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EDITORIAL

The Balancing Act: A Rational Approach to Postintervention Dual Antiplatelet Therapy

Nihar Mehta[1*], Divya Samat[2]

Balancing the risks of ischemic and bleeding events in patients who have undergone coronary angioplasty with drug-eluting stents (DES) is a delicate task. Individuals recovering from myocardial infarction are at increased risk of recurrent ischemic events, highlighting the potential benefits of rigorous secondary prevention measures.[1] Dual antiplatelet therapy (DAPT), combining aspirin with P2Y12 inhibitors such as clopidogrel or ticagrelor, forms the cornerstone of post-percutaneous coronary intervention (PCI) care aimed at preventing stent thrombosis and lowering the risk of ischemic events. Current medical guidelines recommend a 6-month duration of DAPT for stable coronary disease and 12 months for acute coronary syndrome (ACS).

Aspirin: the Great?

For many years, aspirin was considered the wonder drug, with lifelong aspirin therapy being recommended for secondary prevention of ACS. However, with the advent of more potent drugs in the market, guidelines are being revised with the importance shifting to achieving an equilibrium between ischemic risk and bleeding risk.

The HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis- EXtended Antiplatelet Monotherapy) study recruited 5,530 patients who were randomly assigned to take clopidogrel 75 mg or aspirin 100 mg once daily for 24 months. Clopidogrel was found to be beneficial in patients with respect to thrombotic and bleeding outcomes.[2]

The CAPRIE study, which included approximately 20,000 patients with coronary, peripheral, and cerebrovascular disorders, also demonstrated that clopidogrel was more effective than aspirin for preventing adverse cardiovascular events.[3]

Moreover, studies have shown that the effects on the coagulation system of P2Y12 receptor and DAPT are similar.[4,5]

To Cut the Long Story Short

The recommended duration for DAPT post-PCI in stable coronary disease is 6 months and in ACS is 12 months as per guidelines.[6,7] DAPT prolongation can be considered in patients who have tolerated it well and are not at high bleeding risk (HBR).

On the contrary, early discontinuation should be considered for those who are at HBR or who develop significant overt bleeding.

The STOP-DAPT2 randomized 3,005 patients to clopidogrel monotherapy after 1-month DAPT (clopidogrel group) versus 12 months DAPT followed by aspirin monotherapy (aspirin group) after PCI with a 5-year follow-up. The results showed that clopidogrel was numerically, but not statistically superior to aspirin in cardiovascular ischemic outcomes without any difference in major bleeding outcomes.[8]

Recently, multiple reasons have led to consideration of shorter DAPT duration beyond HBR patients:

- Reduction in bleeding risks, especially since nearly 40% of patients undergoing PCI are considered HBR[9]
- Excess risk of gastrointestinal bleeding with aspirin
- Lower risk of stent thrombosis beyond 1–3 months with the latest generation of DES[9]

Several studies have found that short DAPT for 1–3 months followed by a P2Y12 inhibitor monotherapy (clopidogrel or ticagrelor), when compared to DAPT for 12 months, reduces the risks of bleeding without increasing the thrombotic/ischemic risks.[10]

However, the newer 2021 guidelines recommended that shorter-duration DAPT followed by P2Y12 inhibitor monotherapy can be considered in ACS patients 3–6 months after PCI (class IIa), in selected patients 1–3 months after PCI (class IIa), and in patients with HBR in 1 month after PCI (class IIb) to lower the bleeding risks.[11]

The Balancing Act

While preventing ischemic events, such as stent thrombosis and myocardial infarction, is still the primary role of DAPT, in recent times, the emphasis has shifted to finding an equilibrium between ischemic and bleeding risk for the individual patient. This change comes as it has been recognized that bleeding is a relevant factor which also contributes to hard outcome endpoints, such as all-cause mortality.[12] Thus, studies have been planned to evaluate newer regimens with shorter DAPT to reduce the risk of bleeding without increasing the risk of ischemic events, as described in the STOP-DAPT3 study.

