLR < 3.3 was labeled as 0. Out of 330 patients, 212 (64%) are male, whereas 118 (36%) are female. Among all the variables, a statistically significant association was observed between CCF, smoking, beta blocker intake, and any form of malignancy with elevated NLR value.

From Table 3, we can derive the results of univariate logistic regression for NLR > 3.3 as a threshold. Table 3 depicts that age,

Table 1: Statistics on continuous variables

Parameters	*Mean (SD)*	*Minimum*	*Maximum*
Age	60.4 (13.5)	22	82
Weight	70.3 (9.5)	43.8	85.6
Neutrophil	4.4 (1.5)	0.9	11.1
Lymphocyte	1.7 (0.6)	0.5	3.9
NLR	2.7 (1.0)	1.5	7.0
Pre-op SpO_2	97.1 (1.4)	95	99

CCF, smoking, and malignancy were highly associated with NLR > 3.3 and stood out as statistically significant variables. However, after multivariate analysis, malignancy and use of beta blockers were highly associated with elevated NLR.

For the NLR threshold of NLR > 4.5, malignancy was highly associated with *p*-values < 0.05 in the univariate analysis and was statistically significant. Furthermore, individuals with any sort of malignancy had a substantially higher NLR than patients without malignancy (Table 4).

NLR was found to have a significant relationship with comparative biomarkers like ASA PS, RCRI, ARISCAT, and GUPTA's risk index. According to Table 5, increased value of NLR exhibits a statistically significant association with the aforementioned biomarkers.

Discussion

The NLR is a biomarker that can be useful for diagnosing systemic inflammation.[11] NLR as a preoperative risk stratification tool can be beneficial since NLR is derived from routine complete blood count (CBC), which is a part of preoperative and postoperative workup.[8] The usefulness of NLR for evaluating the prognosis of various diseases, including cancer, community-acquired pneumonia (CAP), hemorrhagic stroke, sepsis, and recently acute coronary syndrome, has been investigated.[1114] Elevated preoperative NLR is also known to be associated with increased morbidity and mortality in cardiac and major vascular surgeries postoperatively.[15,16] However, NLR has not been adequately investigated for assessment and stratification of preoperative risk among patients scheduled for noncardiac surgical procedures.

In our study, most of the patients attending the preadmission clinic were scheduled for orthopedic surgery (51%), followed by neurosurgery (28%), general surgery (11%), and the rest (9%) for urology and other noncardiac surgeries. Among the study subjects, 21.5% patients had an elevated NLR value (>3.3). An independent association was observed between CCF and NLR values of >3.3. This finding confirms the fact that NLR serves as a useful predictor of long-term prognosis in acute decompensated heart failure.[16] In our study, a strong association has also been observed between the occurrence of malignancy and NLR values of >3.3 and 4.5. This reaffirms the established role of NLR in prognosis, and predicting mortality and recurrence in patients with cancer.[17] After univariate analysis, age, CCF, smoking, and malignancy were increasingly associated with NLR > 3.3. However, after multivariate analysis, malignancy and use of beta blockers were highly associated with elevated NLR. For the NLR threshold of NLR > 4.5, malignancy was associated with elevated NLR. NLR was also found to be significantly associated with ASA physical status, ARISCAT score, RCRI, and Gupta's postoperative respiratory failure risk.

In the present study, increased medication usage, which indicates the presence of multiple comorbidities, was associated with NLR values >4.5. This emphasizes the relationship of increased NLR and presence of multiple comorbidities in the study population. In a study on NLR in patients with community-acquired pneumonia by de Jager et al., pneumonia severity (CURB-65 score), clinical characteristics, complications, and outcomes were related to the NLR and compared with C-reactive protein (CRP), neutrophil count, and white blood cell (WBC) count, and it was found that NLR value exhibits superior prognostic accuracy for assessment of the severity and outcome of CAP relative to the conventional markers of infection. This aligned with the result of the current study, where it has been observed that increased NLR is related to the presence of systemic illness.[18] A study by Kuikel et al. on NLR to predict the adverse outcomes in 3,340 patients suffering from community-acquired pneumonia observed that NLR was more useful in predicting mortality than C-reactive protein levels, white blood cell count, neutrophil count, or lymphocyte level alone, Pneumonia Severity Index (PSI) level, PSI class, procalcitonin, and CURB-65. So, this study found NLR as an easy-to-measure and simple marker to predict outcomes in patients having CAP, and likewise our study observed NLR as a potential perioperative risk assessment biomarker.[12] NLR and its relation with the occurrence of atherosclerotic events were observed in a study by Adamstein et al. In the CANTOS, JUPITER, SPIRE-1, SPIRE-2, and CIRT trials, baseline and on-treatment NLRs were obtained from 60,087 randomized participants and were followed to determine the incidence of major adverse cardiovascular events. As per this study, NLR could predict the risk of cardiovascular events and all-cause mortality independently.[19] Our study also showed an association of NLR with perioperative risk. Imtiaz and colleagues found a significant correlation between the raised NLR value and increased risk of being diagnosed with hypertension and diabetes mellitus, and likewise our study showed the presence of various systemic illnesses to be associated with raised NLR.[20]

A study to determine NLR as a predictive marker of metabolic syndrome (MS) by Liu et al. concluded that as NLR increases, the risk of MS also increases, and NLR values can be a valuable tool to predict the development of MS. Similarly, our study found an independent association between malignancy and NLR.[21]

Park et al. investigated the incidence of MACEs 5 years after STEMI and observed an association between elevated NLR and higher mortality rates among patients surviving 30 days following successful coronary intervention; this was in uniformity with our study, where the prognostic value of NLR was examined.[22] Similar findings have been observed in the study by Shah and colleagues, where they observed that an NLR value above 4.5 was independently associated with coronary heart disease (CHD)-related death in the general healthy population. They also showed that the study participants who were in the intermediate risk category of the Framingham Risk Score (FRS), NLR permitted reclassification of those patients as having a lower or higher risk of cardiovascular mortality, and also NLR could independently predict CHD-related death in asymptomatic patients.[15] In a study conducted by Adamsson et al. to find any correlation between coronary events and blood neutrophil and lymphocyte counts, it was found that neutrophil counts were associated with increased incidence of coronary events.[23] Venkatraghavan et al.

Table 2: Categorical variable analysis

		NLR < 3.3	*NLR > 3.3*	*Total*	*p-value*
		0	*1*		
Gender	0	168	44	212	0.62
	1	90	28	118	
IHD	0	231	61	292	0.3
	1	27	11	38	
CCF	0	252	68	320	0.003*
	1	4	6	10	
HT	0	152	39	191	0.5
	1	106	33	139	
Smoker	0	164	33	197	0.009
	1	94	39	133	
Resp. infection	0	232	62	294	0.48
	1	26	10	36	
COPD	0	243	65	308	0.36
	1	15	7	22	
OSA	0	235	65	300	1
	1	23	7	30	
Resp. malign.	0	256	72	328	1
	1	2	0	2	
GI. malign.	0	253	69	322	0.5
	1	5	3	8	
CKD	0	255	70	325	0.6
	1	3	2	5	
Urin. malign.	0	254	68	322	0.12
	1	4	4	8	
Anemia	0	236	68	304	0.56
	1	22	4	26	
CVA.TIA	0	246	67	313	0.63
	1	12	5	17	
Breast and gyne. malign.	0	250	69	319	0.94
	1	8	3	11	
Diabetes	0	237	67	304	0.93
	1	21	5	26	
Insulin	0	255	69	324	0.23
	1	3	3	6	
OHA	0	238	69	307	0.4
	1	20	3	23	
HT. meds	0	183	52	235	0.94
	1	75	20	95	
NSAIDs	0	147	45	192	0.4
	1	111	27	138	
	1	16	10	26	
Beta blocker	0	230	58	288	0.05*
	1	28	14	42	
Diuretics	0	235	67	302	0.7
	1	23	5	28	
Malignancy	0	220	52	272	0.001
	1	35	18	53	
	2	3	2	5	

*IHD, ischemic heart disease; CCF, congestive cardiac failure; HT, hypertension; Resp. infection, respiratory infection; COPD, chronic obstructive pulmonary disease; Resp. malign., respiratory malignancy; GI malign., gastrointestinal malignancy; CKD, chronic kidney disease; Urin. malign., urinary malignancy; CVA, cerebrovascular accident; TIA, transient ischemic attack; Breast and gyne. malign., breast and gynecological malignancy; OHA, oral hypoglycemic agent; HT meds., medication for hypertension

Table 3: Results—univariate logistic regression for the threshold = (3.3 ≤ NLR < 4.5)

	Univariate logistic regression analysis			*Multivariate logistic regression results*		
Variables	*Odds ratio*	*95% CI range*	*p-value*	*Odds ratio*	*95% CI range*	*p-value*
Age	1.02	(0.9–1.041)	0.04	1.02	(0.99–1.04)	0.075
Surgery	1.2	(0.95–1.51)	0.11	0.97	(0.53–1.79)	0.934
IHD	1.54	(0.72–3.28)	0.22	1.01	(0.41–2.47)	0.978
CCF	2.55	(1.24–5.25)	0.003	1.84	(0.85–4.03)	1.12
Smoker	2.06	(1.21–3.49)	0.007	2.33	(1.30–4.19)	0.004
COPD	1.7	(0.68–4.45)	0.24	0.99	(0.35–2.77)	0.992
Insulin	3.69	(0.7–18.71)	0.11	1.68	(0.28–10.09)	0.568
Beta blocker	1.98	(0.98–4.00)	0.05	1.43	(0.65–3.15)	0.366
Malignancy	1.99	(1.15–3.44)	0.01	2.19	(1.22–3.924)	0.008

Table 4: Results—univariate logistic regression for the threshold = (NLR > 4.5)

	Univariate logistic regression results			*Multivariate logistic regression results*		
Variables	*Odds ratio*	*95% CI range*	*p-value*	*Odds ratio*	*95% CI range*	*p-value*
Smoker	1.05	(1.00–1.11)	0.036	3.05	(1.06–8.76)	0.037
COPD	1.08	(0.98–1.20)	0.1	1.85	(0.44–7.58)	0.396
Beta blocker	1.102	(1.02–1.18)	0.01	3.4	(1.14–10.12)	0.028
Malignancy	1.07	(1.01–1.13)	0.016	3.27	(1.36–7.85)	0.008

Table 5: Results—logistic regression on other biomarkers with elevated NLR

Variables	*Odds ratio*	*95% CI range*	*p-value*
Gupta's Index	3.11	(2.89–53.68)	0.019
RCRI	2.55	(0.27–3.47)	0.022
ASA PS	1.88	(1.16–3.05)	0.01
ARISCAT	0.83	(0.50–1.39)	0.04

found that 26.6% of their study population had an NLR value of >3.3. They also observed a correlation between NLR and the preoperative risk stratification indices, like ASA PS, and RCRI score. Our study also observed a significant relationship between NLR and the preoperative risk stratification indices, like ASA PS, RCRI, ARISCAT score, and Gupta's postoperative respiratory failure risk.[8]

Shibutani and associates found that higher value of preoperative NLR is related to poor survival in patients suffering from colorectal cancer. It was found that cancer-specific mortality was significantly ($p < 0.001$) more in the patients with a high NLR, which was an independent risk factor for poor survival. It was concluded that preoperative NLR measurement is a convenient biomarker and predictor of a poor prognosis after surgery for colorectal cancer.[24]

However, we acknowledge certain limitations in our study. This study is not formulated to evaluate the usefulness of preoperative NLR to assess and stratify perioperative risks and predict perioperative major cardiovascular adverse events and mortality. Instead, this cross-sectional study is intended to give a "snapshot" of the distribution and prevalence of NLR in a subset of the patients during their pre-anesthesia check-up before their operation and to link this biomarker to the occurrence and prevalence of comorbidities of those patients. Further research is required to establish the ideal function of this biomarker as a perioperative risk stratification tool. The present study sets the platform for the evaluation of the role of NLR in future research considering the optimal cutoff value of NLR and the association between increased NLR and adverse health outcomes in the perioperative period.

In conclusion, elevated value of NLR is associated with increased occurrence of systemic illness, and the association is statistically significant. Congestive cardiac failure and malignancy had a significant relationship with increased NLR at >3.3 and >4.5, respectively. NLR has also been found to have a significant association with the comparative anesthesia risk indices, like the American Society of Anesthesiologists Physical Status (ASA PS) Classification System, Revised Cardiac Risk Index (RCRI), Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score, and Gupta's postoperative respiratory failure risk.

Hence, NLR, an easily available and measurable biomarker, may be useful as a preoperative anesthetic risk stratification tool. It would be particularly appropriate for tertiary care hospitals where the patient load is huge and patients often have multiple comorbidities.

Author Contributions

SDG2, SN1, KKP3, AC4: conceptualization, visualization, design of study, and literature search, investigation, methodology, project administration. KKP3, SN1: data curation, software, formal analysis. SN1, SDG2, AC4: writing the original draft. SDG2, KKP3, AC4: supervision, validation, manuscript editing, and manuscript review.

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CTRI number: Registration not done as it is an observational study.

Ethics declaration: Approval from the Ethics Committee of our institution was taken. Written informed consent was obtained from

every participant after providing a detailed explanation of the purpose and procedure of our study.

IEC approval number and date: RKC/412; 09/03/2021.

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ORIGINAL ARTICLE

Effects of Omega-3 Fatty Acids on Tobacco Craving in Tobacco Users: A Single-blind, Randomized, Placebo-controlled Study

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Abstract

Background: Tobacco use and its smoke produces oxidative stress in the body, which eventually triggers cell damage by lipid peroxidation. Smokers report lower levels of omega-3 fatty acids (FAs) in their serum as compared to nonsmokers. Omega-3 deficiency impairs neurotransmission, resulting in hypofunctioning of the mesocortical system, which is a reward and dependency system that can raise tobacco cravings, disrupting tobacco quitting efforts. Omega-3 polyunsaturated fatty acid (PUFA) regulates stress, anxiety, and negative emotions that are associated with tobacco urges. Limited research has assessed the supplementation effect of omega-3 PUFA [in the form of alpha-linolenic acid (ALA)] on tobacco craving.

Aim: We aimed to explore the effects of omega-3 PUFA (ALA) on the frequency of tobacco use per day, tobacco dependence, and tobacco craving when compared to placebo in regular tobacco users.

Materials and methods: Regular tobacco users ($n = 83$) recruited from the Tobacco Cessation Clinic were randomly allocated to two groups. Group I was the omega-3 PUFA group, supplemented with 10 mL/day of omega-3 PUFA in the form of ALA (5.1 gm) for 180 days, and the other group received a placebo for the same duration. The outcome was evaluated by means of a case record form (for demographic parameters), self-reports of tobacco use (for frequency of tobacco use per day), as well as psychometric measures (for tobacco dependence and tobacco craving). The evaluations were carried out at baseline and after 180 days of intervention.

Results and conclusion: The frequency of tobacco use per day, tobacco dependence, and tobacco craving were found to be significantly decreased ($p < 0.0001$) in the group receiving omega-3 PUFA (ALA) at the end of supplementation. This is a novel approach that ALA supplementation reduces tobacco cravings in regular tobacco users in comparison to a placebo. Thus, omega-3 FAs may be an adjuvant tool in quitting tobacco use by reducing nicotine dependence and tobacco craving. Further studies are necessary with large samples to understand the possible association and explore the probable nonpharmacological approaches for tobacco cessation.

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Introduction

Chronic exposure to tobacco smoke, a toxic cocktail of chemicals, leads to progressive pulmonary dysfunction plus carcinogenic lung injury.[1] Over time, exposure to the hazardous components of tobacco smoke produces oxidative stress, which eventually triggers cell damage by lipid peroxidation.[2] Fatty acids (FAs) are carboxylic acids that can be classified as either saturated or unsaturated, with carbon chain lengths ranging from 2 to 36 atoms of carbon.[3] FAs having two or more double bonds are called polyunsaturated fatty acids (PUFAs). One of them is omega-3 FA (the first double bond between the third and fourth carbons when counting from the CH_3 end).[4,5] The three main omega-3 FAs are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).[6]

Smokers report lower levels of DHA and EPA in their serum as compared to nonsmokers because tobacco smoke inhibits metabolism, bioavailability, plus the absorption of omega-3 FAs.[7–9] Incorporation of Omega-3 FAs into neural membranes increases membrane fluidity, and[10] its deficiency disrupts neurotransmission, leading to hypofunctioning of the mesocortical system, i.e., a reward and dependence system[10,11] which may increase tobacco use urges, interfering with and weakening tobacco cessation.[12] n-3 PUFA deficiency is associated with increased sensitivity to stress.[13]

Epidemiological research has demonstrated an inverse relationship between n-3 PUFA levels and the prevalence of psychological distress, anxiety disorders, and depression.[14–16] On the contrary, a diet high in n-3 PUFAs improves the psychosocial well-being of patients and shows no increase in aggressive behaviors due to stressful situations.[17–19] Omega-3 FA consumption may elevate brain serotonin levels.[20] Omega-3 FAs are reported to have antistress and regulatory effects on hypothalamic-pituitary-adrenocortical responsiveness by decreasing their activation.[21] Supplementation with PUFAs enhances the capacity for stress coping within the cerebral-limbic system.[22,23]

Essential FAs are crucial for maintaining optimal health; however, they cannot be produced endogenously and must be acquired through dietary intake.[24] The fattiest organ of the body is the brain, which comprises almost 40% PUFA, which is vital for brain development as well as its functioning.[25] Brain pathology plays a role in the development of mood disorders.[26] A three-month supplementation with EPA and DHA led to significant reductions in anger, anxiety scores,[27] impulsive aggressive behavior,[28] symptoms of depression,[29] negative moods,[30] distress symptoms, and basal cortisol secretion.[21]

Prevailing pharmacologic studies with the intervention of first-line treatment [nicotine replacement therapy (NRT), including gums, patches, lozenges] and second-line treatment (such as clonidine, varenicline) have been sparsely done for tobacco cessation. Studies using omega-3 supplementation to treat stress reactions in tobacco users are very rare.[31,32] Tobacco cessation causes psychological stress, which causes the maintenance of cessation.[33] Omega-3 PUFAs help relieve this psychological stress and

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associated symptoms, and thus could help sustain cessation.[34] Smokers have lower levels of EPA and DHA than nonsmokers.[7] Limited research has been conducted thus far on the effects of omega-3 PUFAs on cravings for smokeless tobacco.

Not only tobacco abstinence but also exposure to tobacco cues could heighten tobacco craving by manifesting increased anxiety, stress, negative emotions, increased blood pressure (BP), restlessness, irritability, and a strong desire to use tobacco. Stress can weaken a smoker's ability to resist tobacco urges and compel their use more intensely to get greater satisfaction and reward from tobacco use.[35] The neural networks involved in processing psychological stress and substance cues have a significant overlap, with alterations that occur in corticostriatal limbic circuits that underlie both the emotional and reward processes linked to stress and substance cue-induced craving, as well as a greater likelihood of relapse into addiction.[36]

For this reason, the study was designed to investigate the effects of omega-3 PUFA (ALA) as an edible-grade vegetarian source supplement on tobacco craving in regular tobacco users who refused to take any drug assistance for quitting.

We hypothesized that omega-3 PUFA (ALA) dietary supplementation might have an effect on both daily tobacco consumption and tobacco cravings among regular tobacco users.

Materials and Methods

The sample size has been calculated by the statistician on the basis of a previous study by Rabinovitz (2014).[22] The calculated sample size was 42 in each group, and after adding 20% dropouts in follow-up losses, the total sample size was 100 (50 in the omega-3 PUFA group and 50 in the placebo group) with a confidence level of 95% and a power level of 80%.

From a pool of 100 screened tobacco users, 90 were included in the study. Four participants refused, leaving 86 to be randomized into two groups through a computer-generated randomization table: 45 in the omega-3 PUFA group and 41 in the placebo group. Among the omega-3 PUFA group, 43 of 45 subjects completed the follow-up, with two discontinuing the intervention, while in the placebo group, 40 completed the follow-up, with one follow-up loss. Thus, a total of 83 subjects completed the follow-ups.

The study participants were recruited from the tobacco cessation clinic at King George's Medical University, meeting inclusion criteria aged between 18 and 60 years, fulfilling ICD-10 criteria for tobacco dependence, of either sex, i.e., both male and female, and being free from significant medical or surgical conditions.

Pregnant or nursing mothers, subjects suffering from any comorbidities, and subjects under conventional treatment for comorbidities were both excluded from the study. Subjects who chose pharmacological treatment (including NRT) for tobacco cessation were excluded. We have also excluded the subjects who have already consumed flaxseed or other commercially available omega-3 PUFA as nutritional supplements in the past 3 months. The study received approval from the Institutional Ethics Committee of King George's Medical University, India, and has been registered at the Clinical Trials Registry-India (identifier CTRI/2022/02/040681). Informed consent was obtained from all study participants following a comprehensive explanation of the study.

See Table 1 for demographic and basal characteristics at baseline of the total sample and by the two groups (Omega-3 PUFAs and Placebo Group). There were no significant baseline differences in these characteristics.