Every coin has two sides, as does the antiplatelet dilemma. According to findings from the SMART-DATE trial conducted in South Korea, which was a randomized noninferiority trial, there was no significant difference in all-cause mortality and stroke rates between patients receiving 6-month and 12-month durations of DAPT. However, the 6-month DAPT group experienced a higher incidence of myocardial infarction due to stent thrombosis, while the 12-month DAPT group had a higher rate of bleeding. With the increased risk of myocardial infarction associated with 6-month DAPT and the wide noninferiority margin observed, caution is advised against concluding that short-term DAPT is safe for patients with ACS undergoing PCI with newer-generation DES. Prolonged DAPT should continue to be the standard of care for patients who are not at excessive risk of bleeding.[13]

Similarly, a study by Kinlay et al. tracked patients undergoing PCI with second-generation DES in the Veterans Affairs Healthcare System from 2006 to 2016. Their study examined the outcomes of different durations of DAPT, including death, myocardial infarction, stroke, and major bleeding over a period of up to 13 years. The results indicated that patients who discontinued DAPT after 9 months following PCI with second-generation DES had lower

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long-term risks of major bleeding and ischemic events.[14] Conversely, discontinuation of DAPT before 9 months was associated with an increased risk of both cardiovascular and noncardiovascular death.

Switching from Aspirin to P2Y12 Monotherapy

In a network meta-analysis conducted by Luo et al., various DAPT regimens were compared for their safety and efficacy. The study included long-term DAPT (L-DAPT), standard DAPT (Std-DAPT), aspirin monotherapy after short-term DAPT (S-DAPT + As), and P2Y12 inhibitor monotherapy after short-term DAPT (S-DAPT + P2Y12). According to their findings, S-DAPT + P2Y12 exhibited the lowest risk of bleeding. Furthermore, S-DAPT + As had significantly lower bleeding risk compared to Std-DAPT and L-DAPT, aligning with current guideline recommendations. However, both S-DAPT + P2Y12 and S-DAPT + As showed inferior efficacy compared to L-DAPT in terms of myocardial infarction (MI), stent thrombosis, and cardiovascular and cerebrovascular adverse events. Despite L-DAPT posing the highest bleeding risk, it demonstrated superior efficacy in these ischemic outcomes. Stroke and all-cause mortality did not show statistically significant differences among the four interventions.[15]

Consequently, long-term DAPT (>12 months) may be recommended to mitigate ischemic events in patients without a high risk of bleeding.

Similarly, in a meta-analysis by Khan et al., various durations and regimens of DAPT following PCI with DES were compared. These included short-term (<6-month) DAPT followed by aspirin or P2Y12 inhibitor monotherapy, midterm (6-month) DAPT, 12-month DAPT, and extended-term (>12-month) DAPT. The study revealed that short-term DAPT followed by P2Y12 inhibitor monotherapy reduces major bleeding compared to 12-month DAPT, whereas extended-term DAPT decreases myocardial infarction incidence at the cost of increased bleeding events. There were no significant differences in ischemic endpoints or major bleeding risks observed between midterm or short-term DAPT followed by aspirin monotherapy versus 12-month DAPT. Furthermore, no significant differences in mortality were noted across the different DAPT strategies.

Therefore, the overall clinical benefit appears to be in favor of short-term DAPT followed by P2Y12 inhibitor monotherapy due to comparable effectiveness in MI prevention and better safety with fewer major bleeding events. Extended-term DAPT remains relevant for patients with low bleeding risk but high ischemic risk, such as those with ACS.[16]

How Short is Too Short?

In individuals with a high risk of bleeding events undergoing PCI, a systematic review and meta-analysis found that an abridged 1- or 3-month DAPT regimen was associated with both lower bleeding and cardiovascular mortality and was similarly effective for the prevention of ischemic events. Notably, this was unrelated to the clinical presentation or the type of antiplatelet agent administered after short DAPT discontinuation, compared with a ≥6-month DAPT regimen.[17]

Options of P2Y12 Monotherapy

An optimal antiplatelet strategy hinges on the equipoise between ischemic and bleeding risks. While there are studies demonstrating the long-term safety of clopidogrel, there are certain considerations prior to selection of clopidogrel as monotherapy. There could be variability of platelet reactivity with clopidogrel due to CYP450 polymorphism, especially in Asians. Clopidogrel is costlier than aspirin and does not have the preventive effect against colorectal adenocarcinoma that aspirin affords. When on lifelong clopidogrel, planning future noncardiac surgery is challenging. Surgical procedures are accepted with patients on aspirin but not on clopidogrel. Nevertheless, the data from recent studies favors clopidogrel as long-term single antiplatelet therapy. Compliance to clopidogrel has shown to be more than aspirin.[18] In some patient populations such as patients with gastrointestinal and cerebral bleeding, clopidogrel is a viable alternate to aspirin.[19]

Recently, the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) study demonstrated that discontinuation of aspirin 3 months after PCI and continuing ticagrelor monotherapy does not result in a change in the ischemic or bleeding episodes.

Recommendations

To date, optimal antiplatelet regimens after PCI are unclear for a broad range of patients.

- A personalized approach: When determining the optimal intensity and duration of DAPT following PCI, it is crucial to take into account each patient's individual risk of both ischemic events and bleeding. This personalized approach may justify DAPT durations ranging from as short as 1 month to potentially lifelong treatment, depending on clinical judgment and risk assessment after DES placement.[20]
- De-escalation of DAPT: The de-escalation of DAPT must be meticulously tailored to each patient. Premature de-escalation following PCI can potentially be detrimental, particularly in individuals with ACS. Therefore, DAPT should generally be maintained as the standard of care for at least 1 month, and possibly up to 3 months in ACS patients and those at high risk of ischemic events. After this initial period, transitioning to a single P2Y12 inhibitor may increasingly be considered the preferred approach, with aspirin potentially in the back seat.
- Bleeding risk scores: Bleeding risk assessment tools, personalized antiplatelet therapy based on genetic factors, and platelet function testing are among the potential beneficial strategies available for Asian populations. The PRECISE-DAPT score (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy), which evaluates factors such as age, hemoglobin levels, white blood cell count, creatinine clearance, and history of prior bleeding, has shown moderate effectiveness in predicting bleeding events.[21]
- Optimal revascularization: The importance of good revascularization performed by an experienced professional in a timely manner to reduce the incidence of future ischemic events must be stressed.

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Draupadi Weeps Again: Time to Awaken the Krishna Within

Agam Vora[1*], Mangesh Tiwaskar[2]

The medical community recently endured a heartbreaking tragedy with the brutal rape and murder of a young medical student in Kolkata. The tragic event at R G Kar Medical College in Kolkata is particularly distressing. While the reasons behind it may be complex—whether linked to a drug racket, a personal vendetta, or even the accused's questionable history as a womanizer and porn addict—the fact remains that justice appears elusive. There is a troubling sense that evidence has been tampered with and political influence is shielding the guilty. It's time for society to awaken. She could have been anyone's daughter. How can a woman be treated this way, especially in a country like India, where it is said, "यत्र नार्यस्तु पूज्यन्ते रमन्ते तत्र देवताः" ("where women are honored, divinity blossoms")? This incident painfully reminds us of the disrobing of Draupadi in the Mahabharata. In that moment of distress, Lord Krishna intervened to save her.

This incident is not isolated but part of a disturbing pattern of violence against healthcare professionals. Once revered as individuals "next to God," doctors now face increasing aggression, distrust, and systemic violence. As we navigate this grim reality, it prompts a difficult but necessary introspection into the erosion of trust between society and the medical profession, and the collective responsibility we bear in remedying this situation.

The sacred doctor–patient relationship, historically anchored in trust and mutual respect, has significantly deteriorated over recent decades. In the past, physicians served as trusted family advisors, deeply involved in their patients' lives and health journeys. However, over time, this bond has transformed into a more transactional model, driven primarily by commercial interests. The commercialization of healthcare has turned medicine into a profit-oriented industry, with corporate hospitals often perceived as prioritizing financial gain over patient welfare. This shift has further deepened public skepticism, eroding the trust that once defined the profession.

Simultaneously, medical education has morphed into a substantial financial burden, placing immense pressure on young doctors who face staggering costs to obtain a degree. This environment fosters distrust, particularly when the public suspects doctors' motivations to be financially driven rather than altruistic. The staggering debt and systemic pressures create a new generation of physicians burdened by the necessity to recover their investments, thereby straining the traditional model of healthcare delivery. Many patients, on the other hand, often fail to grasp these realities, harboring unrealistic expectations of quick, inexpensive, and guaranteed results.