The study employed a single-blind, randomized, placebo-controlled, parallel-group design. Tobacco users were asked to take the omega-3 rich supplement in place of tobacco when they feel cravings. Subjective craving was reported on two occasions (day 0: baseline and day 180: follow-up). Refer to the flow chart in Figure 1 for an overview. Each PUFA bottle contained 10 mL of food-grade pure flaxseed oil with 5.1 gm of omega-3 PUFA (ALA). The placebo bottles contained mustard oil. Both oils in 10 mL quantities were supplied to the subjects in identical black glass coded bottles. Subjects were advised to consume 1 bottle of oil (10 mL) per day for a period of 180 days (6 months). The PUFA and placebo bottles were well tolerated, with no adverse effects reported. During follow-up interviews, participants from both study groups reported experiencing minimal aftertaste, bitterness, or odor. Compliance was ensured by regular reminders via SMS/WhatsApp and phone calls on a weekly basis to the subjects. We also maintained contact with a family member of each subject to help monitor their compliance. In both groups, adherence to the supplementation protocol was admirable.

Each subject was assessed at two intervals: initially at baseline and then after 180 days of treatment during the follow-up. Demographic measures and tobacco use measures were obtained at baseline itself. Also, at baseline and 180-day follow-up, subjects completed the Fagerström Test for Nicotine Dependence (FTND),[37] the Fagerström Test for Nicotine

Table 1: Demographic and basal characteristics at baseline of total sample and by group[†]

	All participants (n = 83)	*Omega-3 PUFA group (n = 43)*	*Placebo group (n = 40)*	*Statistics*
Age (years)	47.19 ± 10.25	47.16 ± 11.04	47.23 ± 9.47	$p = 0.9782^{ns}$
Gender (male)	75 (90.36%)	40 (93.02%)	35 (87.5%)	$p = 0.394^{ns}$
Gender (female)	8 (9.64%)	3 (6.98%)	5 (12.5%)	
Marital status				
Married	78 (93.98%)	41 (95.35%)	37 (92.5%)	$p = 0.586^{ns}$
Single (unmarried)	5 (6.02%)	2 (4.65%)	3 (7.5%)	
Tobacco users				
Smokers	22 (26.51%)	10 (23.26%)	12 (30%)	$p = 0.487^{ns}$
Smokeless tobacco users	61 (73.49%)	33 (76.74%)	28 (70%)	
Age at the beginning of regular tobacco use (years)	28.37 ± 12.27	27.84 ± 12.64	28.95 ± 11.99	$p = 0.5169^{ns}$
Duration of tobacco use (years)	19.73 ± 11.71	20.31 ± 13.08	19.59 ± 10.18	$p = 0.6416^{ns}$
Frequency of tobacco use per day	8.63 ± 6.7	10.19 ± 8.34	6.95 ± 3.72	$p = 0.1138^{ns}$
FTND and FTND-ST scores	5.88 ± 2.19	6.23 ± 2.21	5.58 ± 2.15	$p = 0.0642^{ns}$
QSU-brief and QSU-brief (modified) scores	49.61 ± 9.13	49.7 ± 9.9	49.53 ± 8.34	$p = 0.4461^{ns}$

$^{ns}p > 0.05$; [†]data are described as n (%) or mean ± standard deviation

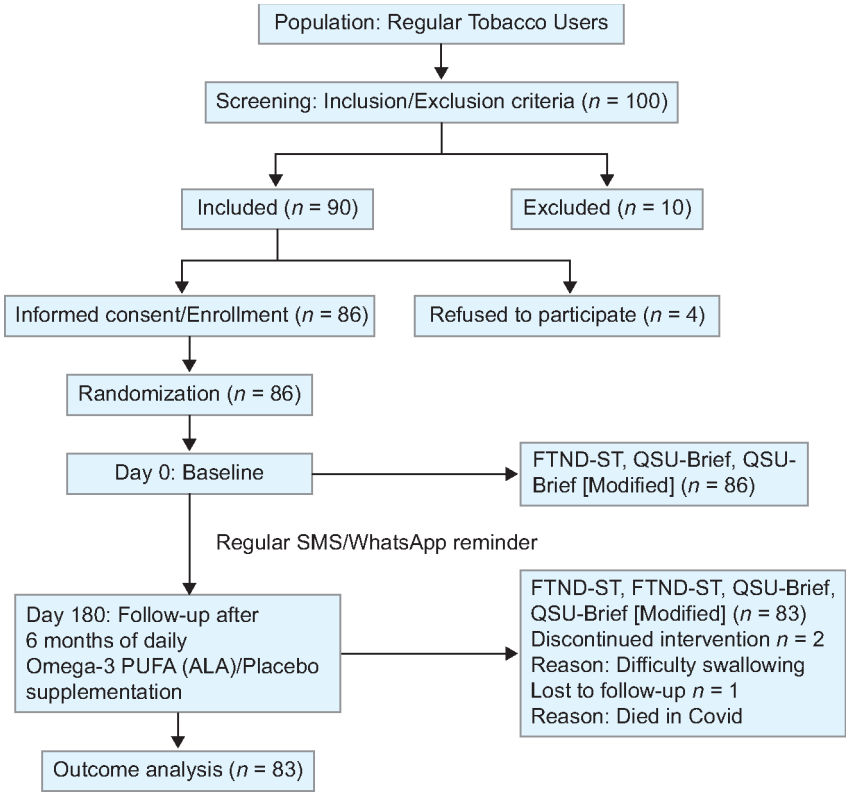

Fig. 1: Flowchart diagram, mapping study subjects and procedures

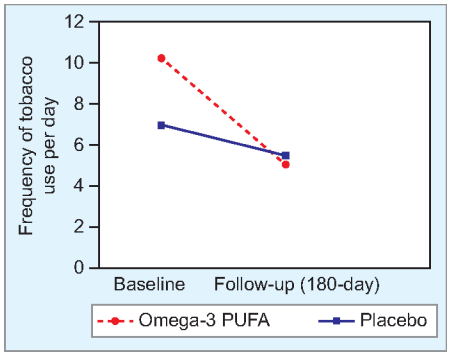

Fig. 2: Frequency of tobacco use daily (mean values) of regular tobacco users at baseline, after 180 days of daily supplementation of omega-3 PUFAs or placebo. The frequency of tobacco intake/day was summed to yield the total frequency per day

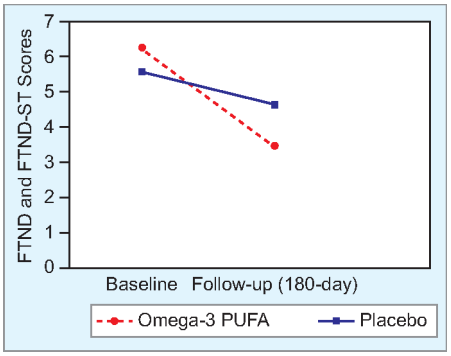

Fig. 3: Nicotine dependence level (mean values) of regular tobacco users at baseline, after 180 days of daily supplementation of omega-3 PUFAs or placebo. Scores assigned to all six items of the questionnaire were summed up to yield a total score

Dependence-Smokeless Tobacco (FTND-ST),[38] the Questionnaire on Smoking Urges-Brief (QSU-Brief),[39,40] and the Questionnaire on Smokeless Tobacco Urges (Modified Questionnaire for Smokeless Tobacco from QSU-Brief).

Statistical Analysis

Results are shown as the mean ± standard deviation. Statistical analyses were performed using Microsoft Excel 2021, GraphPad Prism 5, and SPSS 24 (Statistical Package for the Social Sciences 24). The effect of PUFA and placebo treatment within the respective groups was examined by a Wilcoxon matched-pairs signed rank test and a matched-pairs *t*-test accordingly. The comparison of baseline characteristics involved using the Chi-squared test for qualitative variables and the unpaired *t*-test along with the Mann–Whitney *U* test for quantitative variables. Unpaired *t*-tests and Mann–Whitney *U* tests were also applied for follow-up comparisons of both groups. The statistical significance of the difference is confirmed with $p < 0.05$.

Results

All over, there were 83 tobacco users, out of whom 22 were smokers, 61 were using smokeless forms. In the omega-3 PUFA group, 10 were smokers, and 33 were smokeless tobacco users, while in the placebo group, 12 were smokers and 28 were smokeless tobacco users.

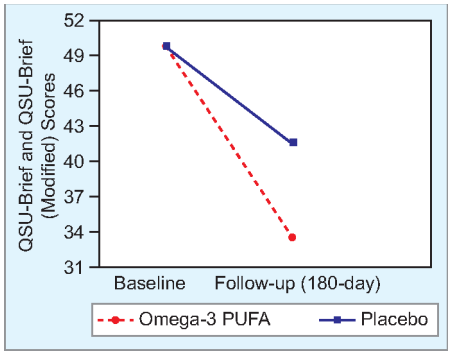

Fig. 4: Tobacco craving level (mean values) of regular tobacco users at baseline, after 180 days of daily supplementation of omega-3 PUFAs or placebo. Scores assigned to all 10 items of the questionnaire were summed up to yield a total score

The frequency of tobacco use per day did not have a significant difference ($p = 0.1138$) at baseline among the two groups. The subjects in the omega-3 PUFA group exhibited a significant decrease ($p < 0.0001$) from 10.19 ± 8.34 at baseline to 5.05 ± 4.83 after 180 days of supplementation in the frequency of tobacco use/day. Similarly, the placebo group also showed a significant decrease ($p = 0.0001$) from baseline to 180-day follow-up; however, their mean values had a minor difference, i.e., between baseline (6.95 ± 3.72) and follow-up (5.45 ± 3.85), representing a less significant decrease in frequency of tobacco use per day in the placebo group (Fig. 2). However, there was no significant change ($p = 0.37$) when we compared the follow-up of the omega-3 PUFA group with the placebo group (Table 2).

The difference in nicotine (tobacco) dependence was not statistically significant ($p = 0.0642$) between the omega-3 PUFA group (6.23 ± 2.21) and placebo group (5.58 ± 2.15) at baseline. The omega-3 PUFA group ($p < 0.0001$) and placebo group ($p < 0.0001$) showed a significant decrease in nicotine dependence after 180 days of supplementation, comparing their respective baselines to follow-up (Fig. 3). Moreover, no significant change ($p = 0.0578$) was found when the follow-ups of the omega-3 PUFA group were compared to the placebo group (Table 2).

There was no significant difference in tobacco craving between the omega-3 PUFA and placebo groups at baseline ($p = 0.4461$). The omega-3 ($p < 0.0001$) and placebo groups ($p < 0.0001$) showed a significant decrease in tobacco craving after 180 days of supplementation, comparing their respective baselines to follow-up (Fig. 4). Furthermore,

Table 2: Comparison of major findings (baseline-follow-up) within the group[T]

	Omega-3 PUFA baseline (n = 43)	*Omega-3 PUFA follow-up (n = 43)*	*Placebo baseline (n = 40)*	*Placebo follow-up (n = 40)*	*p^1 value*	*p^2 value*	*p^3 value*
Frequency of tobacco use per day	10.19 ± 8.34	5.05 ± 4.83	6.95 ± 3.72	5.45 ± 3.85	$p < 0.0001$***	$p = 0.0001$***	$p = 0.37^{ns}$
FTND and FTND-ST Scores	6.23 ± 2.21	3.44 ± 2.66	5.58 ± 2.15	4.6 ± 2.73	$p < 0.0001$***	$p < 0.0001$***	$p = 0.0578^{ns}$
QSU-brief and QSU-brief (Modified) Scores	49.7 ± 9.9	33.65 ± 10.72	49.53 ± 8.34	41.6 ± 10.77	$p < 0.0001$***	$p < 0.0001$***	$p = 0.0012$**

$^{ns}p > 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; [T]data are described as mean ± standard deviation; p^1: comparison between the mean baseline and follow-up of omega-3 PUFA group; p^2: comparison between the mean baseline and follow-up of placebo group; p^3: comparison between the follow-ups of the two groups

on comparing follow-ups between the two groups, a significant difference ($p = 0.0012$) was observed in tobacco craving (Table 2).

Discussion

The role of omega-3 in smoking addiction has been a trending topic of controversial debate for the past two decades. It serves as a nutritional supplement by supplementing with omega-3s, particularly EPA and DHA. It plays an ambiguous role by decreasing both the incidence of smoking and cigarette cravings. Hence, the present study evaluates the effect of omega-3 PUFA's (ALA) daily supplementation for 180 days on tobacco intake frequency/day, nicotine dependence, and tobacco craving. Moreover, we have attempted to explore the research not only on smokers but also on smokeless tobacco users.

Various studies have been conducted to show the beneficial effects of omega-3 FAs (EPA and DHA) on smokers, which we have discussed. Scaglia et al. demonstrated a negative and statistically significant association between the consumption of omega-3 FA-rich fish and smoking, with smokers consuming less of these foods compared to nonsmokers.[7]

The deficiency or lower concentrations of omega-3 FAs affect dopaminergic neurotransmission, leading to hypofunctioning of the mesocortical and mesolimbic pathways responsible for reward sensation.[41–43] Also, this hypofunctioning, in turn, might result in a higher craving reflex and impede smoking-quit efforts. Therefore, re-establishing omega-3 PUFA levels in the body may reduce tobacco consumption.[13] The association between omega-3 FAs and smoking addiction has been demonstrated by the reduced levels of omega-3 FAs observed in smokers.[7–9,44] Not only tobacco addiction but also omega-3 PUFA effects intake of other addictive substances such as alcohol, cocaine, opioids, by replenishing the brain's function, reducing sensitization to dopamine on substance abuse.[45–47] The physiology behind craving is its association with dopaminergic pathways, which leads to the sensation of craving tobacco in dopamine's absence.[48] Partial agonists at the α4β2 nicotinic acetylcholine receptor (α4β2 nAChR) can promote the release of adequate dopamine to alleviate cravings by inhibiting nicotine binding and its subsequent reinforcing effects.[49,50]

A study performed by Sadeghi-Ardekani et al. reported a greater reduction in nicotine dependence, cigarette craving (QSU scores), and frequency of cigarettes smoked per day among heavy smokers in the omega-3 FA group (fish-oil-derived omega-3 FA) compared to the placebo group for 3 months, and the difference between the two groups increased from baseline to 3-month follow-up.[51] This study supports our study for the effect of a decrease in frequency of tobacco use per day, dependence, and craving among tobacco users. However, significant changes in these characteristics in the placebo group could be due to the placebo effect. Alternatively, in a different experiment, DHA supplementation was administered to a small group of smokers for a few weeks at a low dose, without a control group, and did not result in a decrease in the number of cigarettes smoked during the treatment period.[52]

Furthermore, interventions done among women in the form of a single session of brief intervention or simple advice to quit tobacco were able to show a statistically significant difference in the number of tobacco chews per day and FTND scores.[53] Similarly, we also state a significant change in the frequency of tobacco use per day and its dependence, but with a nutritional intervention and not a behavioral intervention (for quitting tobacco), as reported by the above-mentioned study. Moreover, higher rates of smoking cessation were documented by a significant decrease in measures of nicotine dependence on the FTND scale (from baseline to follow-up) in a group (51%) provided with a combination of nicotine replacement therapy (nicotine gum) and individual counselling as compared to another group (8%) only receiving NRT and simple advice.[54] Corresponding to this, other drugs such as bupropion SR,[55] varenicline,[56] and buprenorphine-naloxone[57] have proven their efficacy to decrease tobacco craving, tobacco dependence, and tobacco use frequency per day, respectively. On a contrasting note, our research centered on the role of a dietary supplement (omega-3 PUFA) without pharmacological intervention and has sustained a significant change in the results of tobacco dependence, its craving, and its frequency of use per day in the omega-3 PUFA group.

More intriguingly, a Brazilian study[58] reported that supplementation (90 days) of fish oil capsules (omega-3-PUFA) and mineral oil (placebo) was accompanied by a significant reduction ($p = 0.03$) in the levels of nicotine dependence, according to the FTND test. Our study results agree with these findings, as we have also found a significant reduction in nicotine dependence among tobacco users. Rabinovitz conducted a randomized, placebo-controlled study involving 48 regular cigarette smokers. The study found that intake of 2710 mg of EPA and 2040 mg of DHA per day over 1-month significantly reduced self-reported daily smoking and cravings for tobacco.[22] Similarly, our study elucidates that omega-3 FAs were effective in significantly reducing the levels of tobacco craving, as observed in the study by Rabinovitz.

Conclusion

This study, performed in regular tobacco users with daily supplementation of omega-3 PUFAs for 180 days (10 mL/day), found a significant decrease after the follow-up (180 days) in the frequency of tobacco use per day, its dependence (measured by FTND), as well as decreased craving (measured by QSU-Brief) when compared to baseline. The findings of our study indicate that daily supplementation with omega-3 FAs could play a promising role as an adjuvant tool in reducing nicotine dependence levels as well as tobacco cravings. Despite certain limitations, including a small sample size and the assessment of omega-3 PUFA in serum, this study offers valuable insights. Additionally, the study was open to participants of both sexes, though the number of females recruited was very small. This study helps in providing a noteworthy

direction towards further research on both forms of tobacco (smoking as well as smokeless) and nonpharmacological management for tobacco cessation.

Source of Support

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Conflict of Interest

None.

Author Contributions

Anjali Singh, data collection, analysis, interpretation of the results and writing the manuscript; Narsingh Verma, conceptual idea, study framework designing and supervision; Surya Kant, subject enrollment, reviewing and critical feedback; Ajay Kumar Verma, subject enrollment, reviewing and critical feedback; Adarsh Tripathi, verified the analytical methods; Kshitij Bhardwaj, supplied necessary resources and supplements.

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ORIGINAL ARTICLE

Risk of Tuberculosis with the Use of Inhaled Corticosteroids in Delhi/NCR

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Abstract

Background: Tuberculosis (TB) is a global health concern caused by Mycobacterium tuberculosis, primarily affecting the lungs. In addition to TB, chronic respiratory conditions like Chronic Obstructive Pulmonary Disease (COPD) and asthma are becoming more prevalent globally. Inhaled corticosteroids (ICS) are commonly used for COPD and bronchial asthma management, but some recent studies suggest a potential association between ICS usage and an increased risk of TB, raising concerns that they may lower lung immunity and enhance tuberculosis infection.

Aims and objectives: This research study was performed with an aim to investigate whether there is a link between inhaled corticosteroids (ICS) use and the risk of developing tuberculosis (TB) in COPD patients. The primary objective is to study whether the use of inhaled corticosteroids increases the risk of tuberculosis infection. The secondary objective is to compare the risk of TB in vulnerable populations with underlying comorbidities using inhaled corticosteroids.

Materials and methods: This is an observational, analytical study conducted over 2 months in patients with COPD who have been receiving inhaled corticosteroids for more than 2 years.

Results: A total of 97 COPD patients on ICS were recruited and categorized into TB ($n = 4$) and non-TB ($n = 93$) groups based on final outcomes. The mean ICS duration for the non-TB and TB groups was 24.8 and 48.0 months, respectively.

Conclusion: Despite being on ICS for more than 2 years, there was no significant correlation between ICS usage and TB infection. However, the study highlighted the significance of a prior TB history as a risk factor for increased reactivation ($p < 0.001$). Additionally, anemia was observed in reactivated TB cases, suggesting potential implications for identifying underlying chronic diseases in COPD patients.

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Introduction

Tuberculosis (TB) is a global health concern caused by Mycobacterium tuberculosis, primarily affecting the lungs. Despite available drugs and vaccines, TB remains a significant issue in developing countries. The World Health Organization (WHO) aims to end the TB epidemic by 2035 through the "End TB Strategy," emphasizing vaccination, early detection, and timely treatment.[1] India has the highest TB burden, contributing to 26% of global incident cases in 2021.[2] In addition to TB, COPD is one of the top three causes of mortality globally, and 90% of these incidents occur in low and medium-socioeconomic countries. Chronic obstructive pulmonary disease, often referred to as emphysema or chronic bronchitis, is a common lung disease that causes restricted airflow and breathing problems.[3] Patients with COPD exacerbations may develop end-stage COPD if they are not managed promptly with evidence-based therapies. In line with the objectives to address this public health issue, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated in 1998, with the aim of providing guidance, based on the best available scientific evidence, for the management of COPD. Inhaled corticosteroids are commonly used for COPD management, but some recent studies suggest a potential association between ICS usage and an increased risk of TB, raising concerns as they may lower lung immunity and enhance tuberculosis. The present study was carried out with an aim to ascertain an association between ICS use and risk of TB infection, and also to compare the risk of TB in vulnerable populations with underlying comorbidities.

Materials and Methods

The present study is based on data retrieved from the medical records of adult patients who were admitted to the Respiratory and Medicine Department at Sharda Hospital and School of Medical Sciences and Research, Greater Noida, Uttar Pradesh. After the approval of the ethics committee, the data were collected and anonymized. It is an observational analytical study. The study period was 2 months (3rd August 2022–3rd October 2022), and a total of 97 COPD patients were recruited. After a sample size calculation, all patients had been on inhaled corticosteroids for an average of more than 2 years. Study tools included sputum microscopy, chest X-ray, Mantoux test, ESR, and HRCT, if required.

Inclusion Criteria

All individuals above 18 years of age who were prescribed at least one of the following inhalational corticosteroids: beclomethasone, budesonide, triamcinolone, or fluticasone. All patients were prescribed a combination of a short-acting beta-agonist (SABA), salbutamol, and a short-acting muscarinic antagonist (SAMA), ipratropium, or a combination of long-acting beta-2 agonists (LABA)/long-acting muscarinic receptor antagonists (LAMA) and inhalational corticosteroids (ICS) (budesonide/formoterol, fluticasone/salmeterol).

Exclusion Criteria

Patients below 18 years of age, Patients in any stage of pregnancy, People living with HIV, and people already having chest infections.

Study Design and Conduct

This study focused on patients who had used inhaled corticosteroids (ICSs) or combinations of bronchodilators for at least 3 months. Information on ICS prescription and diagnosed tuberculosis (TB) cases occurring after initiating respiratory medications was collected, utilizing sputum microscopy, chest X-ray, ESR, and Mantoux test results. Covariates such as age, sex, and comorbid conditions known to increase TB risk were considered.

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Statistical Methods

All the data obtained were statistically analyzed in Microsoft Excel using mathematical functions. Means and standard deviations summarized continuous variables, while frequencies and percentages expressed categorical variables. Statistical significance was set at $p < 0.001$.

Results

Table 1 and Figure 1 show that the majority of the study participants (43) were aged 60 years or older, followed by 38 participants aged 41–60 years, and the remaining 16 participants were aged 40 years or younger. As shown in Table 2 and Figure 2, nearly half of the study participants (55) were male, and the remaining 42 were female. The *p*-value for age and gender is > 0.05, which is insignificant. Table 3 and Figure 3 represent comorbidities. The maximum number of participants (89 of 97 recruited) had no prior history of comorbidities. Only eight patients have had comorbidities, out of which five subjects had HTN, two subjects had a history of CAD, and one subject had diabetes mellitus. Covariates, in addition to age and gender, included comorbidities, which were also analyzed. The *p*-value for the above is > 0.05, which is also nonsignificant. Table 4 and Figure 4 display that a large number of study participants (89) have had no history of tuberculosis (TB). Only eight subjects had a history of tuberculosis, of which five subjects were in the non-TB group, and three subjects were in the TB group. However, this difference was statistically significant ($p < 0.001$). This implies that a previous history of tuberculosis can be a risk factor for increased reactivation, which may or may not be associated with ICS use. Table 5 and Figure 5 show that all study participants have used inhaled corticosteroids (ICS). However, 56 subjects had a history of smoking, and 11 subjects had a history of alcohol consumption. There was no significant difference between the Non-TB and TB groups. As shown in Table 6 and Figure 6, all the study participants were normally built with adequate nourishment. However, 12 subjects had pallor, out of which nine were in the non-TB group, and three

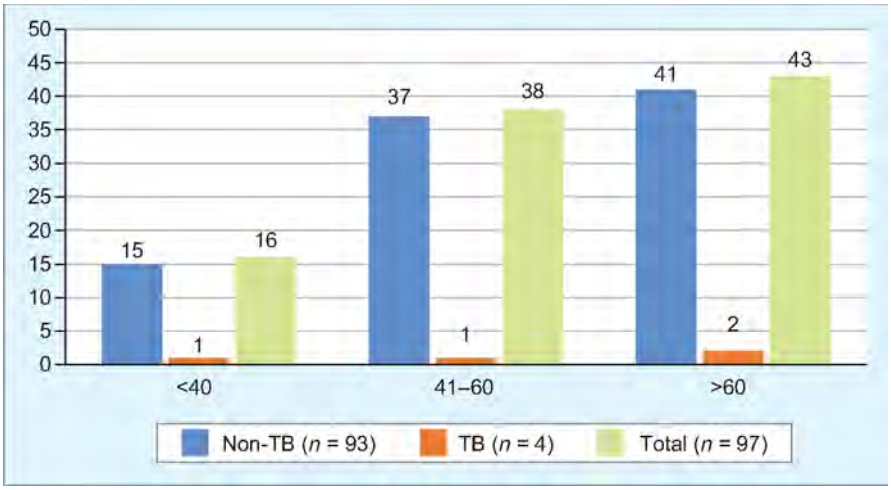

Fig. 1: Study participants according to age

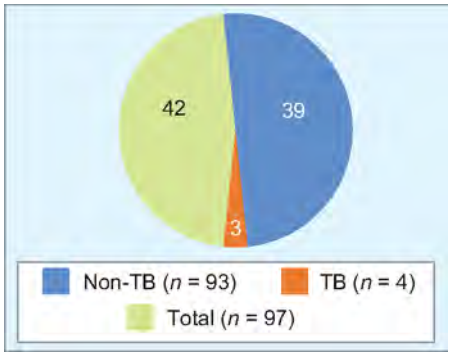

Fig. 2: Study participants according to gender

Table 1: Frequency distribution of study participants according to age

Age (in years)	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value (Chi-square)*
<40	15	1	16	0.808
41–60	37	1	38	
>60	41	2	43	

Table 2: Frequency distribution of study participants according to gender

Gender	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value (Fisher's exact test)*
Female	39	3	42	0.215
Male	54	1	55	

Table 3: Frequency distribution of study participants according to past history of disease

Past history of disease	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
Hypertension	5	0	5	0.806
Coronary artery disease	2	0	2	0.919
Diabetes mellitus	1	0	1	0.959

Table 4: Frequency distribution of study participants according to history of tuberculosis

TB history	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
No	88	1	89	<0.001
Yes	5	3	8	

Table 5: Frequency distribution of study participants according to personal history

Personal history	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
ICS usage	93	4	97	–
No significant family history	93	4	97	–
Smoking				
No	40	1	41	0.434
Yes	53	3	56	
Alcohol				
No	83	3	86	0.387
Yes	10	1	11	

Table 6: Frequency distribution of study participants according to general physical examination

General physical examination	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
Normal built	93	4	97	
Adequate nourishment	93	4	97	
Pallor				
No	84	1	85	0.006
Yes	9	3	12	
Icterus				
No	93	4	97	
Clubbing				
No	92	3	95	0.081
Yes	1	1	2	
Cyanosis				
No	93	4	97	
Lymphadenopathy				
No	93	4	97	
Edema				
No	92	4	96	0.959
Yes	1	0	1	

Table 7: Frequency distribution of study participants according to mean age, ICS duration, and vitals

	Non-TB					*TB*					*Total*					*p-value (Chi-square)*
	Mean	*SD*	*Range*	*Min*	*Max*	*Mean*	*SD*	*Range*	*Min*	*Max*	*Mean*	*SD*	*Range*	*Min*	*Max*	
Age	56.6	14.2	61	20	81	56.3	12.6	28	40	68	56.5	14.1	61	20	81	0.966
ICS duration (in months)	24.8	34.6	179	1	180	48.0	64.2	132	12	144	25.7	36.0	179	1	180	0.208
Pulse rate	84.5	9.1	80	40	120	85.5	3.8	8	80	88	84.5	8.9	80	40	120	0.820
Respiratory rate	20.6	2.6	19	16	35	20.5	1.9	4	18	22	20.6	2.5	19	16	35	0.918
SpO_2	96.5	6.2	59	40	99	97.3	1.5	3	96	99	96.5	6.0	59	40	99	0.811
BP (Sys)	117.5	12.2	69	100	169	120.0	8.2	20	110	130	117.6	12.0	69	100	169	0.685
BP (Dias)	74.9	7.8	40	60	100	72.5	9.6	20	60	80	74.8	7.8	40	60	100	0.549

subjects were in the TB group; this difference was statistically significant ($p < 0.001$). Table 7 delineates that the mean duration for the use of inhalational corticosteroids was 25.72 months. Table 8 and Figure 7 convey that the majority of study participants (93) had no evidence of Tuberculosis (TB) on chest X-ray, and only four subjects had evidence of active tuberculosis. However, this difference was statistically significant ($p < 0.001$). Figure 8 shows that the majority of study participants (96) reported as AFB-negative on sputum microscopy, and only one subject reported as AFB-positive on sputum microscopy. One participant was found to be AFB positive and also showed signs of active tuberculosis (TB) on chest X-ray. ESR was not considered for all the patients; hence, it was analyzed.

Discussion

The primary objective of our study is to ascertain the likelihood of developing TB with ICS use in COPD patients. The present study has not proven any such correlation between ICS use and risk of TB development, despite the fact that they were on ICS for approximately 24 months. However, our study demonstrated that a previous history of tuberculosis can be a risk factor for increased reactivation with a statistically significant *p*-value ($p < 0.001$). Dong et al. conducted randomized controlled trials to assess the impact of ICS on the causation of TB and influenza in COPD patients. The risk of TB and influenza in patients with COPD, from their study the number needed to harm to cause one additional TB event was lower for patients with COPD treated with ICSs in endemic areas than for those in nonendemic areas (909 vs 1,667, respectively); hence, TB risk may not be directly correlated to ICS use as the NNT is not

Table 8: Frequency distribution of study participants according to the investigation

Investigations	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
Chest X-ray				
Infective etiology, such as tubercular	0	4	4	< 0.001
No evidence of TB	93	0	93	
Sputum microscopy				
AFB negative	93	3	96	0.041
AFB positive	0	1	1	
ESR				
No	93	4	97	

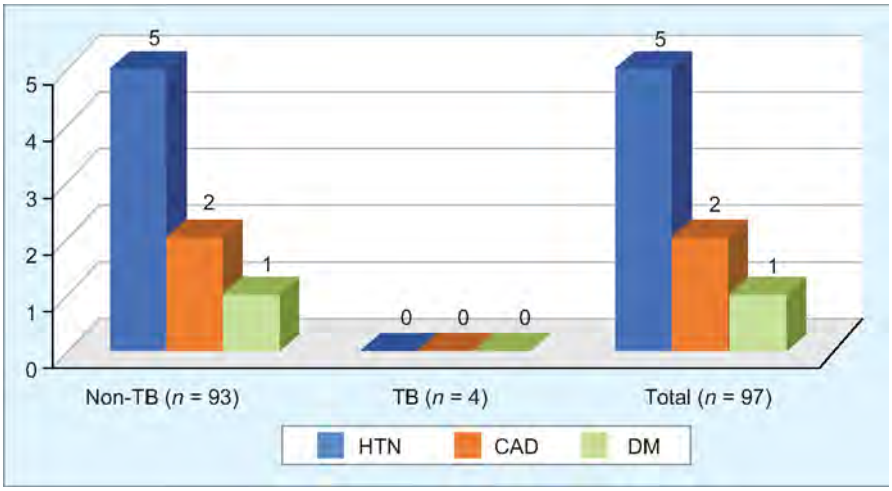

Fig. 3: Study participants according to past history of disease

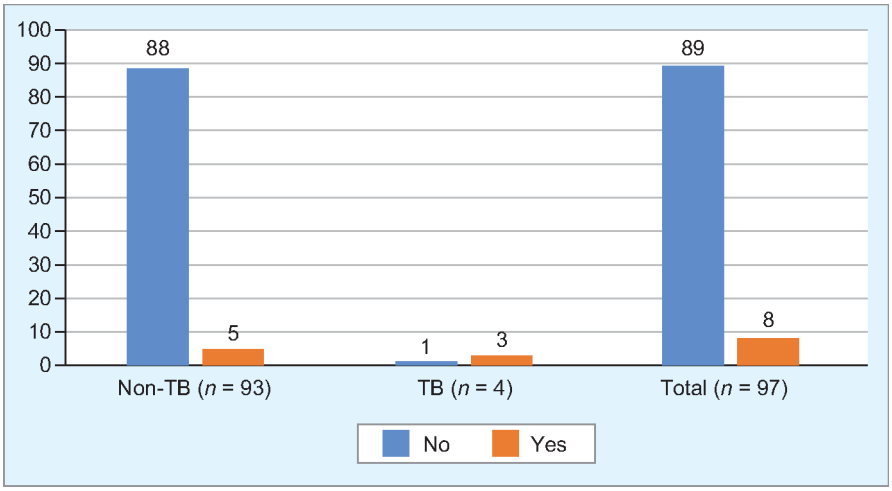

Fig. 4: Study participants according to history of tuberculosis

comparable in both the groups.[4] Castellana et al. conducted a systematic review and meta-analysis in Italy in 2018 to evaluate the effects of inhaled corticosteroids (ICS) on the risk of TB in patients with COPD, which was registered on PROSPERO. Their study demonstrated that ICS use was associated with an increased risk of TB compared with no ICS use (OR = 1.46; 95% CI 1.06–2.01; $p = 0.02$; $I_2 = 96\%$). However, when considering PAF (Population Attributable Fraction), the contribution of ICS to the epidemiology of TB seemed to be limited, leading them to suggest that the risk should be taken into account on an individual basis.[5] Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 2022[6] discusses the benefit of triple therapy with a long-acting beta 2-agonist (LABA)/long-acting muscarinic antagonist (LAMA)/inhaled corticosteroid (ICS). This combination is associated with reduced mortality compared with LABA/LAMA therapy in symptomatic patients with a history of frequent and/or severe exacerbations. Chang-Hoon-Lee et al. conducted a case-control study in 2013 to establish the relationship between inhaled corticosteroids and TB, in which they concluded that the use of ICS increases the risk of TB with an adjusted OR (aOR) of 1.20; 95% CI 1.08 to 1.34. The association was dose-dependent (p for trend < 0.001). However, they noted a limitation in their study of recruiting heterogeneous patients with various respiratory diseases, which could have led to the obfuscation of the actual effects of the drugs on the risk of TB.[7] Notably, their results are in contrast to our study results, emphasizing the need for an individualized approach to assess the risk associated with ICS use.

The secondary objective of our study is to compare the risk of TB in vulnerable populations with underlying comorbidities who are also on ICS for a long duration. Since our study is based on a simple random sampling, the majority of our patients, almost 92%, are found to have no underlying comorbidities. Hence, we could not establish the relationship between TB and comorbidities. However, our study has proven that a previous history of tuberculosis can be a risk factor for increased reactivation ($p < 0.001$). Moreover, study results showed that people with reactivated TB were noted to be anemic, and this difference was statistically significant ($p < 0.001$) when compared to the non-TB group. The current study implies that a previous history of tuberculosis can be a risk factor for increased reactivation, and also screening of the comorbidities should be an important component in the management of a COPD patient, as anemia may have been caused by the underlying chronic disease apart from COPD.

According to a study conducted by Chung et al. in Taiwan titled "Use of inhaled corticosteroids and the risk of tuberculosis. A countrywide study of 8091 TB patients and 32,364 non-TB patients denoted that long-term use of ICS is associated with a 2.04-fold

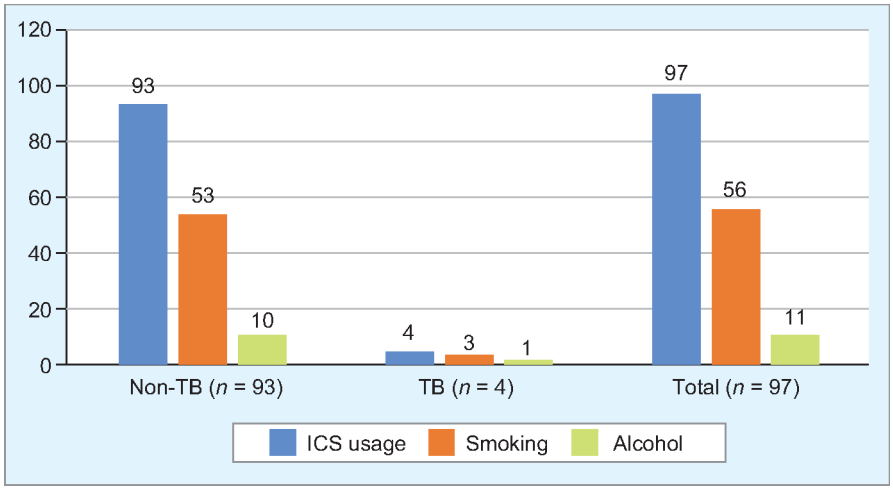

Fig. 5: Study participants according to personal history

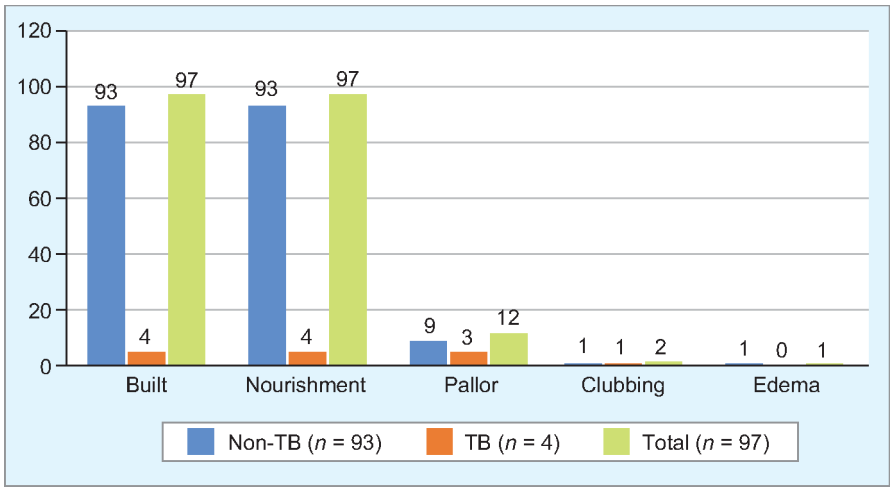

Fig. 6: Study participants according to general physical examination

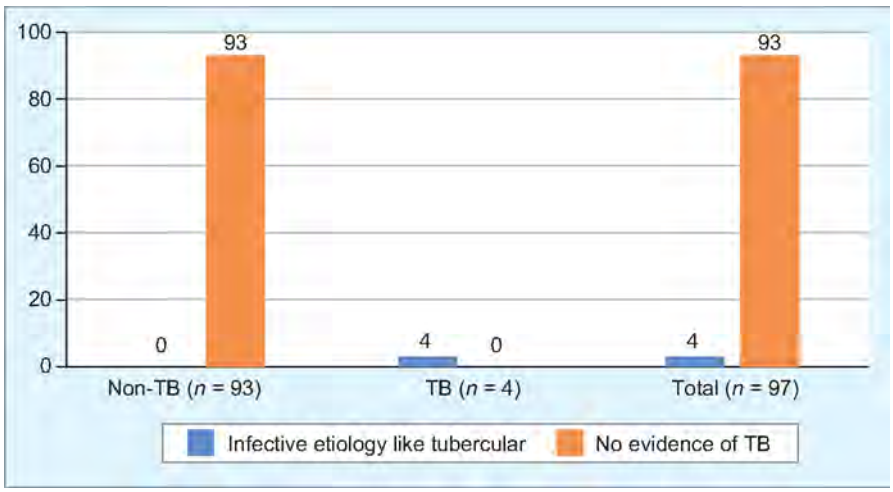

Fig. 7: Study participants according to chest X-ray

increased risk of developing TB (adjusted OR (aOR), 1.20; 95% CI 1.08 to 1.34). In a country with an intermediate TB burden, it was determined that using ICS raises the risk of developing TB. Their results are contrary to ours. However, the majority of their patients were known to have diabetes mellitus, liver cirrhosis, cancer, and end-stage renal failure, and were already on oral steroids and DMARDS (disease-modifying agents), which may explain the underlying immunodeficiency. However, they have also demonstrated that study participants with pre-existing TB history have displayed an 8.5-fold increased risk of TB development compared with other participant who has no prior TB history; these results are similar to our study.[8] The other study conducted by "Venkitakrishnan et al. in South India shows a slightly increased risk of TB reactivation, with only one additional TB reactivation occurring out of 909 COPD patients receiving ICS in endemic locations, which demonstrates the low size of this risk with a population attributable percentage of 0.49%, in a high burden country for tuberculosis."[9]

The most recent (2023) GOLD Report states that a single COPD exacerbation can triple the lung function decline in mild COPD patients. It also emphasizes the use of blood eosinophils in deciding whether to initiate ICS. The current GOLD report strongly favors ICS use if history of hospitalizations for exacerbations of COPD, and if ≥ 2 moderate exacerbations of COPD per year, or history of concomitant asthma, and also if eosinophils ≥ 300/µL. This study also proposes to de-escalate ICS if patients develop frequent episodes of pneumonia or if they have preexisting tuberculosis, and if the blood eosinophil count is <100/ µL.[10] Malerba et al. conducted research in Italy to review the rationale for the single-inhaler LABA/LAMA for COPD. The study concluded to consider LAMA/LABA combinations rather than monotherapy, and their study also highlighted the consideration of ICS use in COPD patients if their sputum shows an elevated eosinophil count.[11]

To acknowledge our results, the strengths and limitations of our study must be elucidated. All the covariates in our study had *p*-values > 0.05, indicating they were not significant, and none were on any immunosuppressive medications. One of the main strengths of this study is having fewer confounding variables. Hence, this study infers the effect of ICS in quantifying the risk of future TB development in COPD patients.

Limitations

Since the present research is an observational analytical study with a small sample size, it limits the generalizability. Hence, more randomized controlled trials with large sample sizes are required to ensure the external validity in a diverse socio-economic population.