Patients today expect rapid appointments, minimal investigations, and free consultations, all while continuing to indulge in unhealthy lifestyles—smoking, poor diets, lack of exercise, and inadequate sleep. Despite these choices, they expect doctors to offer miraculous solutions. When reality falls short, this disconnect breeds dissatisfaction. Moreover, a lack of understanding about healthcare economics fuels frustration. Many patients remain unaware that doctors typically control only a small fraction of overall medical costs. They fail to see that hospital expenses, pharmaceuticals, and diagnostic services often fall outside a physician's purview, yet the physician bears the brunt of public discontent.

For young doctors entering this complex and often hostile environment, the barriers to establishing independent practices are daunting. The costs of setting up a clinic, the bureaucratic hurdles requiring countless approvals, and the lack of institutional support create an atmosphere of disillusionment and fear. These obstacles dissuade many from pursuing careers in clinical practice, leaving the field to those with the resources and connections to navigate this complicated landscape. Furthermore, recent policy changes that allow practitioners from less rigorous fields, such as homeopathy and Ayurveda, to practice modern medicine without adequate training, only add to the confusion, undermining the public's confidence in trained professionals.

Caught in this vicious cycle, many doctors find themselves resorting to defensive medicine—ordering unnecessary tests and procedures to safeguard against litigation or physical violence. This practice, although rooted in self-preservation, drives up healthcare costs and exacerbates the very mistrust it aims to mitigate. The consequences are severe: the mental health of doctors is crumbling under immense pressure, with burnout, depression, and professional dissatisfaction becoming pervasive. Young professionals, whose aspirations to serve once drove them, now hesitate to pursue clinical careers, fearing physical assault and professional humiliation.

Reversing this cycle requires a deep and concerted effort to rebuild the trust that has been lost. Enhancing security measures in hospitals and clinics is critical, as is implementing and enforcing stricter laws to deter acts of violence against healthcare professionals. Simplifying the bureaucratic process for setting up medical practices would encourage more doctors to establish independent clinics, thereby fostering a more personal and community-oriented approach to healthcare. Improved communication between doctors and patients is equally essential. A more transparent dialogue regarding the medical process, cost structures, and the limitations of healthcare would foster a greater appreciation for the efforts of doctors and reduce the hostility borne out of misunderstanding.

Public awareness campaigns could play a pivotal role in educating society about the complexities of medical practice and the realities of healthcare economics. Society needs to reflect deeply on its collective attitude towards healthcare and doctors, questioning whether we truly wish to create a safe and supportive environment for those we expect to care for us. We often look to the outside world, hoping for divine intervention to right the wrongs and protect the vulnerable.

Lord Krishna stood by Draupadi in her moment of despair, intervening to protect her dignity. Yet, his message went beyond that single act—he urged us not to be silent spectators to such injustices but to awaken the Krishna within ourselves. He will not descend from the heavens to fight our battles; he already resides within each of us as a spark of courage and righteousness. It is up to us to

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ignite that divine essence and stand against every wrong, embodying the spirit of Krishna through our actions.

Let us vow to stand up against injustice and ensure that no other Draupadi ever faces humiliation again. It is our collective responsibility to be the change-makers, the protectors, and the guardians of dignity and honor. Each one of us carries the power to make a difference, and together, we can rebuild the trust between doctors and society, creating a safer and more supportive environment for healthcare providers and patients alike.

Let us collectively pray for a healthier tomorrow, striving to ensure dignity for all.

ORIGINAL ARTICLE

A Study of the Progression, Complications, and Outcome of Mucormycosis in a Case of Coronavirus Disease 2019 Pneumonitis at a Tertiary Care Hospital in Gujarat

Mit K Makadia[1], Praful Dudhrejia[2], Pankaj Patil[3], Milan Parida[4*]

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Abstract

Introduction: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused coronavirus disease 2019 (COVID-19) has been connected to numerous opportunistic bacterial and fungal infections. Mucormycosis is a fatal opportunistic disease that became much more common with the second COVID-19 wave. We plan to look into the prognosis and course of mucormycosis following COVID-19, as well as the risk of mucormycosis in cases with COVID-19 pneumonitis.

Materials and methods: Just 100 verified cases of mucormycosis that were admitted to a civil hospital in Rajkot between April 2021 and March 2022 were included in this retrospective cross-sectional investigation. Data gathered from medical records included diagnoses, vital signs, test findings, microbiological information, usage of antibiotics, and outcomes. After entering the data into Microsoft Excel, we performed analysis and computations to determine frequency, percentage, and the Chi-squared test for variable comparison.