Conclusion

In conclusion, the current research has not shown any evidence of new TB risk in COPD patients who are on ICS for approximately 2 years. However, our study demonstrates

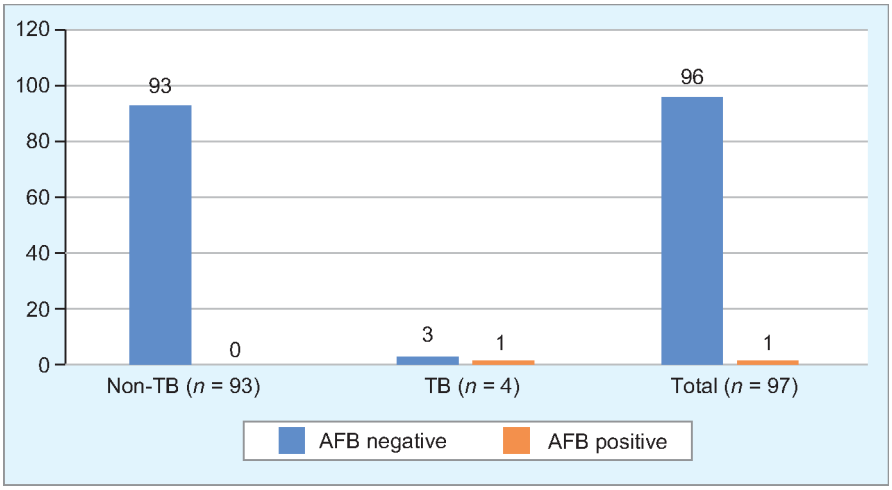

Fig. 8: Study participants according to sputum microscopy

that a previous history of tuberculosis can be a risk factor for increased reactivation, which is worth highlighting. Anemia of chronic disease is probably the most common type of anemia associated with COPD. Even so, anemia may not always be attributed to an untreated or progressive COPD, but may also be caused by any other underlying chronic diseases, such as tuberculosis, especially in countries with a high prevalence of TB. We propose a future scope for new research to decide whether concomitant comorbidities have any added role in the causation of TB in COPD patients who are on ICS. Frequent exacerbations of COPD accelerate disease progression and may contribute to premature mortality outcomes. Therefore, our study suggests that prescribing inhaled corticosteroids, especially during COPD exacerbations, is justified, as the benefits outweigh the risks.

Acknowledgments

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ORIGINAL ARTICLE

A Study Comparing Tuberculosis-related Stigma in Healthcare Providers and Receivers

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Abstract

Background: Global efforts to reduce tuberculosis (TB) are severely hampered by stigma. With a high number of TB infections, India struggles with the widespread stigma surrounding the illness, which makes it difficult to diagnose and treat patients promptly. To shed light on an important but often ignored component of TB management, we calculate the prevalence of TB-related stigma and variability in the manifestation in different groups.

Methods: After calculating the sample size, we stratified them into different groups: patients with TB, healthcare workers providing TB services, and family members living with the patients. A validated, predesigned questionnaire was employed to assess stigma across various domains. MS Excel was used to compile the data, and Epi Info 7 to analyze it.

Results: Health professionals made up the largest percentage of those who experienced stigma (11.78%), followed by family members (8.91%), and patients (6.05%). The association of stigma with different groups of study participants was statistically significant, implying that stigma exists variably in the other groups. The majority of the patients (3.50%) perceived stigma at their home, whereas the majority of the family members faced stigma in the community (5.41%). Healthcare workers face stigma majorly in the community (7.96%).

Conclusion: Stigma related to TB lays its foundation in varied perceptions by society. Societal norms determine acceptable and undesirable behaviors. Our study reveals major roadblocks on the way to TB eradication in the country and reveals a picture that can be extrapolated to most communities throughout. Aiming to reduce stigma will, in turn, improve treatment-related outcomes in TB and pave the way for smoother management and eradication.

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Introduction

Stigma, as defined by the World Health Organization, is a "mark of shame, humiliation, or disapproval causing an individual to be rejected, discriminated against, and excluded from engaging in various activities."[1] In the course of the history of tuberculosis (TB), it has posed a problem not only due to its serious health impacts but also through its social aspects. India leads in numbers out of the 8 countries responsible for the maximum burden of TB in the world.[2] Around 10 million people suffered from TB on a global scale in 2019, and about 1/3 of them went unreported.[3] India hosts 27% of cases of TB in the world.[4] About 73% of the people in the country harbor stigmatizing and discriminatory behavior toward TB patients.[5] This stigma stands as an obstacle to getting medical help and becomes a reason for significant suffering added to the illness. Stigma is not limited to patients but extends to their family members and also to the healthcare workers involved in TB caregiving. These range from subtle exclusions at school or workplace to people being thrown out of their houses and estranged from families. Often, both public and private health sector staff are accused of having discriminatory attitudes.[6] It is also noteworthy that education and awareness disseminated seek to target the medical aspects of the disease, and factors that lead to discrimination and stigmatization against patients often remain unaddressed.[5] Since stigma is associated with increasing the burden of the infectious pool and chain of transmission in the household, followed by the community, ultimately delaying seeking care and leading to a poorer prognosis, focus on this becomes imperative.[7,8] Sadly, India's TB eradication programs and strategies have never prioritized addressing social implications at the forefront. Keeping in mind that increased acceptability for the disease and utilization of healthcare services at the earliest will result in sooner and more widespread screening, testing, and diagnosis of TB, as well as improved treatment adherence and outcomes, we aim to bring the above to light. This study focuses on comparing stigma between the provider and receiver end of TB service and would add to the insufficient data on the social facet of the disease. Ending the stigma and discrimination associated with TB diminishes, and may even eliminate, the fearful nature of the disease, thus leading to a higher acceptability of healthcare services. This would reinforce the national TB strategy plan, with the goal of eliminating the disease by 2025.

Methods

This study was conducted in the district of Bhopal, Madhya Pradesh. The sample size was estimated based on the prevalence of TB stigma from the reference study, which reported a rate of 73%.[5]

$$\text{Sample size } (n_0) = z^2pq/e^2$$

Where p, prevalence, is 73%; q (100 – p) comes to 27; e is allowable error, which is taken to be 5%; and z is 1.96 (confidence interval of 95%).

The sample size as estimated by this comes out to be:

$$n_0 = 313.7$$

Therefore, the sample size (n_0) was determined to be 314. Stratified sampling was employed to divide the sample of 314 equally into three categories:

1. 105 patients.
2. 105 family members.
3. 104 healthcare workers.

We obtained the ethical clearance from the Institutional Ethical Committee (registration no. ECR/1055/Inst/MP/2018) under letter no. 30692/MC/IEC/2022 dated 04/08/2022. This study was conducted across 13 tuberculosis units (TU) located in the Bhopal district (Table 1). With the District TB Officer's approval, a list of

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TB patients seeking treatment at the respective TUs, along with their contact details, was obtained through the Nikshay portal. A total of 105 patients were selected evenly from the 13 TUs in the Bhopal district, utilizing a simple random sampling technique. Upon consent, the investigator visited the patients' homes and conducted interviews with the patients and 1 family member present, preferably the primary caregiver, with responses recorded in the questionnaire. Additionally, 104 healthcare workers involved in providing TB services were interviewed (Fig. 1).

Furthermore, each question or scenario was translated into the local language to maintain its original context and ensure understanding by the participants.

As for the study tool, a predesigned questionnaire was utilized, which was internally validated by pulmonologists and externally validated by the District Tuberculosis Officer (DTO). This questionnaire was developed with reference to the stigma assessment tool created by the Stop TB Partnership and hosted by UNOPS. Participants were questioned about their personal encounters with TB-related stigma, observations of stigma experienced by others, the role of stigma as a hindrance to accessing TB services, and suggestions for enhancing TB services, laws, and policies. The questionnaire encompassed various domains as outlined in (Fig. 2).[9]

Table 1: List of TUs in Bhopal district

S. no.	*TU in Bhopal district*	*DMC in Bhopal district*
1	DH Jaiprakash Hospital	2
2	Jawaharlal Nehru hospital	3
3	Civil Hospital Berasia	3
4	TB Hospital Bhopal	3
5	District TB Centre	3
6	Kailash Nath Katju hospital	2
7	AIIMS Bhopal	3
8	CHC Gandhi Nagar	2
9	Pulmonary Medicine Centre (Gas Rahat)	2
10	PHC Misrod	3
11	CHC Kolar	3
12	People's College of Medical Sciences and Research Centre	1
13	Civil Hospital Bairagarh	2

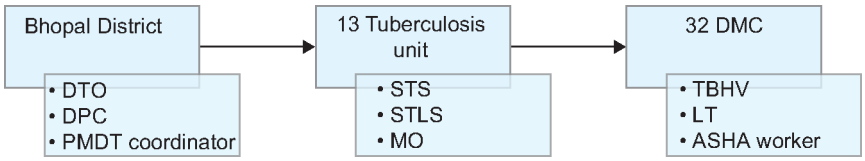

Fig. 1: National TB program healthcare workers organizational structure

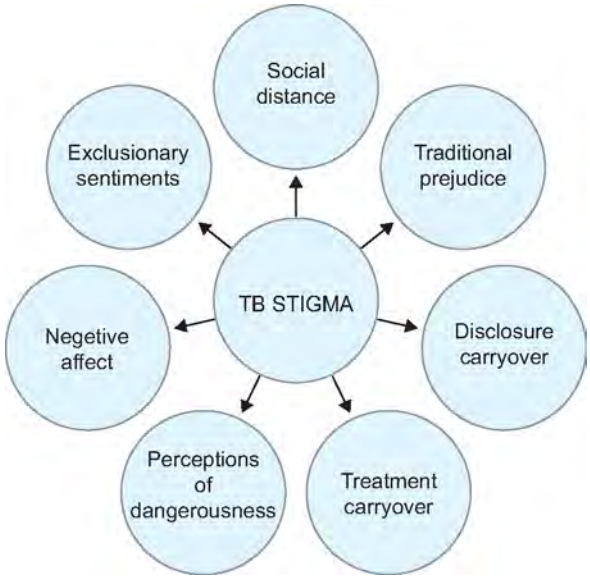

Fig. 2: Domains of TB stigma

Inclusion Criteria

- Tuberculosis patients of 18 years or older.
- Patients with proper communication and comprehension of the questionnaire's content.
- Patients who have provided consent to participate in the research and to share their perspectives on the issue honestly.
- Family members living with TB patients of 18 years or older, serving as caregivers, and willing to participate.
- Healthcare workers willing to participate and are employed under the National Tuberculosis Elimination Program (NTEP).

Exclusion Criteria

- Individuals not consenting to participate.
- Individuals under 18 years of age.

The data was collected and organized in Microsoft Excel, and subsequent analysis was conducted using CDC's Epi Info 7 software. Chi-square analysis was done to find any association between stigma and different participant groups.

Results

Table 2 demonstrates the association of stigma among different groups of the study. The maximum proportion of the population who faced stigma were health workers (11.78%), followed by family members (8.91%), and patients (6.05%). The association of stigma with different groups of study participants was statistically significant, with a *p*-value of 0.017, implying that stigma exists variably in the different groups.

Table 3 explains the prevalence of stigma observed among different groups, that is, whether they have seen others facing stigma related to TB. The majority of them were healthcare workers (12.73%), followed by family members (11.78%), and patients (7.96%). The association of secondary stigma with different groups was not statistically significant. This question was asked to see observed stigma in society, where all 3 groups responded invariably.

Table 4 shows the proportional distribution of study participants according to the places where they have faced stigma. The majority of the patients (3.50%) perceived stigma at their home, followed by at work (1.91%), and the least proportion faced it in the community (0.63%), whereas the majority of the family members faced stigma in the community (5.41%), followed by at home (1.91%), and at work (1.59%). Healthcare workers faced stigma majorly in the community (7.96), followed by

Table 2: Association of stigma with different groups of study participants ($n = 314$)

Group	*Have you ever faced stigmatizing behavior from others because of your TB status/a family member having TB/ having to work with TB patients?*		*Total*	*Pearson Chi-square*	*df*	*p-value*
	No n (%)	*Yes n (%)*				
Patients	86 (27.38)	19 (6.05)	105 (33.43)	8.149	2	0.017*
Family members	77 (24.52)	28 (8.91)	105 (33.43)			
Healthcare workers	67 (21.33)	37 (11.78)	104 (33.12)			
Total	230 (73.24)	84 (26.75)	314 (100)			

*p-value < 0.05 is statistically significant

Table 3: Association of stigma observed by patients, family members, and healthcare workers, with respect to different groups of study participants ($n = 314$)

		Have you seen any other person being stigmatized because of TB?		*Total*	*Pearson Chi-square*	*df*	*p-value*
		No n (%)	*Yes n (%)*				
Group	Patients	80 (25.47)	25 (7.96)	105 (33.43)	5.660	2	0.059
	Family members	68 (21.65)	37 (11.78)	105 (33.43)			
	Healthcare workers	64 (20.38)	40 (12.73)	104 (33.12)			
Total		212 (67.51)	102 (32.48)	314 (100)			

Table 4: Proportional distribution of study participants according to the places where they have faced stigma ($n = 314$)

Place where participants faced stigma	*Group*			*Total*
	Patients n (%)	*Family members n (%)*	*Healthcare workers n (%)*	
No stigma	86 (28.34)	77 (24.52)	67 (21.33)	230 (73.24)
Health facility	0 (0)	0 (0)	9 (2.86)*	9 (2.86)
Community	2 (0.63)	17 (5.41)	25 (7.96)	44 (14.01)
Home	11 (3.50)	6 (1.91)	3 (0.95)	20 (6.36)
Work	6 (1.91)	5 (1.59)	0 (0)*	11 (3.50)
Total	105 (33.43)	105 (33.43)	104 (33.12)	314 (100)

*Work and health facilities were evaluated as single entity for healthcare workers

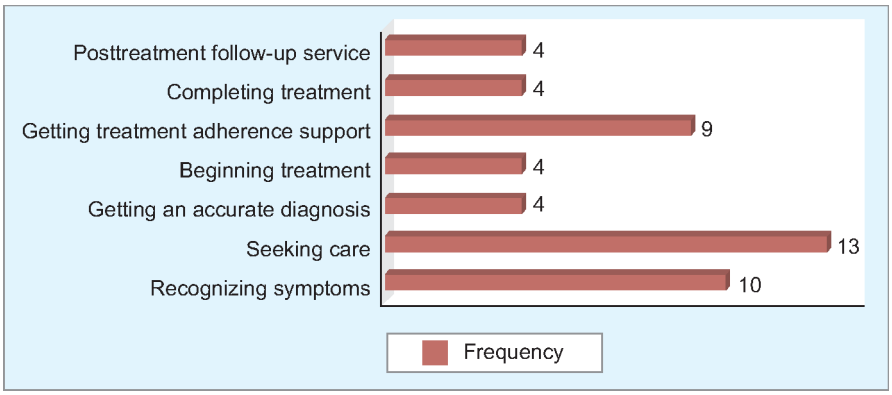

Fig. 3: Frequency distribution of patients and family members according to various aspects in which stigma acts as barrier ($n = 210$)

at home (0.95%), and health facility or work (2.86%).

Figure 3 conveys how stigma acts as a barrier during the course of TB. The leading aspect in the course of disease and utilization of TB services where stigma acts as a barrier to patients and family members, where seeking care was reported in 13 (6.2%), followed by recognizing symptoms in 10 (4.7%), and getting treatment adherence support in 9 (4.3%). Others are posttreatment follow-up service ($n = 4$), beginning treatment ($n = 4$), completing treatment ($n = 4$), and getting an accurate diagnosis ($n = 4$).

Discussion

Tuberculosis, despite being easy to diagnose and a treatable disease, claims at least 3 lives every minute.[10] However, this path of management and, ultimately, the eradication of TB have many obstacles to be overcome by the community as a whole. Among these, stigma and associated discrimination faced by those with or impacted by TB continue to be a significant barrier.

Keeping the above in mind, we chose this study to assess the biggest barrier faced during TB management: the stigma associated with it. In our study population, which included 105 patients and their family members, along with 104 healthcare workers, it was found that the maximum proportion of the study population that faced stigma were healthcare workers, that is, 11.78%. This data is strikingly similar to a study conducted by Muhandiki et al. in Tanzania,[11] which revealed that about 50% of the recruited healthcare workers perceived stigma. This was followed by family members and patients, 8.91 and 6.05%, respectively.

The study also revealed a significant association of stigma with different groups of study participants. Among the participants, 32.48% have reportedly observed others being subjected to stigma, with healthcare

workers forming the major chunk, which can be attributed to them being surrounded by patients and their families throughout, and also being surrounded by other patients and their kin in healthcare centers.

While assessing the places the participants have experienced this stigma, it was found that patients were subjected to most stigma at home, followed by workplace settings, and least in the community. This may be because of their confinement at home due to the illness and also because most conceal their illness status. The majority of the family members face stigma in the community, followed by home, and lastly, work. This may be attributed to them being more mobile and engaged in the community. Healthcare workers face the most stigma in the community, followed by home, and lastly, work, keeping in accordance with acceptance of the illness and its nature by their fellow workers. However, as they are the link of the important chain of transmission of any communicable disease to the community, the stigma is explained. The above has also been mentioned by Courtwright and Turner in their study assessing TB stigma, pathways, and intervention.[12]

While assessing the various aspects of how stigma acts as a barrier during the course of TB for patients and their family members, the leading was seeking care, followed by recognizing symptoms and getting treatment adherence support. Other aspects like getting a diagnosis, beginning and getting treatment, and post follow-up care were at the lower end. This can be explained by the active role of healthcare workers in the latter chunk, and hence better acceptance. The above findings are in accordance with the study conducted by Muhandiki et al. in Tanzania,[11] where the maximum percentage was at seeking care; however, it differs, with the percentage of the aspect of beginning of treatment being lower in our study.

Stigma is a social determinant of health and acts as a barrier to treating the disease in multiple ways. People may be reluctant to seek and complete medical care when diseases are stigmatized due to concern over the social and economic repercussions that may accompany a diagnosis. Due to stigma, a patient who exhibits TB symptoms may dismiss the idea of having the disease, which may prevent them from recognizing symptoms. Even if the patient is aware that their symptoms may be related to TB, they may still be reluctant to seek medical attention due to stigma. Patients who choose to seek care may choose to obtain unqualified views rather than receive an accurate diagnosis from a designated microscopy facility. People anticipate that receiving care at a nearby public institution will make their TB status known to others due to the visibility of TB testing and treatment facilities. Even when patients go to a clinic for therapy, social condemnation from family members, relatives, or the community lowers treatment compliance. Instead of receiving antitubercular therapy from a DOTS facility, patients who have been diagnosed with TB may choose to self-medicate or obtain prescriptions from quacks. Patients on antitubercular therapy may quit taking their medication as soon as they feel better because they ostensibly want to be free of the burden of having TB, which may lead to reduced treatment compliance and, eventually, treatment failure. Thus, at any stage of the disease course as described, stigma can act as a barrier to utilization of TB services. A study conducted in India estimated that about 200,000 patients in the national TB program undergo pretreatment loss to follow-up (PTLFU) each year.[6] This refers to patient dropout after diagnosis but before treatment registration, which is a serious gap in TB care in India and around the world. Proper adherence is critical to avoid the development of multidrug-resistant TB (MDR-TB).[13]

The study throws light on the necessity for the national TB response and various programs to include stigma-reduction interventions along with other measures. It should be kept in mind that these must be well-researched, though simple, and be developed through community engagement. Further research in this field needs to be encouraged along with continuous surveillance for the same.

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ORIGINAL ARTICLE

Neck Circumference: A Screening Tool for Predicting Metabolic Syndrome in Obese Children

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Abstract

Background: In recent days, neck circumference (NC) has been suggested as a screening technique for overweight individuals because it is easy to measure, does not require instruments such as a stadiometer or weighing scale, and does not require calculations as in body mass index (BMI). Moreover, NC correlates with many fat-related anthropometric measurements and cardiovascular risk factors.

Aims: The objective of this study was to find the association of higher NC with metabolic syndrome (MetS), insulin resistance (IR), and other metabolic complications.

Settings and design: Tertiary care teaching hospital, cross-sectional study.

Methods and materials: A total of 211 overweight and obese children aged between 5 and 13 years were recruited. Anthropometric parameters such as weight, height, NC, and waist circumference (WC) were measured. Fasting blood glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, aspartate transaminase (AST), and alanine transaminase (ALT) were estimated. Homeostasis model assessment of insulin resistance (HOMA-IR) and MetS were derived.

Statistical analysis used: Independent *t*-test and Chi-square analysis were applied for continuous and categorical variables, respectively, to find the association.

Results: Out of 79 children in the high-NC group, 11 had MetS, whereas only 4 had MetS in the low-NC group of 132 children, which was statistically significant ($X^2 = 8.87$; $p = 0.003$). Logistic regression analysis showed a significant association between high neck circumference and waist circumference ($p = 0.00$; AOR = 1.164).

Conclusions: High NC reflects high BMI and can predict MetS in overweight and obese children.

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Introduction

Childhood obesity is becoming an increasing concern, especially in developing nations, such as India, where rapid urbanization, changes in dietary patterns, and sedentary lifestyles are contributing factors. More number of children and adolescents are becoming overweight, as highlighted by CNNS survey, which is alarming because it can cause lifestyle health hazards such as cardiovascular diseases in adulthood.[1] The rise in pediatric obesity is indeed concerning because it's closely tied to an increase in metabolic syndrome (MetS) in younger populations.[2]

Abdominal circumference and body mass index (BMI) are frequently utilized as screening tools, particularly in children and adolescents, but their limitations, such as interobserver variation, the need for undressing in females, and the difficulty of identifying accurate landmarks in children due to fat distribution, make them less practical as primary screening tools in certain settings. Neck circumference (NC) is emerging as a promising alternative. It is a simpler, noninvasive measurement that does not require specialized equipment, such as stadiometers or scales, and it avoids some of the cultural or logistical challenges associated with waist circumference (WC) measurements, such as undressing. NC also appears to correlate well with fat distribution patterns, particularly central adiposity, and is associated with various metabolic complications, such as hypertension, insulin resistance, and dyslipidemia. The fact that respiratory movements or postprandial abdominal distention would not change NC measurement values makes it even more appealing as a practical tool.[3,4] Nevertheless, at present, in clinical settings, NC is not utilized as a tool for segregation of obese children due to the paucity of studies in the published literature. We attempted to examine the link between NC (upper body fat deposition) and MetS, insulin resistance (IR), and other metabolic complications.

Materials and Methods

This project was undertaken from January 2022 to December 2022. It was done at a tertiary pediatric setting after obtaining permission from the Ethics board of the institute. Informed consent and assent from older children were obtained before their inclusion in the study. The study population comprised children aged 5–13 years with an adult-equivalent BMI >23 kg/m^2. Children with a BMI of more than 27 kg/m^2 were categorized as obese. Children with a BMI between 23 kg/m^2 and 27 kg/m^2 were categorized as overweight. Weight, height, NC, and WC were recorded. Quetelet index [weight in kg/(height in m)^2] was used for calculating BMI.

Blood pressure (BP) was measured after having the participants rest for 5 minutes in the sitting position. Blood pressure was checked manually by a sphygmomanometer using the Korotkoff method. A flexible ruler tape was used for measuring NC at the thyroid cartilage level.[5] WC was measured at the midpoint between the lower last rib and the iliac crest. WC was measured by a nonstretchable tape to the nearest 0.1 cm while the participant stood in an upright posture.

Fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-C), aspartate transaminase (AST), and alanine transaminase (ALT) were assessed using standard reagent kits. Low-density lipoprotein (LDL-C) and very low-density lipoprotein (VLDL) levels were calculated from the triglyceride value using Friedewald's formula. The chemiluminescence method was used for estimating fasting insulin levels. The homeostasis model assessment of insulin resistance (HOMA-IR) is calculated as:

HOMA-IR = [Fasting glucose (mg/dL) × fasting insulin (μIU/mL)]/405.[6,7]

The criteria set by the International Diabetes Federation (IDF) were used for defining metabolic syndrome (MetS). Diagnosis of MetS was made for the children with abdominal obesity (defined by WC >90th percentile for the child's age and sex) along with at least three metabolic parameters:[8,9]

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1. TG >150 mg/dL.
2. HDL-C <40 mg/dL.
3. SBP or DBP >130 or 85 mm Hg, respectively.
4. FBG >100 mg/dL.

Considering the sensitivity and specificity of neck measurement as 62% and 86% observed by Kurtoglu et al.,[10] with alpha error as 5%, error of margin as 20% and the proportion of MetS as 11%, the minimum required sample size would be 206 using the formula given below.[11]

- Formula for sensitivity:
  - Step 1: $TP + FN = Z^2\alpha/2 \times SN\ (1-SN)/w^2$
  - Step 2: $N1 = (TP + FN)/P$
- Formula for specificity:
  - Step 1: $FP + TN = Z^2\alpha/2 \times SP(1-SP)/w^2$
  - Step 2: $N2 = (FP + TN)/(1-P)$

Z-alpha is the table value from the standard normal distribution corresponding to the area (1–alpha)/2, here 1.96 for 5% alpha. SN is sensitivity. SP is specificity. w is the margin of error. P is the proportion of MetS.

The receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated to evaluate the diagnostic accuracy in predicting MetS. For examining the associations between variables, an independent *t*-test was used for continuous variables, and a Chi-square test was used for categorical variables.

Results

A total of 158 obese and 53 overweight children were recruited, which included 106 boys and 105 girls, aged from 5 to 13 years. The mean age was 10 years (SD = 2.18) and 9 years (SD = 1.82) for boys and girls, respectively. All clinical and metabolic parameters are summarized in Tables 1 and 2. Out of 211 children, 15 children satisfied the criteria for MetS.

Receiver operating characteristic analysis was plotted, taking MetS as the yardstick. The AUC for NC was 0.766, 95% CI = 0.689–0.882 for boys, whereas it was noted as 0.749, 95% CI = 0.683–0.808 for girls (Table 3 and Fig. 1). The cutoff value for NC 31.5 cm has the maximum sensitivity and specificity. The study parameters were compared between two

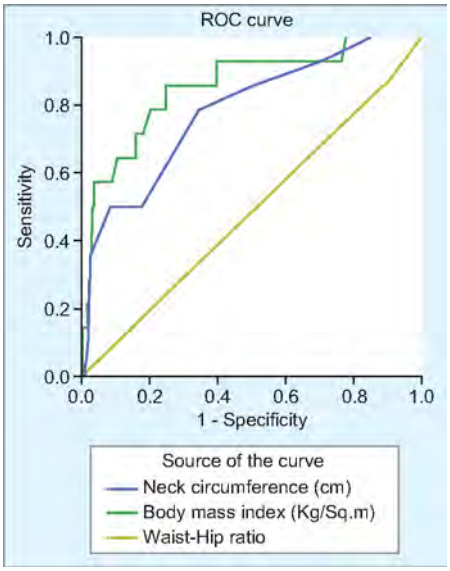

Fig. 1: ROC curve [receiver operating characteristic analysis was carried out regarding the presence of MetS as the gold standard. The area under the curves (AUC) for NC was 0.766 (95% CI = 0.689–0.882) for boys and 0.749 (95% CI = 0.683–0.808) for girls. Cutoff value for NC 31.5 cm has the maximum sensitivity and specificity]

Table 1: The anthropometric and biochemical characteristics of the study population stratified by gender

Variables	*All (n = 211)*		*Male (n = 106)*		*Female (n = 105)*		*t-test p-value*
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	
BMI (kg/m^2)	23.65	3.44	24.08	3.92	23.23	2.83	0.07
SBP (mm Hg)	112.80	8.40	106.83	11.75	106.33	9.59	0.31
DBP (mm Hg)	72.38	7.93	72.58	8.51	72.18	7.35	0.71
Cholesterol (mg/dL)	155.97	36.23	156.49	38.74	155.46	33.71	0.83
TG (mg/dL)	111.34	52.90	110.61	50.32	112.07	55.56	0.83
HDL (mg/dL)	36.30	7.81	36.22	7.71	36.39	7.94	0.84
LDL (mg/dL)	102.19	28.374	103.26	26.296	101.14	30.382	0.87
VLDL (mg/dL)	21.99	10.51	21.76	10.05	22.22	10.99	0.58
AST (IU/L)	39.96	14.37	39.85	15.32	40.08	13.44	0.91
ALT (IU/L)	43.18	21.25	42.99	20.34	43.37	22.22	0.897
Insulin (IU/L)	8.73	5.17	9.37	5.48	8.09	4.78	0.073
HOMA-IR	1.81	1.08	1.96	1.13	1.66	1.01	0.042

Table 2: The anthropometric and biochemical characteristics for the two groups with neck circumference >31.5 cm and NC <31.5 cm

Variables	*NC > 31.5 cm*		*NC < 31.5 cm*		*t-test p-value*
	Mean	*SD*	*Mean*	*SD*	
Age (years)	11.07	1.64	9.31	1.95	0.00
BMI (kg/m^2)	25.48	3.16	22.56	3.12	0.00
SBP (mm Hg)	110.7	8.96	116.98	6.77	0.35
DBP (mm Hg)	74.42	8.05	71.16	7.63	0.00
WC (cm)	82.51	7.34	72.59	6.33	0.00
Cholesterol	162.57	47.93	152.02	26.32	0.07
TG (mg/dL)	110.86	47.24	111.63	56.19	0.91
HDL (mg/dL)	36.13	6.45	36.41	8.54	0.78
LDL (mg/dL)	108.03	35.04	98.70	22.95	0.04
VLDL (mg/dL)	21.75	9.35	22.14	11.17	0.79
AST (IU/L)	42.24	15.96	38.59	13.20	0.09
Insulin (μIU/L)	11.40	5.18	7.12	4.47	0.00
HOMA-IR	2.36	1.02	1.48	0.97	0.03

Table 3: Area under the curve

Test result variable (s)	*Area*	*Std error*	*p-value*	*95% confidence interval for AUC*	
				Lower bound	*Upper bound*
Neck circumference (cm)	0.782	0.065	0.000	0.654	0.910
Body mass index (Kg/m^2)	0.855	0.057	0.000	0.744	0.966
Waist–hip ratio	0.485	0.082	0.850	0.325	0.645

In this table, the AUC is 0.78 for NC. This suggests a 78% chance that the physician measuring the NC will correctly distinguish a non-MetS patient from a MetS patient based on the measurement of the NC readings. However, with a *p*-value < 0.001, it indicates that this NC has acceptable discriminating ability

groups of NC above and below the 31.5 cm cutoff value.

BMI was found to be significantly higher in higher NC (>31.5 cm) group (*p*-value = 0.00). WC was high in high NC group ($p = 0.00$). DBP was elevated in the high NC group ($p = 0.00$). LDL-C levels were high in the high NC group ($p = 0.037$). The high NC group had more insulin values ($p = 0.00$) and HOMA-IR values ($p = 0.04$).

In low NC group, NC values correlated with BMI ($r = 0.44$, $p = 0.01$); WC ($r = 0.42$, $p = <.001$); HOMA-IR ($r = 0.18$, $p < 0.05$). Similarly, in the high NC group, positive correlation was found with BMI ($r = 0.39$, $p = 0.01$); WC ($r = 0.40$, $p = 0.01$); HOMA-IR ($r = 0.23$, $p = 0.03$).

A statistically significant association between obese children and high NC compared to the overweight group was found (*p*-value = 0.04). Out of 79 children in the high NC group, 11 had MetS, whereas only four had MetS in the low NC group of 132 children, which was statistically significant ($X^2 = 8.87$; $p = 0.003$). Logistic regression confirmed a significant association between high neck circumference and waist circumference (*p-value* = 0.00; AOR: 1.164).

Discussion

Many studies conducted in adults have proven that NC would serve as an effective tool to identify individuals with metabolic risks.[12] However, fewer studies have examined NC as a detector of IR and derangements of MetS parameters in children.[10,13] It is evident from recent reports that NC is a reliable and pragmatic tool that provides consistent results in identifying upper-body fat accumulation. Thus, we attempted to explore the relationship of NC with both MetS and IR.

We found that NC was associated with BMI, which is concordant with previous similar studies.[13–15] Although we use BMI routinely to assess body fat content, it is not a high-standard tool to find body fat distribution. NC can give the details of upper body fat distribution, and as proven in other studies, it can be used as an alternative to predict obesity. We also found that NC is significantly associated and positively correlated with WC, as demonstrated by many previous observational studies.[10,13,15] NC offers several advantages over WC as a measurement tool. Additionally, adolescents prefer NC in comparison to WC as it is more acceptable in Indian settings. Given these benefits, NC can be used as a reliable alternative to waist circumference.

In obese subjects, high NC increases vulnerability for hypertension, as demonstrated by Nafiu et al.[16,17] In our study, NC was associated with DBP, which is similar to Nafiu et al.[17] NC was also linked with LDL-C levels, which is concordant with two previous observational studies.[10]

Neck circumference was associated with insulin levels and HOMA-IR according to Kurtoglu et al. Similarly, in our study, we observed a correlation of NC with insulin and HOMA-IR, aligning with the findings of Kurtoglu et al.[10] Additionally, our observations revealed a positive association of NC and MetS, which is consistent with meta-analysis of adult subjects conducted by Ataie-Jafari et al.[18] Although the precise mechanism linking upper body fat to metabolic risk factors remains unclear, early evidence suggests that subcutaneous fat of upper body release free fatty acids which play a significant role in the development of metabolic complications.[19]

Neck circumference can be a simple and effective tool for predicting upper body fat and metabolic syndrome MetS identification in children is a significant progress in pediatric research. We highlight the need for larger studies to confirm these results and solidify the role of NC as a standard screening method. The limitation related to the study sample being from a single ethnic group is significant. Ethnic variations in fat distribution patterns, metabolic risk factors, and even anthropometric measurements could affect how NC correlates with MetS. The other reason for the lower cut-off in our study is the inclusion of children only up to 13 years, whereas most studies included the study population up to 15–18 years of age. Age-wise cutoff values for NC were not possible as the sample size was smaller.

What this study adds: Neck circumference can predict metabolic syndrome in children with obesity.

Sources of Support

Nil.

Conflict of Interest

None.

Author contributions

The manuscript had been read and approved by all the authors. SP Tharanidharan and Srinivasan Thiagarajan conceived the idea and designed the research work, while SP Tharanidharan and Srinivasan Thiagarajan were involved in collecting the data and literature review. Data analysis was done by SP Tharanidharan and Srinivasan Thiagarajan, and the manuscript was prepared by SP Tharanidharan and Srinivasan Thiagarajan. All authors contributed to the initial drafting and critical revision of the manuscript.

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REVIEW ARTICLE

Modern Device-based Renal Denervation Approach for the Management of Uncontrolled Hypertension

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Abstract

Uncontrolled hypertension can result from untreated high blood pressure (BP) or the inefficacy of established antihypertensive therapeutic regimens. Renal denervation (RDN) is a nonpharmacologic catheter-based intervention that achieves targeted renal sympathetic nerve ablation to modulate sympathetic activation. RDN is suitable for those with uncontrolled primary hypertension, resistant to therapy or intolerant to drugs, and who have a favorable renal artery anatomy. Long-term data demonstrate RDN's efficacy in significantly reducing elevated BP. RDN procedures have shown a good safety profile, and no significant difference in adverse events has been reported between RDN-treated and control groups in most clinical trials. Thus, RDN offers an effective and safe approach for sustained BP control.

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Introduction

Hypertension [systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg] is a leading cause of premature mortality. Hypertension prevalence has doubled from 1990 to 2019.[1] Hypertension management involves a combination of pharmacologic and nonpharmacologic approaches tailored to individual patient needs. In 2019, less than half of the individuals diagnosed with hypertension received treatment, and less than half of those who underwent pharmacological treatment achieved control of hypertension, translating to global control rates equal to 23% in women and 18% in men.[1] The main reasons for such poor control are low patient adherence to treatment and lack of proactive clinical management by healthcare providers.[2] Hypertension can be termed uncontrolled when the current treatment plan is ineffective, i.e., when the brachial SBP/DBP remains above the target values (140/90 mm Hg) even with the use of at least three different antihypertensive drugs (including diuretics).[3] Uncontrolled and untreated hypertension is of concern, as it leads to cardiovascular (CV) morbidity and mortality due to the occurrence of peripheral arterial disease, ischemic heart disease, stroke, congestive heart failure, renal disease, and aortic aneurysm.[4]

While pharmacological treatments are essential for managing hypertension, modern device-based approaches offer complementary dimensions to address the challenges in controlling elevated blood pressure (BP) effectively. In essential hypertension, sympathetic nervous system activity varies in terms of severity and complications. Research indicates that overactivation of the sympathetic nervous system occurs in all stages of hypertension.[5] Renal denervation (or RDN) is a nonpharmacologic catheter-based intervention that modulates the activity of the sympathetic nervous system by ablating renal sympathetic nerves in a targeted fashion. RDN can benefit patients with uncontrolled hypertension undergoing pharmacologic and nonpharmacologic antihypertensive therapy. A meta-analysis demonstrated significant reductions in office and/or ambulatory SBP in those (N = 1368) with resistant/untreated hypertension managed by RDN.[6] Recent data on the long-term safety and efficacy of RDN have shown that it successfully decreases BP and may lower the risk of CV and/or renal events for up to 36 months after the intervention.[7]

While RDN is a promising antihypertensive therapy, uncertainties remain about optimal patient selection and its long-term effectiveness. This review aims to collate evidence on RDN, addressing its long-term outcomes, safety profile, and criteria for patient selection in the management of uncontrolled hypertension.

Mechanism of Renal Denervation

Renal arteries have dense innervation with afferent and efferent sympathetic nerve fibers. Activation of afferent fibers increases central sympathetic activity and norepinephrine spillover, while overactivity of efferent fibers promotes sodium reabsorption, increases renin release, and decreases renal blood flow, thus raising BP. RDN helps control BP by reducing efferent signaling, norepinephrine spillover, and plasma renin activity; restoring natriuresis; and decreasing afferent signaling.[8] Figure 1 illustrates the mechanism of RDN, highlighting the afferent and efferent renal nerves and ablation targets.

Preprocedural Evaluation and Patient Selection

Preprocedural evaluation typically involves a comprehensive assessment, including baseline BP, renal function [estimated glomerular filtration rate (eGFR)], renal artery anatomy, and secondary hypertension to ensure that the patient meets the eligibility criteria for the procedure. Since sympathetic nervous system activity increases with age, age is also a factor during patient selection.[9]

Evidence indicates that RDN may benefit patients with severe primary hypertension, irrespective of medication, though the characteristics of an ideal candidate are still being explored.[10] The data suggest that the reduction in BP following RDN is more significant for those with higher baseline SBPs.[10,11]

Renal artery anatomy, including size, tortuosity, and branching, is critical for RDN success and is assessed using imaging modalities such as renal or computed tomography angiography

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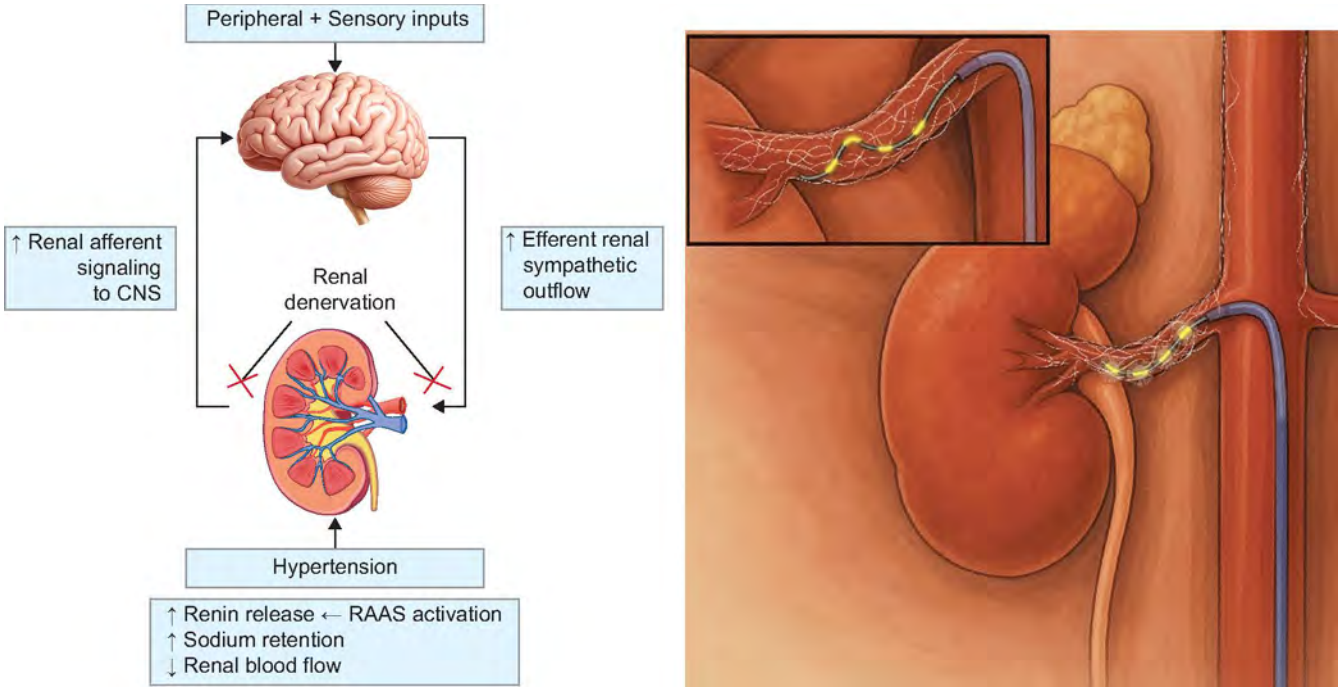

Fig. 1: Representation of the mechanism of action of RDN (CNS, central nervous system; RAAS, renin–angiotensin–aldosterone system)

during preevaluation.[12] Clinical trials for RDN require patients to have a renal artery diameter of 3.0–8.0 mm (with or without accessory arteries). However, studies suggest that accessory renal arteries may have more renal nerve fibers than the main artery; therefore, targeting them during RDN could enhance the procedure's effectiveness.[13,14]

Patient Selection

Renal denervation is primarily opted for patients with (1) inability/difficulty in controlling BP despite using multiple antihypertensive medications, (2) decreased adherence to treatment as the number of medications increases, and (3) low motivation, which is shaped by the perceived risks of hypertension, adverse medication effects, and intolerance to antihypertensive drugs.[3,15,16] Figure 2 presents the patient selection criteria provided by guidelines and relevant medical societies.[3,17–19]

Procedural Considerations and Optimization

Procedural optimization techniques include ablation of the main and accessory renal arteries and their branches, circumferential ablation, and an appropriate number of total ablations.[18] The primary efficacy goal of RDN is to maximize nerve destruction for lowering BP while ensuring arterial integrity, avoiding collateral damage, and minimizing procedure time and contrast volume.[20] Factors to be considered during the optimization of RDN, in addition to factors specific to the use of radiofrequency, have been discussed below and in Figure 2.