Results: About 77.0% of the 100 mucormycosis patients were between the ages of 41 and 70. The bulk of them were male. The most frequent associated comorbidity was diabetes mellitus (DM) (30.0%). The most commonly impacted sinuses were the maxillary and ethmoidal ones. Amphotericin B was administered intravenously to each patient. In total, 82.0% of patients survived while 18.0% of patients died.

Conclusion: Mucormycosis is an extremely rare, serious, and sometimes fatal infection. Because of comorbidities like diabetes and smoking, it went up with COVID-19. The use of glucocorticoids during COVID-19 treatment was the main risk factor.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has been connected to a number of opportunistic bacterial and fungal illnesses.[1] *Aspergillus* and *Candida* have been identified as the main fungal pathogens associated with coinfection in COVID-19 patients.[2]

Recently, mucormycosis in COVID-19 carriers has been reported in several cases worldwide, primarily from India. The main factor that appears to be facilitating mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium [metabolic acidosis, diabetic ketoacidosis (DKA)], high iron levels (increased ferritins), and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated, or background comorbidities). This setting is combined with a number of additional common risk factors, like extended hospital stays with or without mechanical ventilation.[3]

A rare but fatal fungal infection, mucormycosis mainly affects people with weakened immune systems.[4] Mold fungi from the genus *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Absidia* of the order Mucorales, class Zygomycetes, are the source of the angioinvasive disease mucormycosis. The method of contamination is by inhaling spores from a fungus.[5]

Known as the diabetes capital, India currently has the second-largest diabetic population globally. It is noteworthy that in wealthier nations, hematological malignancies and organ transplants are the main causes of mucormycosis, yet in India, diabetes is the most frequent risk factor. However, with a 46% global fatality rate from mucormycosis, diabetes mellitus (DM) continues to be the biggest risk factor associated with the disease.[6] Few cases of mucormycosis, particularly in individuals with DM, have been documented even after a brief course of steroid therapy (5–14 days).

In light of the COVID-19 pandemic, where corticosteroids are often used, these findings should be reexamined. The number of case reports and series involving mucormycosis in COVID-19 infected individuals have significantly increased, especially in India. This prompted us to do a thorough investigation of case reports involving mucormycosis in COVID-19 carriers in order to learn more about the condition's overall characteristics, its temporal correlations with comorbidities, and its relationship to medications employed in the virus.

In the present study, we retrospectively studied around 100 cases of COVID-19 pneumonitis that developed mucormycosis during admission and stay at COVID civil hospital, Rajkot, during the year 2021–2022, to study the risk of mucormycosis in cases of COVID-19 pneumonitis and the progression and outcome of mucormycosis after COVID-19.

Materials and Methods

A retrospective cross-sectional study was conducted between April 2021 and March 2022 on instances of mucormycosis following admission to civil hospital in Rajkot, Gujarat, due to COVID-19 infection. The Institutional Ethics Committee (IEC) granted ethical approval.

With the aid of hospital case records, a convenience sample of 100 patients with mucormycosis following COVID-19 infection admitted to civil hospital, Rajkot between April 2021 and March 2022 were included in the study.

Inclusion Criteria

- Age >18 years.
- Reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test confirmed COVID-19.
- Patient taking standard care (steroid, anticoagulants, and antibiotics).

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Exclusion Criteria

- Pregnant and breastfeeding female.

Between April 2021 and March 2022, a retrospective cross-sectional study was carried out in the PDU Medical College and Civil Hospital in Rajkot. During this time, 100 cases of mucormycosis in patients who tested positive for COVID-19 were examined. Because of the retrospective/observational nature of the study, consent was not required.

During this time, we had gathered information from hospital records about cases of mucormycosis. We have included 100 instances out of around 800 cases that had fungal potassium hydroxide (KOH) positive for *mucor* species, radiological imaging suggestive of alterations in sinusitis or invasive fungal lesion, and clinical symptoms and signs.

Amphotericin B, a systemic antifungal, was used to treat these patients. The liposomal form of amphotericin B was administered to some patients based on their renal and hepatic function as well as their central nervous system (CNS) penetration, while the remaining patients received the lyophilized form of the drug. Every patient required functional endoscopic sinus surgery (FESS) as a surgical intervention. Amphotericin and adverse effects from surgery were addressed during treatment, along with routine testing for serum potassium, creatinine, and hemoglobin. We searched for mucormycosis risk factors and associated outcomes during this time.