Number of Ablations: Analysis of the SIMPLICITY HTN-3 trial data (*post hoc*; *N* = 340) showed that those receiving 12–13 ablations of the renal artery with energy delivery in a pattern with four-quadrants were associated with higher and more consistent reductions in measures such as office/ambulatory SBP and heart rate than those receiving <8 ablations.[21]

Ablation Pattern: The ablation pattern in RDN refers to the distribution of thermal/radiofrequency energy applied to the renal sympathetic nerves during the procedure. The goal of ablation is to disrupt the sympathetic nerves within the renal arteries' adventitia, mostly in the adipose tissue surrounding the artery, while minimizing damage to the proximal endoluminal surface and external elastic lamina.

Ablation of the Distal Branch: Since renal sympathetic nerves are nearer the renal artery lumen, distal denervation is likely to disrupt more sympathetic nerves than proximal denervation, ensuring a consistent treatment effect.[22] A single-center, double-blind study (*N* = 51) found RDN more effective in reducing office and 24-hour ambulatory BP (ABP) when distal segmental branches were ablated than when the trunk of the renal artery was targeted.[23]

Ablation of Accessory Arteries: A comprehensive RDN approach involves denervation of the main and branch/accessory renal arteries to ensure thorough disruption of sympathetic nerve activity and improve BP management.

Postprocedure Assessment

Assessment of BP at Follow-up

The time taken for an apparent BP response could vary from a few days to several weeks. Unlike antihypertensive medications, RDN produces an "always on" effect, suggesting the relevance of measuring BP over 24 hours.[24] However, combinations of ABP measurements, such as baseline nighttime SBP and its variability, should be considered, given that variations in the levels of physical activity and sleep duration may impact ABP readings.[25] To assess early RDN response, a 3–6 months follow-up for office BP and ABP is needed, and annual ABP and home and office BP measurements should be monitored for long-term response.[18] The SIMPLICITY HTN-3 and SPYRAL HTN-ON trials demonstrated that after RDN, reductions in office BP at 6 months and 24-hour ABP at 36 months were significant.[13,26]

Assessment of Renal Function

Renal denervation may lead to decreased kidney function or a transient drop in the eGFR due to hemodynamic changes from rapid BP reduction. However, a meta-analysis using mean follow-up data at 9.1 months demonstrated no significant changes in

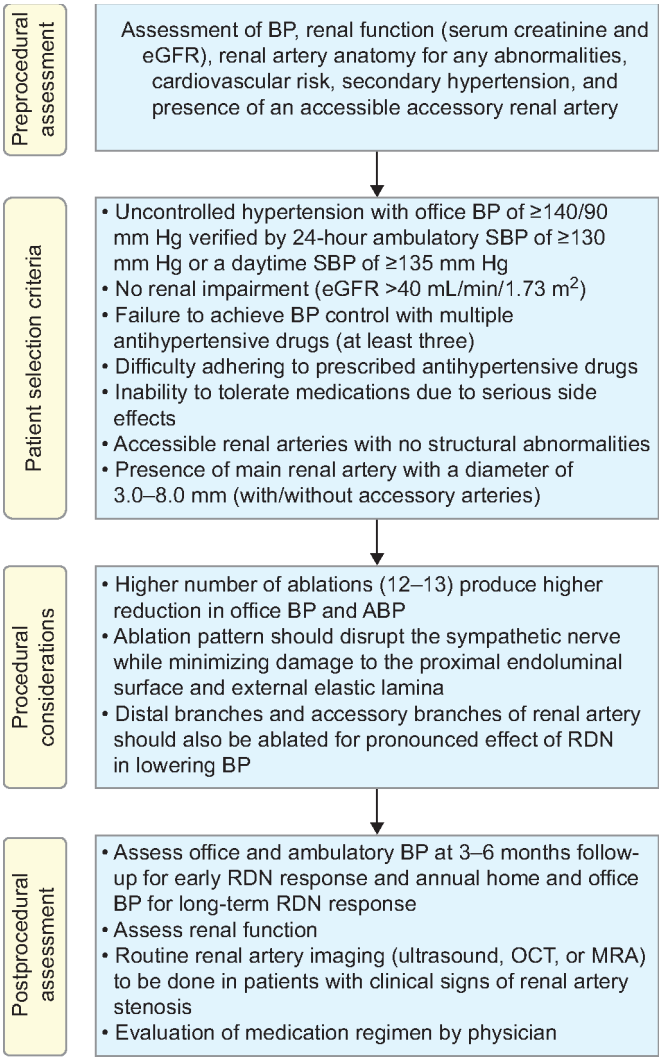

Fig. 2: Flowchart depicting the preprocedural assessment, patient selection criteria, procedural considerations, and postprocedural assessment to be considered for RDN treatment. (MRA, magnetic resonance angiography; OCT, optical coherence tomography; RDN, renal denervation.)

renal function parameters (eGFRs and serum creatinine levels).[27]

Renal Artery Imaging

Renal artery injury, leading to stenosis, dissection, or access site complications, is possible. Routine imaging (ultrasound, optical coherence tomography, or magnetic resonance angiography) should only be done if clinical signs of renal artery stenosis, such as worsening hypertension or renal function, are present.[18]

Clinical Evidence on Renal Denervation

Efficacy

So far, five randomized and sham-controlled studies, namely the SYMPLICITY HTN-3 trial,[28] RADIANCE-HTN SOLO trial,[29] proof-of-concept SPYRAL HTN-ON MED trial,[13] SPYRAL HTN-OFF MED pivotal trial,[30] and RADIANCE-HTN TRIO trial,[31] have assessed the utility of RDN in lowering BP (Table 1). Some studies reported significantly higher reductions in BP after RDN (compared with those in sham control groups) at follow-ups of 2–36 months, while others reported nonsignificant results at 3–6 months. The follow-up data (36 months) from the SPYRAL HTN-ON MED trial have demonstrated that RDN can reduce ambulatory SBP by 18.7 mm Hg compared with 8.6 mm Hg.[33]

The SYMPLICITY HTN-3 trial data on the long-term effects of RDN demonstrated that RDN can significantly reduce office SBP (by 26.4 mm Hg, as compared to the 5.7 mm Hg reduction with a sham control) at the 36-month follow-up.[26] Three-year data from the Global SIMPLICITY Registry (GSR) demonstrated that in-office SBP was lowered by 16.5 mm Hg from baseline after RDN.[34] A study of the 10-year outcomes of RDN in those with resistant hypertension ($N = 107$) showed that the reductions in 24-hour SBP readings (–16.2 mm Hg) were maintained for as long as 10 years after the intervention.[35]

Renal denervation also reduces incidences of major adverse cardiovascular events (MACE). A study based on GSR data ($N = 3,077$ as of March 2022) reported that a 10% increase in the time within therapeutic range for 6 months after RDN was associated with significant reductions in MACE (15%, $p < 0.001$), CV death (11%, $p = 0.010$), stroke (23%, $p < 0.001$), and myocardial infarction (15%, $p = 0.023$) from 6 to 36 months.[36] Overall, RDN is effective in controlling BP, with positive outcomes observed across both radiofrequency and ultrasound-based designs. These findings highlight the robustness of RDN as a therapeutic approach, regardless of the specific technology used in reducing office BP and ABP.

Safety

Most clinical trials demonstrated no significant differences in the occurrence of AEs between RDN and control groups (Table 2). The GSR study reported relatively lower rates of myocardial infarction (2.3% for RDN vs 2.5% for the whole cohort) and CV-related deaths (2.8% for RDN vs. 2.9% for the whole cohort) 3 years after RDN treatment in the resistant hypertension group.[38]

After RDN, the occurrence of renal artery stenosis requiring an intervention is rare.[39] A meta-analysis using 14 randomized controlled trials (RCTs; $N = 511$) showed that in 0.2% of the patients, at a median follow-up of 11 months, renal artery stenosis occurred after RDN.[40] The SIMPLICITY HTN-3 trial, however, showed that renal function did not worsen significantly; instead, the serum creatinine level increased by >50% in 1.4% of those in the RDN group compared with 0.6% of those in the sham group.[28] Furthermore, the composite safety endpoint rate over 48 months was 15% in the RDN group; this was comparable to that in the other intervention groups in the study.[28] Real-world studies by Panchavinnin *et al.* and Vogt *et al.* have reported that no AEs occurred at 10 and 9 years after RDN treatment, respectively.[41,42]

Overall, RDN procedures have demonstrated a good safety profile, and AEs associated with RDN are generally manageable; however, continuous monitoring and adherence to safety protocols in RDN procedures must be maintained.

Clinical Efficacy in High-risk Patients with Hypertension

Analysis of data from the GSR for patients with uncontrolled hypertension ($N = 2,652$) showed significant ($p < 0.0001$) reductions in office SBP at 3 years in all subgroups of

Table 1: Clinical evidence from RCTs on the efficacy of RDN

Study, year	*Study design*	*Sample size*	*Age*	*Comorbidities*	*Follow-up period*	*Office BP reduction from baseline (SBP)*	*Office BP reduction from baseline (DBP)*	*Interpretation*
Radiofrequency-based RDN*								
SPYRAL HTN-OFF MED pivotal trial, 2020[30]	Single-blind, randomized, sham-controlled trial	RDN: 166, Sham: 165	52.4–52.6 years	Type 2 diabetes, coronary artery disease, obstructive sleep apnea, stroke, transient ischemic attack	3 months	RDN: −9.2 mm Hg, Sham: −2.5 mm Hg	RDN: −5.1 mm Hg, Sham: −1.0 mm Hg	The RDN group had a significantly greater reduction in office BP at 3 months than the sham control group.
SPYRAL HTN-ON MED proof-of-concept trial, 2018[13]	Single-blind, randomized, proof-of-concept sham-controlled trial	RDN: 38, Sham: 42	53.0–53.9 years	Type 1 and type 2 diabetes, coronary artery disease, obstructive sleep apnea, stroke, transient ischemic attack	6 months	RDN: −9.4 mm Hg, Sham: −2.6 mm Hg	RDN: −5.2 mm Hg, Sham: −1.7 mm Hg	The RDN group had a significantly greater reduction in office BP at 6 months than the sham control group.
SYMPLICITY HTN-3 trial, 2014[28]	Single-blind, randomized, sham-controlled trial	RDN: 364, Sham: 171	56.2–57.9 years	Type 2 diabetes, obstructive sleep apnea, coronary artery disease, stroke, myocardial infarction, transient ischemic attack, peripheral artery disease, hyperlipidemia	6 months	RDN: −14.1 mm Hg, Sham: −11.7 mm Hg	NR	Compared with the sham control group, the RDN group did not show significant reduction in office BP at 6 months.
SYMPLICITY HTN-3 trial, 2022[26]	Single-blind, randomized, sham-controlled trial	RDN: 364, Sham: 171	56.2–57.9 years	Type 2 diabetes, obstructive sleep apnea, coronary artery disease, stroke, myocardial infarction, transient ischemic attack, peripheral artery disease, hyperlipidemia	36 months	RDN: −26.4 mm Hg, Sham: −5.7 mm Hg	NR	The RDN group had a significantly greater reduction in office BP at 36 months than the sham control group.
SPYRAL HTN-ON MED, 2022[33]	Single-blind, randomized, sham-controlled trial	RDN: 38, Sham: 42	51.0–55.1 years	Type 1 and type 2 diabetes, coronary artery disease, obstructive sleep apnea, stroke, and transient ischemic attack	36 months	RDN: −21.3 mm Hg, Sham: −12.2 mm Hg	NR	Compared with the sham control group, the RDN group did not show significant reduction in office BP at 36 months.
Ultrasound-based RDN**								
RADIANCE-HTN TRIO, 2021[31]	Single-blind, randomized, sham-controlled trial	RDN: 69, Sham: 67	18–75 years	Type 2 diabetes, obstructive sleep apnea, heart failure, prior history of hospitalization for hypertension	2 months	RDN: −9.0 mm Hg, Sham: −4.0 mm Hg	RDN: −5.0 mm Hg, Sham: −1.0 mm Hg	The RDN group had a significantly greater reduction in office SBP at 2 months than the sham control group. However, no significant reduction in DBP was observed in the RDN group compared with the sham control group.
RADIANCE-HTN SOLO, 2018[29]	Single-blind, randomized, sham-controlled trial	RDN: 74, Sham: 72	54.1 years	Type 2 diabetes, obstructive sleep apnea	2 months	RDN: −10.8 mm Hg, Sham: −3.9 mm Hg	RDN: −5.5 mm Hg, Sham: −1.2 mm Hg	The RDN group had a significantly greater reduction in office BP at 2 months than the sham control group.

NR, not reported; *Radiofrequency RDN uses alternating electrical current to create lesions through direct heating at the catheter tip and passive heat transfer to deeper tissues; **Ultrasound RDN uses ultrasound energy to thermally ablate and disrupt the renal efferent and afferent sympathetic nerves to achieve a reduction in systemic arterial blood pressure

Table 2: Clinical evidence from RCTs on the safety of RDN

Sl. no.	*Study, year*	*Study design*	*Sample size*	*Total adverse events*	*Type of adverse events: Procedure-related*	*Type of adverse events: Device-related*	*Type of adverse events: Other*	*Inference*
1	SYMPLICITY HTN-3 trial, 2014[28]	Single-blind, randomized, sham-controlled trial	RDN: 364, Sham: 171	RDN: 11.8%, Sham: 11.6%	None	None	RDN: Death (0.6%), myocardial infarction (1.7%), increase in serum creatinine level >50% (1.4%), end-organ damage (0.3%), vascular complications (0.3%), hypertensive crisis (2.6%), stroke (1.1%), heart failure (2.6%), atrial fibrillation (1.4%), new renal stenosis >70% (0.3%); Sham: Death (0.6%), myocardial infarction (1.8%), increase in serum creatinine level >50% (0.6%), hypertensive crisis (5.3%), stroke (1.2%), heart failure (1.8%), atrial fibrillation (0.6%)	No significant differences in safety outcomes between the RDN and sham groups.
2	SPYRAL HTN-OFF MED Pivotal, 2020[30]	Single-blind, randomized, sham-controlled trial	RDN: 166, Sham: 165	RDN: 0.6%, Sham: 0.6%	None	None	RDN: Hypertensive crisis (0.6%); Sham: Stroke (0.6%)	No differences in safety outcomes between the RDN and sham groups.
3	SPYRAL HTN-ON MED proof-of-concept trial, 2018[13]	Single-blind, randomized, proof-of-concept, sham-controlled trial	RDN: 38, Sham: 42	None	None	None	None	No adverse events were reported in the RDN and sham groups.
4	SPYRAL HTN-ON MED, 2023[32]	Assessor-blinded, randomized, sham-controlled trial	RDN: 206, Sham: 131	RDN: 0%	None	None	None	Major adverse events related to the procedure and device were not reported in the RDN and sham control groups.
5	RADIANCE-HTN TRIO, 2021[31]	Single-blind, sham-controlled trial	RDN: 69, Sham: 67	RDN: 23.2%, Sham: 16.4%	RDN: Access site complication (1%), pain for >2 days (17%); Sham: Pain for >2 days (15%)	None	RDN: All-cause mortality (1%), acute renal injury (1%), acute myocardial infarction (1%); Sham: Coronary revascularization (1%)	No differences in safety outcomes between the RDN and sham groups.
6	RADIANCE-HTN SOLO, 2018[29]	Single-blind, randomized, sham-controlled trial	RDN: 74, Sham: 72	RDN: 11%, Sham: 11%	RDN: Pain for >2 days (11%); Sham: Pain for >2 days (11%)	None	None	No differences in safety outcomes between the RDN and sham groups.

patients with high-risk profiles, such as those with type 2 diabetes mellitus (–16.4 ± 26.8; *n* = 465), chronic kidney disease (CKD) (–11.6 ± 29.6; *n* = 254), isolated systolic hypertension (ISH) (–15.9 ± 23.7; *n* = 477), and atrial fibrillation (–17.6 ± 27.4; *n* = 144), and those older than 65 years (–18.4 ± 28.3 mm Hg; *n* = 472).[43]

Chronic sympathetic overactivation is a hallmark of aging, and RDN has demonstrated clinical feasibility in managing aging-related hypertension.[44] Therefore, its effectiveness in elderly patients should not be discounted.[43] Pooled evidence from the SIMPLICITY HTN-3 trial and GSR data suggests that RDN has a less pronounced effect in patients with ISH than in those with combined systolic–diastolic hypertension.[45,46] However, assessments of arterial stiffness could identify ISH patients who might benefit from RDN.[47] While RDN achieved significant reductions in office and ambulatory SBP after 1 month in CKD patients, there is a lack of strong evidence to support the use of RDN in these patients.[48]

Moving from Evidence to Clinical Practice

Transitioning from evidence to clinical practice in the use of RDN for treating hypertension involves integrating the findings from rigorous clinical studies into routine patient care. Patients with hypertension may have different perspectives on RDN than physicians.[15] A study found that 40% of those not on medications would opt for a one-time procedure, such as catheter-based RDN, over medication, and nearly 30% of those taking medications would choose RDN, with many having high expectations for BP reduction.[49]

Different devices are used for RDN, but the lack of standardized protocols and technical expertise may contribute to the variability in efficacy and safety outcomes across clinical studies. The European Society of Cardiology Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions recommend RDN as an evidence-based treatment for a broad range of patients.[19,50]

Key obstacles to the clinical applicability of RDN include the lack of standardized criteria for identifying responsive patients and the absence of a feedback mechanism to determine sympathetic nerve location and extent of ablation in the renal artery.[50–52] The cost of RDN is another practical challenge, limiting its wide applicability.[18] However, a Markov modeling analysis of RDN's cost-effectiveness in the UK, using a willingness-to-pay threshold of €35,000/quality adjusted life year, found it to be cost-effective with 95% probability for men and women up to 78 and 76 years, respectively. Additionally, RDN may be considered cost-effective for patients with medication-resistant hypertension.[53]

Conclusion

Renal denervation is an effective and safe adjunctive therapy for achieving sustained control of BP and reducing the risk of adverse CV events. Adopting a patient-centered approach by considering comorbidities, responses to previous treatments, and overall CV risk profile is crucial for the successful use of RDN in the management of hypertension. RDN could prove to be cost-effective when considered early in the management of hypertension.

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Conflict of Interest

None.

Author Contributions

All authors have contributed equally to the conception, design, drafting, review and finalization of the manuscript.

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REVIEW ARTICLE

Respiratory Examination for Postgraduate Residents: Unrevealing Expert's Questions and Answers

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Abstract

Physical examination is pivotal for getting a clue about the disease and making a provisional diagnosis. The respiratory examination is considered to be one of the toughest systemic examinations by undergraduate and postgraduate residents. No well-defined literature is available regarding the ideal method and interpretation of respiratory examination findings. There are many questions asked by experts that are hardly found in the literature. This review included a total of 30 important questions and the best possible answers, including expert questions from top institutes that are important for respiratory examination and would help all students (MBBS/MD/DNB/DM) to excel in their practical examination.

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Introduction

Physical examination is crucial for getting a clue about the disease and making a provisional diagnosis. However, there has been a trend toward less emphasis on physical assessment throughout medical school and residency training and increased use of technology-based diagnostic techniques.

It was previously noted that a comprehensive medical history and physical examination were responsible for 88% of all diagnoses in primary care, and this may still be the case today.[1,2] Respiratory system examination is perceived as one of the toughest systemic examinations by undergraduate and postgraduate residents. No well-defined literature is available regarding the ideal method and interpretation of respiratory examination. This review included common questions and answers that are important for respiratory examination and would help all students (MBBS/MD/DNB/DM) to excel in their practical examination.

Methodology

A literature review was performed utilizing various online databases and various clinical books to compile this review. This review of various respiratory examination techniques, their interpretation, various signs, etc., was conducted during the MD/DM respiratory examination. We also asked important questions from leading pulmonologists from various institutes running an MD/DM Pulmonary medicine course, and summarized them in question-and-answer format, along with some basic questions.

Questions and Answers

Q1. Enumerate the signs indicative of respiratory distress.

Ans: There is a rise in the respiratory rate, accessory muscles usage, intercostal retraction, cyanosis, nose flaring, wheezing, and sweating, and leaning forward in a sitting position for deep breathing.

Q2. What are the different signs to look for in hand examination?

Ans: Clubbing, pallor, cyanosis, warm, well-perfused palm (CO_2 retention), tremor, tobacco staining, pulse, skin thinning, bruising, asterixis, skin thickening in scleroderma, arthritic changes in RA-ILD, Gottron's papules, etc.

Q3. What are the causes of clubbing?

Ans: Causes are divided into respiratory and nonrespiratory:

- Respiratory: Bronchogenic carcinoma, ILD, bronchiectasis, lung abscess, empyema.
- Nonrespiratory: Congenital cyanotic heart disease, Bacterial endocarditis, Cirrhosis, Ulcerative colitis, Coeliac disease.
- Point to Remember:
  - Hereditary/acquired.
  - Close mimicker: Chronic paronychia and Heberden nodes (Swelling at the DIP joint in Osteoarthritis).
  - Generally, bilateral conditions occur in hand and feet.
  - Unilateral clubbing (e.g., either after hemiplegia or in an ipsilateral pulmonary sulcus tumour invading the brachial plexus).
  - One finger only: May be due to local injury or median nerve injury.
  - Only Toe: PDA with shunt reversal.
- Be aware of the importance of the Lovibond angle (profile sign) (normally <180°), the hyponychial angle (<192°), the Schamroth sign, the digital index, and the pharyngeal depth ratio.[3]
- Be aware of grading:
  - Grade 1: Nail bed fluctuation.
  - Grade 2: Obliteration of the Lovibond angle.
  - Grade 3: Parrot beaking.
  - Grade 4: Hypertrophic osteo-arthropathy (HOA).
- Clubbing is a common paraneoplastic manifestation of lung cancer (especially in NSCLC).
- Clubbing is seen in IPF and asbestosis, but rarely in sarcoidosis.

Q4. What is the pathogenesis of clubbing?

Ans: There are multiple theories, but the common denominator is vasodilation of vessels in the fingertip, including arteriovenous connections.

Increased platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) release from peripheral megakaryocytes leads to increased vascularity, permeability, and connective tissue changes. The release of both PDGF and VEGF is thought to be enhanced by hypoxia.[4]

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Q5. What should be the patient's position for respiratory examination?

Ans: For the majority of the respiratory system assessment, the patient should be propped up with a pillow and comfortably reclining on a bed or couch (to lean back at a 45° angle).

- For movement of the chest, make the patient lie down and see from the foot end for any lagging in movement.
- To demonstrate paradoxical breathing or the Hoover sign, make the patient lie down.[5]

Q6. What is the anatomical boundary of oblique and horizontal fissure?

Ans:

- *Oblique fissure landmark*: Starting from T2 spine posteriorly to anteriorly mid clavicular line at the position of sixth rib.
- *Horizontal Fissure landmark*: Oblique fissure on the right side meeting a horizontal line which is drawn from sternum at level of fourth costal cartilage.
- Anteriorly, all three lobes (mostly upper), posteriorly upper and lower lobes (Lower lobe predominant), and laterally upper and lower lobes are almost in equal proportion in representation.

Q7. What is the importance of sternal angle?

Ans: Another name for sternal angle is the manubriosternal joint (Angle of Louis, Levis, Ludovic), which is around 162°.[6]

- This angle corresponds to the level of 4th and 5th thoracic vertebrae.
- Forms an imaginary demarcation between the superior and inferior mediastinum.
- Ribs are counted downwards from the second costal cartilage (second intercostal space below), attached with angle.
- It also marks the point of tracheal bifurcation, the origination and termination of the aortic arch, bifurcation of the Pulmonary trunk, and where the azygous vein arches over hilum to enter SVC.

Q8. What are the features of a normal chest and the types of abnormal shapes of chest?

Ans: *Shape of chest* : Normally, the chest is symmetrical bilaterally, forming an elliptical shape in horizontal cross-section, with the transverse diameter greater than the anteroposterior, with a ratio of 7:5. The subcostal angle is 70°, and intercostal spaces are wider anteriorly than posteriorly. It gets deformed by either disease of Rib, vertebra, or underlying lung disease.

- *Barrel-shaped chest*: The anteroposterior diameter is increased, the subcostal angle get wide, and the sternal angle becomes prominent. The amount of trachea palpable above the suprasternal notch is reduced. The buckle handle movement of the ribs (upwards and outwards) changes to a pump handle (up and down motion). It is seen that chronic airflow limitation leads to hyperinflation and markers of severity of airflow limitation. In most of the cases, there is kyphosis, and the ribs become increasingly horizontal. Among rest of the findings are widening of intercostal spaces, elevation of clavicles, shortening of neck, and prominence of the sternum.
- *Pectus excavatum (Funnel chest or* Cobbler's *chest):* The lower portion of sternum has a depression in the case of a cobbler's chest. The cause could be congenital, following rickets in childhood, or a kind of occupational deformity observed in cobblers. The depression in the sternum leads to a prominent cardiac shadow in chest X-ray (Pomfret's heart).
- *Pectus carinatum or pigeon chest or Keeled chest:* There is depression on either side of the sternum, along with a bead, such as an enlargement at the costochondral junction (Rickety rosary), and a transverse groove passing outwards from the xiphisternum to the mid-axillary line (Harrison's sulcus). It may be secondary to childhood asthma, Rickets or localized deformity of the sternum and costal cartilage.
- *Flat chest (phthinoid chest):* The anteroposterior diameter is reduced in chronic nasal obstruction (adenoid hypertrophy, bilateral TB, or childhood rickets).
- Alar chest: The scapula is winged, which occurs in advanced TB.
- *Bulging:* One-sided bulging may be due to pleural effusion, pneumothorax, tumors, aneurysm, cardiomegaly, or scoliosis. Aneurysm of the aorta, pericardial effusion, liver abscess, and tumors of the chest wall can all cause localized bulging.
- *Depression of flattening*: It may be seen in fibrosis, collapse, scoliosis, unilateral muscle wasting due to poliomyelitis, and congenital absence of the pectoralis muscle (Poland's syndrome).
- *Spinal deformities*: Kyphosis and Scoliosis may lead to asymmetry. Both, but especially scoliosis, can lead to respiratory failure.

Q9. What is the difference between abdominal paradox and chest wall paradox?

Abdominal Paradox

Normally, the diaphragm descends in inspiration, and the abdominal wall moves outwards. It moves inwards, then called the abdominal paradox.

This is seen when the diaphragm is paralyzed or in advanced chronic obstructive pulmonary disease (COPD). Consequently, the exhausted diaphragm and abdomen migrate inward with each inspiration as the drop in pleural pressure brought on by the contraction of the intercostal muscles sucks upward. This is referred to as the respiratory or abdominal paradox.

Bimanual palpation, which involves placing one hand over the patient's chest and the other over the belly, is the most effective method of illustrating abdominal paradox.

Inspection of the chest and abdomen in the supine position may reveal paradoxical inward movement of the abdomen, indicative of respiratory muscle weakness.

Dysfunction of the diaphragm in COPD may lead to the development of various clinical signs such as abdominal paradox, Hoover's sign, and tripod position.

Chest Wall Paradox

It can be seen when there are multiple rib fractures allowing the affected segment to move independent of the rest of the chest (Flail Chest). The segment which is fractured moves inward instead of outward, and during exhalation, it moves outward instead of inward.

Q10. What are the accessory muscles of respiration?

Ans:

- Accessory muscles of respiration comprises of the sternocleidomastoid, scalene, trapezius, internal intercostal, and abdominal muscles.
- The usage of accessory muscles is an indicator of disease which is severe and is a marker of reduction of forced expiratory volume in 1 s (FEV_1) to 30% of normal or less.
- The clavicles are elevated by sternocleidomastoid activity, and a clavicle that moves upward by more than 5 mm is a useful indicator of severe obstruction and correlates with a FEV1 of 0.6 L.
- The scalene muscle is usually recruited prior to the sternomastoid muscles.

- Sternomastoids are typically recruited at times of increased ventilation, such as during exercise, and at very large lung volumes.[6]

Q11. What is purse lip breathing and its importance?

Ans: Purse lip breathing (PLB): COPD patients frequently adapt to the usage of the purse lip breathing pattern either spontaneously or as a component of a program of pulmonary rehabilitation.

Patients with PLB frequently exhale with pursed lips. PLB lowers the respiratory rate while exercising and at rest, prolongs exhalation, adds positive end expiratory pressure (keeps the airway patent during exhalation for a longer duration), enhances oxygenation and ventilation while lowering the quantity of carbon dioxide. By extending the expiration time, PLB lowers the respiratory rate.

Q12. What is Hoover's chest sign?

Ans: COPD patients, along with hyperinflation of the lungs may exhibit various abnormalities of chest wall movements, the most common being the paradoxical indrawing of the lateral rib cage (costal margin) known as the Hoover's sign.

Paradoxical movement of the lateral rib cage movement although present in both the upper and lower rib cage, but is seen more prominently on the lower rib cage.

Another phenomenon that can be seen in COPD patients is the anteroposterior ribcage paradox, where inspiratory indrawing of the lower sternum is seen.

It usually occurs with the lateral paradox during early phase of inspiration.

As the severity of airflow obstruction increases, the frequency of this sign also increases.

a. It was demonstrated in 36, 43, and 76% of patients with moderate, severe, and very severe COPD, respectively.

Hoover's sign, when compared to other signs of COPD such as wheeze, rhonchi, and reduced breath sounds, exhibits a good interobserver agreement with a kappa statistic of 0.74.

Inward pulling of the lateral rib cage by the flattening of diaphragm results in the development of Hoover's chest sign.[8–10]

Q13. What is the meaning of the tripod posture?

Ans:

- COPD patients often instinctively adopt a posture to relieve dyspnea in case of respiratory distress, which is known as tripod position.
- The patients sit and lean forward, with their outstretched hands placed on their knees in tripod position.
- This leaning forward position relieves dyspnea due to various mechanisms. The length tension relationship of accessory muscles (pectoralis major and minor) which are attached between the upper limb or shoulder girdle with the ribs is improved due to the lifting of shoulder girdle and fixation of position provided by the arm support.
- In COPD there is flattening of the diaphragm however the tripod position leads to compression of the abdominal contents and pushes the short flattened diaphragm upwards which leads to the restoration of the normal appearance of diaphragm which is dome-shaped.
- The diaphragm function is improved due to optimization of the relationship between length and tension of the diaphragm. The reduction in sternocleidomastoid and scalene muscle recruitment is also a mechanism by which tripod position relieves dyspnea.
- The thoracoabdominal movement is also improved with tripod position.

Q14. What is Campbell and Oliver's sign?

Ans: In patients having chronic airflow obstruction, such as patients with COPD, there is displacement of the trachea in the downward direction during the phase of inspiration. This sign is known as the Campbell sign, which must be differentiated from another sign known as Oliver's sign or the tracheal tug sign, which is seen in patients with an aortic aneurysm where the aortic pulsation is palpable through the trachea.

The depressed diaphragm is pulled downwards, resulting in the Campbell sign. It is best palpated by placing the tip of the index finger on the thyroid cartilage.[11]

Q15. What is the importance of a patient's odor in examination?

Ans:

- The smell may be a clue to habits or addictions.
- Tobacco leaf stains may be visible on teeth, lips, fingers, or clothing, and tobacco or cannabis smoke may leave a characteristic odor on hair and clothing.
- The odor of ethanol or other toxic alcohols may be detected on the breath, as is the odor of ketones during a diabetic crisis.
- Characteristic odors may also arise from certain infections, such as the foul smell of an anaerobic lung abscess, or the sweet smell of a skin and soft tissue infection caused by *Pseudomonas aeruginosa*.

Q16. What are the non-respiratory causes of changes in respiratory rate?

Ans:

- Tachypnea causes: Exertion, excitement, fever, pneumonia, acidosis, and anemia.
- Bradypnea causes: CNS depressant drugs, narcotic poisoning, brain tumor, and pain while breathing (pleurisy).
- Cushing's triad, a sign of increased intracranial pressure, consists of hypertension, bradycardia, and bradypnea or irregular respirations.
- Ratio between heart rate and respiratory rate, also called PRQ (pulse respiratory quotient): 4:1.

Q17. What is trail sign?

Ans: The sternal head of the sternocleidomastoid muscle becomes prominent due to the shifting of the trachea, with the prominence visible on the side where the trachea is shifted. This is known as the trail's sign.

The clavicular head of sternocleidomastoid bilaterally is enclosed by the pretracheal fascia.

With the shifting of trachea there is relaxation of the pretracheal fascia, which covers the sternocleidomastoid on the side where the trachea is shifted, leading to clavicular head becoming more prominent on the same side.

Q18. What are the conditions leading to mediastinum shift other than lung parenchymal and pleural conditions?

Ans: Mediastinum shift may occur in Scoliosis, in pectus excavatum, or in the enlargement of the left ventricle.

Q19. What are the causes of localized tenderness in the chest?

Ans: Local injury leads to rib fracture, e.g., cough fracture, inflammatory condition, intercostal muscle pain (myositis), costochondritis (Teitz syndrome—there is swelling also), metastatic deposit, herpes zoster, empyema.

Q20. Who was the first person to describe percussion?

Ans: Chest percussion was first described back in the year 1761 by Dr Josef Leopold Auenbrugger, who got the idea about percussion after seeing his father striking the barrels in order to determine the liquid level.

Q21. What is the Skodiac resonance?

Ans: A hyper-resonant note just below the clavicle or top of massive pleural effusion due to relaxed lung called Skodaic resonance.[12]

Q22. What should be smallest size of pathological lesion to detect a percussion note?

Ans: Lesions of the lung, which are situated 5–7 cm away from the chest wall or are less than 2–3 cm in diameter, are beyond the reach of conventional percussion.

Auscultatory percussion may be used to overcome this limitation.

It is done by tapping over the manubrium sterni lightly using the distal phalanx of one finger while simultaneously auscultating with a stethoscope over the posterior chest wall. A reduction in the amplitude is usually attributed to an abnormality of the lung.[13]

Point to Remember

- A stony dullness feeling when you percuss on a solid wall or the thigh.
- Tympany note is a drum-like resonance normally on stomach, intestine, trachea. You can also see in Pneumothorax, emphysema, superficial empty cavity.
- Bell typmpany: Tympanic sound heard over the chest in case of a large pneumothorax. To demonstrate need to place a silver coin on the affected side and percussed with another silver coin, the ear or stethoscope placed on the opposite of the chest may detect a clear bell-like sound resembling the sound of "hammer on an anvil."
- Remember the boundary of Kronig's isthmus.
- Clavicular percussion is performed by directly tapping on the middle part of the clavicle, tell about the pathology of the lung apex.
- Coin percussion, shifting dullness, and succussion splash can be seen in hydropneumothorax.

Q23. What are the characteristics of vesicular and bronchial breath sounds?

Ans: See Table 1

Whispering pectoriloquy is absolutely essential in case of doubt about the presence of bronchial breathing as whispering pectoriloquy is always present along with bronchial breath sound.[15]

Other Types of Breath Sound

- Bronchovesicular breath sound.
- It is an intermediary between the features of bronchial and vesicular breathing.
- Intensity as well as pitch of this sound is intermediate with similar duration of inspiratory and expiratory phases.
- This sound can be normally auscultated over the 1st and 2nd intercostal space in the anterior region and between the two scapulae in the interscapular region posteriorly.
- Interrupted or cogwheel breathing.
- Sometimes, there is interruption of the vesicular breath sound during the inspiratory phase and this is known as cogwheel breathing.
- For example, an enlarged mediastinal lymph node obstructing the bronchus or an aneurysm of the aorta, or during nervousness or fatigue.

Q24. What are the types of bronchial breath sounds?

Ans: There are three types of bronchial breath sounds

1. Tubular
- The pitch of this sound is high, and it is a subclass of bronchial breath sound.
- This is seen in cases such as pneumonia (consolidation), at the level above the level of pleural effusion, in pulmonary fibrosis, or in distal collapse, if the collapsed segment is in contact with the chest wall and the bronchus is patent. It can also be seen in a mediastinal tumor compressing over a large patent bronchus.

2. Amphoric
- It is a bronchial breath sound which is low in pitch, along with high pitch overtone.
- Character of this sound is metallic.
- This sound can be artificially produced through blowing over an empty glass or a clay jar's mouth.
- Meaning of the Greek word amphoreus is jar thereby justifying the name of this sound.
- It can be heard over a superficial cavity, which is large in size, measuring at least 5–6 cm in diameter, along with a patent bronchus, and it may also be present in a case of open pneumothorax.
- For this sound to be produced, a smooth wall is needed as it is a good reflector of sound.
- High-pitched overtones are heard due to the sound wave resonance inside the cavity wall or in the pleural cavity.
- A fungal ball or the presence of fluid within the cavity causes the amphoric breath sound to disappear.

3. Cavernous
- It is a low-pitched bronchial breath sound
- It was heard over an irregular, superficial, large cavity with a patent bronchus, an abscess, and a bronchiectatic cavity with a patent bronchus.

Q25. What is the significance of vocal resonance?

Ans:

- Vocal resonance or vocal sounds are produced in the larynx not like breath sound or added sound in the lungs.
- Formants are overtones containing a combination of both low and high frequencies that are present in vowel sounds.
- Usually, in a healthy individual, the speech is incomprehensible as the high frequencies are lost owing to the air-filled lungs, leading to the filtration of the sound.

Table 1: Depicts difference between the vesicular and breathing sound[14]

Vesicular breath sound	*Bronchial breath sound*
Soft, rustling in quality and low-pitched sound. The inspiratory phase is usually lengthier than the expiratory phase (I: E ratio 2:1 during tidal breathing). The intensity and pitch of the inspiratory phase are more than those of expiration. No pause between inspiration and expiration.	It is usually auscultated anteriorly over the manubrium and posteriorly in the region between the C7 and T3 vertebrae. It is high-pitched, loud, and hollow in quality. Expiratory phase is lengthier than the inspiratory phase, which leads to a change in the I:E ratio from normal 3:1 to 1:2. There is a gap between the inspiratory and expiratory phases due to the absence of the alveolar phase. Bronchial breath sound is accompanied by whispering pectoriloquy.

- In cases where the air inside the lungs is replaced by fluid or solid substances or when the alveoli undergo atelectasis, the transmission of these voice sounds is improved and becomes sharply differentiated.
- Transmitted speech can be classified into three categories, namely: egophony, bronchophony, and whispered pectoriloquy.
- Sounds with an increase in intensity and clarity are present in bronchophony.
- For whispered pectoriloquy to be elicited, the patient is asked to whisper words such as "one-two-three" or "ninety-nine" while the examiner auscultates simultaneously with a stethoscope. Usually, the words can only be heard faintly. However, in cases of consolidation where the air is replaced by solid substances, the sounds that are whispered are heard distinctly and with more clarity.
- The word "egophony" is derived from the word "ego" which means goat in the Greek language. It was initially described by Laënnec in the year 1816. For egophony to be elicited, the patient is asked to say the word "Ee," which gets converted to "A." Egophony is seen in patients with pleural effusion or consolidation.[16]

Q26. What is the difference between wheeze, rhonchi, crackles, and crepitus?

Ans:

- Crackles are divided into fine (previously called crepitus) and coarse type (previously called rales). Rhonchi is an older term for Wheeze.
- First, in 1957, Robertson classified additional sounds into two main categories: continuous and interrupted sounds. Continuous sounds were then classified further into two categories, i.e., high- and low-pitched wheeze. Interrupted sounds were further classified into three types, namely: coarse, medium, and fine crackles.[17] Eventually, the International Lung Sound Association in the year 1976 changed the terminology to simplify it: Discontinuous sound was classified into fine and coarse crackles, and continuous sounds were classified into wheeze and rhonchi.[18]
- According to the American Thoracic Society, wheeze has been defined as a high-pitched continuous sound having a frequency of 400 Hz or more, and rhonchi has been defined as low-pitched sounds that are continuous, having a frequency of 200 Hz or less.[19]
- Wheeze is generally louder in intensity than the breath sounds that are underlying and is usually audible at the open mouth or by auscultation over the trachea and sometimes at a short distance from the patient.
- Rhonchi are low-pitched sounds and are therefore best heard over the wall of the chest.
- Generation of wheeze occurs by the bronchial wall oscillation, which is due to the airflow, and pitch of the wheeze is dependent on the bronchial wall's mechanical properties.

Q.27. What are squeaks or squawks?

Ans: Squeaks, also called Squawks, are wheezes present in inspiration and are short in duration (less than 200 ms). Squawks can be found in cases of interstitial lung disease due to various etiologies, especially in cases of hypersensitivity pneumonitis. It can also be present in cases of pneumonias and bronchiolitis obliterans. The mechanism of production of squeaks is not completely understood; however, according to Forgacs, it is produced due to the peripheral airway oscillation, which is present in the lung zones that are deflated while their walls remain in contact for a longer duration of time and open up in late inspiration.

Q28. Define crackles and the mechanism of formation?

Ans:

Discontinuous adventitious lung sounds, which are explosive in nature and non-musical usually auscultated in the inspiratory phase and sometimes during expiration and are known as crackles.

Classification of crackles can be done based upon the duration of sound, its loudness, pitch, and timing of the respiratory cycle, along with the relationship with change in posture of the body or coughing (Table 2). It is also classified based on different phases of respiration (Table 3).

Small airways are the location for the production of fine crackles, whereas medium crackles are produced due to bubbling of the air through the mucus present in small bronchi and coarse crackles are produced in the large bronchi or in the bronchiectasis segments.

Table 2: Differences between fine and coarse crackles

Fine crackles	*Coarse crackles*
Auscultated in the mid to late phase of inspiration.	It can be auscultated during both the inspiratory and expiratory phases of respiration.
High pitched.	Low pitched.
A change in posture of the body leads to alteration; however, there is no alteration by coughing.	Alteration may occur due to coughing; however, posture change doesn't lead to any change.
They are not transmitted to the mouth.	It may transmit to the mouth.
Sudden opening of small airways during the phase of inspiration, which are collapsed during the expiratory phase, leads to the production of fine crackles.	Passage of gas through the airways, undergoing opening and closing intermittently, leads to the production of coarse crackles.

Table 3: Classification of crackles based on respiratory time and their causes

Timing	*Early inspiratory*	*Mid-inspiratory*	*Late-inspiratory*	*Pan-inspiratory*	*Expiratory*
Condition	COPD	ILD, Acute pneumonia (coarse type)	ILD (profuse at the end), resolution phase pneumonia (Fine type), heart failure	Bronchiectasis, heart failure	COPD, bronchiectasis, IPF

Mechanism: It was believed earlier that the crackles are produced due to the air passing through the large and medium-sized airways while they are filled with secretions, leading to the production of bubbling sounds.

However, the crackles that persist after coughing, which are seen in many patients and localized predominantly in the inspiratory phase, poses as a argument against this theory.[20]

Therefore, another theory for the production of crackles was proposed by Forgacs, which said that the small airways that collapsed during the phase of expiration are opened with a snap during the inspiratory phase as gas pressure gradient develops across these collapsed airways which leads to the production of sounds known as crackles.

The collapsed airways open with a snap, inducing a rapid equalization of gas pressures, which causes oscillations of the column of gas, leading to the production of crackles.[21]

Q29. What are the characteristics of pleural rub?

Ans: Pleural rub is a nonmusical sound, short in duration and explosive, grating, rubbing, creaky, or leathery in character, which can be auscultated during both inspiratory and expiratory phases of respiration. The component of the expiratory phase mirrors the inspiratory component.

The mechanism of the pleural rub has been postulated as the rubbing of the pleural surface against itself after it becomes inflamed during respiration. It is important to differentiate pleural rub from crackles in clinical examination.

Q30. What is tidal percussion?

Ans: Tidal percussion is a way to assess the diaphragm movement by percussing the chest during tidal breathing. We start from the infraclavicular region and keep percussing till liver dullness is reached. At this time, the patient is asked to take a deep breath, and we percuss to see if the area with liver dullness has become resonant. This shift of the liver dulless suggests that the diaphragm has moved down with respiration and suggests a likely normal diaphragm function.

Important Sign to Remember

Coin test: It is usually performed in patients with pneumothorax, a large bulla, or in hydropneumothorax.

The patient should be either in a sitting or standing posture. A metallic coin is placed horizontally against the chest just beneath the clavicle's midpoint, and the coin is struck with another coin's edge. The diaphragm of the stethoscope is placed at the same point on the back. The coin test is deemed to be positive if a high-pitched metallic bell-like sound is heard with the help of a stethoscope, which is placed at the back.

Scratch sign test: The scratch sign is a positive sign seen in pneumothorax. It can be done while sitting or in a supine posture. The diaphragm of the stethoscope is placed at the sternum midpoint and the chest wall surface. The skin is lightly scratched with a fingernail, and auscultation is done to differentiate sounds between the pathological side and the normal side. The sound auscultated is louder in intensity when the side of the pneumothorax is scratched.

Succussion splash: It is also called the Hippocratic succussion. This sign is detected in cases of hydro- or pyo-pneumothorax. It is also seen sometimes in cases of herniation of stomach or intestine through the diaphragm, and a large cavity containing air and fluid in the lungs.

The site that contains the air along with fluid is selected with the help of percussion and the stethoscope is placed on the pathological side. The patient is then shaken by the clinician side to side. On auscultation a sound which is splashing-like is heard which can also be heard sometimes by an unaided ear.

Hamman's sign: Louis Hamman was the first to describe Hamman's sign back in the year 1939. This can be produced in patients with pneumomediastinum and pneumothorax, particularly in cases of left-sided pneumothorax. It is also known by the name of mediastinal crunch. A crunching, crackling sound is auscultated over the 3rd to 5th intercostal space over the precordium, which is synchronized with the heartbeat. Hamman's sign is diagnostic of pneumomediastinum and is more sensitive for diagnosing pneumomediastinum when compared to chest X-ray; however, it can be seen only in 20% of the cases.

D'Espine's sign: D'Espine's Sign is one of the earliest clinical findings that can be elicited in cases of tracheobronchial lymph node enlargement and was first described by a French physician named Jean Henri Adolphe D'Espine, by noting that in some cases a whispered sound may be auscultated over the spinous process of upper thoracic vertebrae.

Normally, the sound auscultated over the spine is less intense than the vesicular breath sounds heard at the same level on both sides of the spine. The D'Espine's sign is described to be positive when the breath sound which is auscultated over the vertebrae is louder than the corresponding lung sounds auscultated bilaterally at the same level.

A positive D'Espine's sign indicates the presence of a posterior mediastinal mass, for example presence of an enlarged lymph node.

Dahl sign: Patches of hyperpigmentation or bruising above the knee are found in COPD caused by the constant 'tenting' position of hands or elbows.

Litten's sign: This is also called the diaphragm phenomenon, demonstrated during percussion. It refers to a loss of diaphragmatic movement on one side, indicating a paralyzed hemidiaphragm. This sign elicits a sound produced during percussion in the lower intercostal spaces between expiration and inspiration.[22]

Conclusion

Residents need to do an honest practice of various methods to elicit even a subtle finding. It is very important to examine a patient as a short case without a history and imaging to master respiratory examination. Respiratory assessment includes interpretation of vital signs; inspection of the patient's breathing pattern, skin color, and respiratory status; palpation, percussion to identify anatomical & pathological lung abnormalities. Diagnosis always includes pathological lesion, location, etiology, any complications, and comorbidities, for example, consolidation of the right upper lobe, pneumonia, with pleural effusion (severity mentioned), with diabetes and CKD.

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POINT OF VIEW

"Academic Overdose" among Healthcare Professionals

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Abstract

Introduction: "Academic overdose (AO) leads to a state of mental and emotional saturation with constant academic input, to the point that learning and productivity decline and may lead to mental exhaustion and burnout, affecting quality of life (QOL)." Medical conferences (MC) are essential for knowledge dissemination, academic recognition, and professional transformation. This AO stems from the pressure to present research, networking, and demanding clinical and academic responsibilities. Adding to this are unlimited, exhaustive, and irritating queries from patients and attendants arising from internet searches.

Discussion: In recent years, the frequency of MCs and continuous medical educations (CMEs) has increased across local, national, and international levels. While this growth offers educational opportunities, it has also led to content redundancy, extended sessions, and a lack of audience engagement. The healthcare professionals (HCPs) have high academic expectations to be achieved in multiple domains, such as position, sustainability, promotions, and excellence in clinical practice; they also maintain scholarly, educational, and administrative responsibilities, and balancing these is highly challenging and may lead to emotional exhaustion and burnout, exacerbated by academic preparation for MC presentations. MCs have various advantages and disadvantages and require structural reforms to attract more participants and to be recognized as being of very high standards. Restructuring of MCs seems logical, and MCs must remain accessible, affordable, and academically oriented.

Conclusion: MCs offer learning, innovations, professional networking, and knowledge and experience sharing, while at the same time needing to be more inclusive, ethical, cost-effective, and image-building opportunities. Associated risks of exhaustion, sleep deprivation, burnout, and financial constraint necessitate restructuring of MCs.

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Introduction

"Academic overdose (AO) leads to a state of mental and emotional saturation with constant academic input, to the point that learning and productivity decline and may lead to mental exhaustion and burnout, ultimately affecting quality of life (QOL) and productivity." Medical conferences (MC) are essential for knowledge dissemination, academic recognition, and professional transformation. However, the overwhelming volume of content may lead to cognitive overload among healthcare professionals (HCPs), including students, postgraduate trainees, early researchers, and faculty educators.

This AO stems from the pressure to present research, networking, and demanding clinical and academic responsibilities. Adding to it are unlimited, exhaustive, and irritating queries of the patients and attendants arising out of internet search.

Key sources of AO among HCPs are MCs, continuous medical education (CMEs), research publications, teaching responsibilities, administrative duties such as committee work, curriculum planning, and compliance with institutional standards, grant and funding applications for research demand detailed proposals and follow-ups, academic monitoring such as publications, citations, and teaching evaluations, credential maintenance, certifications, and documentation, mentoring, and peer reviewing of papers and evaluation of others' academic work, occurring in isolation or in combination. There are many reasons for AO, but the most common is MC, which attracts because of academic glamour and recognition; therefore, we are discussing MC in detail.

Discussion

In recent years, the frequency of MCs and CMEs has increased across local, national, and international levels. While this growth offers educational opportunities, it has also led to content redundancy, extended sessions, and a lack of audience engagement.[1]

Healthcare professionals have high academic expectations to be achieved in multiple domains like position, sustainability, promotions, and excel in their clinical practice, maintain scholarly, educational, and administrative responsibilities, and balance among these is highly challenging and may lead to emotional exhaustion and burnout exacerbated by academic preparation for MC presentations.

The AO not only affects HCPs' physical, mental, and emotional well-being but also has implications for MC attendance and financial sustainability and interests of the organizers, usually HCPs and pharmaceutical companies (PC).[2]

Medical conferences have various advantages and disadvantages and require structural reforms to attract more participants and to be recognized as of very high standards.

Advantages of Medical Conferences

- Medical conferences are full of academic glamour and provide important platforms for interactions, valuable professional connections, networking, and sharing knowledge and research, and making you visible and credible in the fraternity.
- Medical conferences are an integral part of academic career development and offer the opportunity for recognition, inspiration, orientation toward research, and connection with colleagues.
- Short sessions allow more presenters to be accommodated.
- Medical conferences abstracts may get published in indexed journals; an added advantage of presenting on these platforms.
- Awards and acknowledgments gained through these MCs boost reputation and academic standing.
- Workshops help skill development and improve public speaking, presentation skills, and critical feedback.

Disadvantages of the Medical Conferences

- Extended hours of neck-to-neck sessions with limited or no discussion lead to decreased engagement of the audience.
- Studies indicate a high prevalence of stress and burnout among emergency HCPs[3] and medical students due to academic

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demands, heavy workloads, exams, and the pressure to publish in journals.
- Burnout characterized by emotional exhaustion, depersonalization, anxiety, depression, other mental health issues, and reduced personal accomplishment negatively impacts students' ability to learn and perform well in their studies and clinics.
- Overwork, sleep deprivation, and exhaustion do occur due to academic preparation, along with demanding clinical responsibilities and scheduling of the MCs.
- Conflicting messages from prominent speakers, especially in pharma-sponsored content, and conflict of interest may blur the line between education and promotion.
- Healthcare professionals working in emergency medicine, dealing with sick and dying patients, as well as the pressure to maintain personal, social, academic, and professional commitments, contribute to emotional drain out in 25–77.8% HCPs.[3]
- There is a strong association between burnout and major medical errors (MME) among 7,905 members of the American College of Surgeons' survey of self-assessment of MME revealed that 8.9% HCPs made a major medical mistake in the last 3 months, and it remained a common reason for morbidity and mortality. About 70% HCPs accepted the MME to be individual rather than system related, and this had a statistically significant adverse relationship with mental QOL in all domains of burnout, that is, emotional exhaustion, depersonalization, and personal accomplishment, and symptoms of depression.[4] All the abovementioned factors are exaggerated due to frequent MC participation as a speaker or faculty.
- Medical education should be free from any industry pressure, including pharmaceutical sponsorship. PC are significant contributors to CMEs, and restricting them could affect CMEs financially, limiting educational opportunities. Adhering to transparent disclosures, ethics, and strict rules and regulations, HCPs and PC can work together to enhance CMEs without compromising its integrity.[5]
- Despite the importance of MC, attending MCs is not intuitive, as these are glamorous mega events. Attendees do enter with expectations, invest a lot of time, energy, and effort, and walk away with a feeling that they did not reap the benefits. This may lead some to avoid MCs and limits their ability to advance their own career and contributions toward medical education.[6]
- Hierarchical focus may marginalize early-career professionals and underrepresented but valuable contributors.
- Theoretical sessions may be irrelevant to clinical practice. Exhaustive, neck-to-neck sessions and information overload may lead to less retention and minimal long-term benefit if not reinforced, diminishing the overall value of the MC.

Restructuring of the Medical Conferences Seems to be Logical in View of Academic Overdose

- Medical conferences organizers should consider more breaks, reduce the number of sessions, avoid repetitions, encourage authentic contributions and youngsters by listening to them, and offer alternative networking opportunities.
- Establish clear ethical guidelines for industry sponsorship and ensure transparency.
- Encouraging a healthy balance between academics and physical limitations and considerations is crucial.
- Ensuring a balanced, inclusive, and focused approach will sustain the educational and collaborative benefits of MCs.
- Glamour-driven elements such as celebrity dinners and elaborate mementos deviate from academic goals.
- Medical conferences must remain accessible, affordable, and academically oriented.

Conclusion

Medical conferences offer learning, innovations, professional networking, and knowledge and experience sharing, and at the same time need to be more inclusive, ethical, cost-effective, and image-building opportunities.

Associated risks of exhaustion, sleep deprivation, burnout, and financial constraints necessitate restructuring of MCs. Balancing content delivery, interaction, and discussion with attendees is crucial for sustained beneficial impact, and the purpose for which these gatherings are designed is key to the success of MCs.

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Fasciolopsis buski Diagnosed by Upper Gastrointestinal Endoscopy

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A 36-year-old male patient from rural South Bengal, India, presented to our hepatology outpatient department (OPD) with upper abdominal discomfort, anorexia, indigestion, and chronic diarrhea with passage of loose stools 3–4 times per day for 6 weeks. He was afebrile without any weight loss. He did not give any history of skin changes, arthralgia, or oral ulceration. He gave a history of consumption of water chestnuts. He had no history of travel or intake of alcohol or any medications. Physical examination did not reveal any lymphadenopathy, thyroid mass, organomegaly, or abdominal mass. Blood reports showed anemia with a hemoglobin of 78 gm/L (normal range 130–170 gm/L), and total leukocyte count showed eosinophilia (12%). Liver function test showed mild hypoalbuminemia. Human immunodeficiency virus, hepatitis B virus surface antigen, and antihepatitis C virus antibody were nonreactive. Abdominal ultrasonography was normal. Initial stool examination was normal. On upper gastrointestinal (GI) endoscopy, multiple flat, leaf-like, fleshy structures attached to duodenum were found, which were extracted endoscopically (Fig. 1 and Supplementary Video S1). They were morphologically identical to adult form of *Fasciolopsis buski* (3.5 cm × 1.5 cm × 0.5 cm) (Figs 2 and 3). He was treated with tablet praziquantel (75 mg/kg, in three divided doses for 1 day). The next day, stool examination showed eggs of *F. buski* (morphologically, eggs of *F. buski*, *Fasciola hepatica*, and *Fasciola gigantica* are similar) (Fig. 4). A few adult worms of *F. buski* were also expelled through feces for 2 days. From the 3rd day onward, stool examination did not show any eggs or adult forms of *F. buski*, and he was asymptomatic for a 6-month follow-up period.

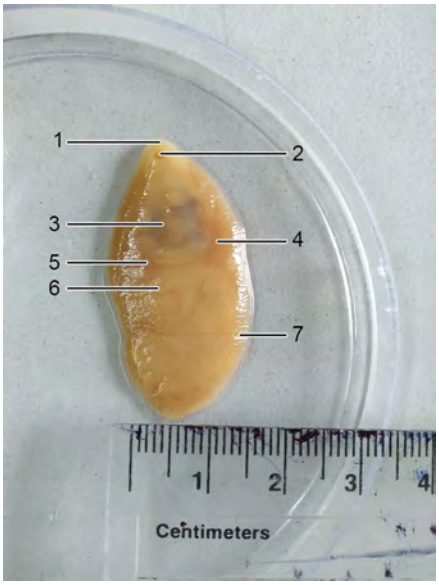

Fig. 2: Adult worms of *F. buski*: (1) Oral sucker; (2) Ventral sucker; (3) Unbranched intestinal caeca; (4) Uterus; (5) Ovary; (6) Testis; (7) Vitellaria

Fasciolopsis buski is the largest human small intestinal fluke (trematode). It is endemic in Southeast Asian countries, including India. In India, very few cases were reported from Bihar, Uttar Pradesh, and other northeastern states.[1–4] Risk factors are consumption of improperly cooked or raw aquatic plants (particularly water chestnuts, watercress, or bamboo shoots) where metacercaria, the infective stage of the fluke, attach. Infection is usually asymptomatic. Symptoms are due to heavy infection that causes inflammation, ulceration, and microabscesses of the intestinal mucosa where flukes attach. Symptoms are anorexia, nausea, vomiting, diarrhea, abdominal pain, dyspepsia, malabsorption, and weight loss. Fatal heavy infection causes extensive intestinal inflammation, ulceration, perforation, small bowel stricture, abscess formation, and hemorrhage.[5] It is diagnosed by identification of characteristic bile-stained egg with an operculum at one end in the stool. Sometimes eggs and adult worms are recovered from stool after anthelmintic therapy.[5] Peripheral blood eosinophilia may be present. It can also be diagnosed by upper GI endoscopy, and direct removal of the adult worms during endoscopy may be possible. It is treated by tablet praziquantel, 75 mg/kg, in three divided doses for 1 day.

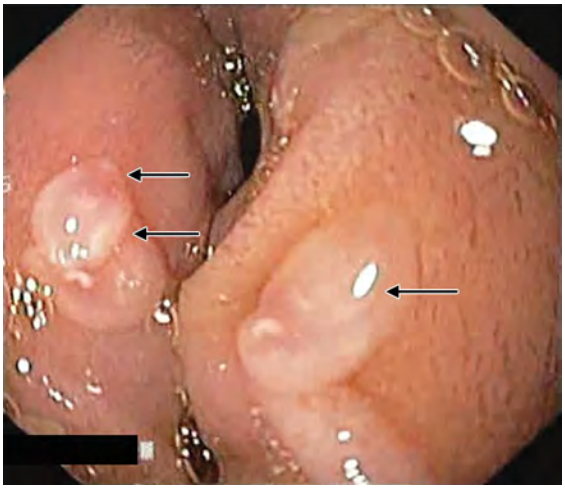

Fig. 1: Endoscopic view of duodenum showing adult worms of *F. buski* attached to mucosa. Black arrows

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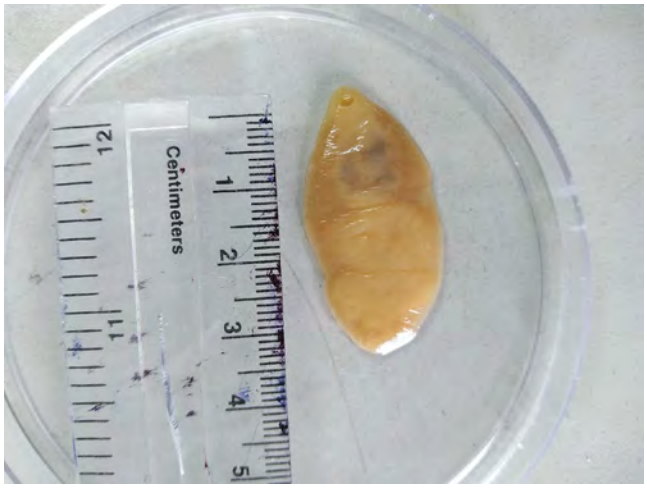

Fig. 3: Adult worms of *F. buski*

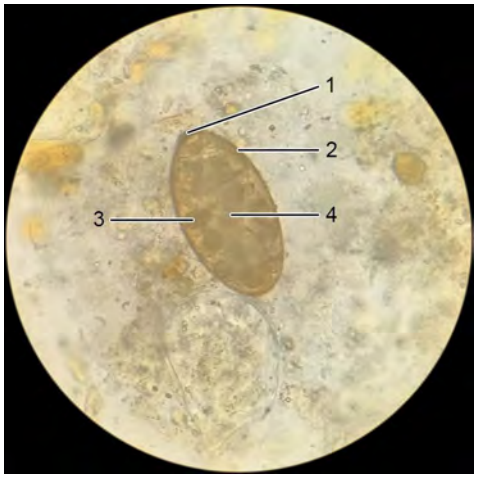

Fig. 4: Egg of *F. buski*—bile-stained, operculated, in wet mount preparation of stool in high-power field (×40 magnification): (1) Operculum; (2) Eggshell; (3) Yolk cell; (4) Ova

High index of suspicion is required to diagnose *F. buski* in a patient who consumes raw or improperly cooked freshwater plants and who presents with chronic diarrhea, features of malabsorption, and peripheral blood eosinophilia. If there is high suspicion but eggs of fluke cannot be recovered from the stool, then upper GI endoscopy should be done.

Acknowledgments

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Conflict of Interest

There is no actual or potential conflict of interest to disclose.

Supplementary Material

Supplementary Video S1 is available online at the journal website.

Video S1: Endoscopic view of duodenum showing adult worms of *F. buski* attached to mucosa and endoscopic extraction of the adult worms

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