We included the risk factors in favor of the following:

- Random blood sugar (RBS) (normal ≤150 mg/dL).
- Glycated hemoglobin (HbA1c) value (normal ≤5.6%).
- Serum ferritin level (normal ≤198 µg/L).
- Past comorbidities.
- DKA.

(As per our laboratory reference value)

We looked into and examined the patients' age and sex distributions, clinical symptoms, developments, and consequences. A thorough physical examination was performed, along with other tests such as an RBS, HbA1c, urine ketone, serum ferritin, fungal KOH, computed tomography (CT)/ magnetic resonance imaging (MRI), and full blood count.

The Epi Info program, version 7.1.5.2, was used to evaluate data that was imported into Microsoft Excel 2016 from the Centers for Disease Control and Prevention, Atlanta, United States. Frequencies and percentages were calculated for categorical data, and the Chi-squared test was used to compare the variables.

Results

Just 9.0% of the 100 patients with mucormycosis presented before the age of 40, with the remaining 27.0% falling between the ages of 61 and 70, 26.0% between the ages of 51 and 60, 24.0% between the ages of 41 and 50, and 14.0% between the ages of 71 and 90. About 43.0% of the patients were female and 57.0% of the patients were male. The age and gender distribution of the cases is displayed in Table 1. Tobacco addiction affected 34.0% of patients, while risk factors for diabetes and hypertension affected 30.0 and 21.0% of patients, respectively.

Table 2 shows that 68% of patients were admitted to the hospital due to COVID. Of those, 40% showed evidence of mucormycosis after 21–30 days of testing positive for the virus, while 36 and 21% showed symptoms within 20 and 31–40 days, respectively, of testing positive for the virus. Consequently, 97% of patients who tested positive for COVID went on to get the illness in 40 days or less.

Table 3 shows that the most common presenting symptom for mucormycosis was maxillary sinusitis (35%), while the second and third most common presentations seen among patients were rhino-orbital and rhino-orbital-cerebral mucormycosis, respectively.

Table 4 demonstrates that, of 100 patients, 72.0% require oxygen assistance during COVID in different ways (16.0, 33.0, 20.0, and 3.0% respectively) *via* nasal cannula or venti mask (VM), nonrebreather mask (NRBM), bilevel positive airway pressure (BIPAP), or invasive mechanical ventilation. In 28% of cases, oxygen supplementation was not provided. During treatment, 69.0% of patients required steroids, 65.0% took antiviral medications, while only 3% of patients received tocilizumab.

Table 5 demonstrates that only 12.0% of patients had blood sugar levels >300 mg/dL upon admission, 25.0% had HbA1c values ≥6.5, 46% of patients had higher serum ferritin levels, and 89% of cases had a higher neutrophil-to-lymphocyte ratio (NLR). High NLR and ferritin levels are significantly

Table 1: Demographic and comorbidity profiles of COVID-19 infected patients

Variable	*No. of patients (%) N = 100*
Age-group (years)	
21–30	2
31–40	7
41–50	24
51–60	26
61–70	27
71–80	11
81–90	3
Gender	
Male	57
Female	43
Addiction	
Tobacco	34
Alcohol	1
Tobacco and alcohol both	4
No addiction	61
Underlying risk factor	
Diabetes	30
Hypertension	21
Chronic obstructive pulmonary disease (COPD)	4
Hypothyroidism	3
Chronic kidney disease (CKD)	2
Liver disease	2
Malignancy	2
No risk factor	36

Table 2: Basic information of diseases among COVID-19 infected patients

Variable	*No. of patients (%) N = 100*
Hospitalized due to COVID	
Yes	68
No	32
Presentation of symptoms after days of COVID positive	
≤20 days	36
21–30 days	40
31–40 days	21
>40 days	3

Table 3: Types of presentation of mucormycosis among COVID-19 infected patients

Presentation of patients	*No. of patients (%)*
Maxillary sinusitis	35
Rhino-orbital	16
Rhino-orbital-cerebral	13
Cavernous sinus thrombosis	11
Palatal	10
Orbital	5
Rhino-cerebral	5
Rhino-palatal	4
Periorbital	1
Total	100

correlated with the risk of mucormycosis. Rhizopus was the most often discovered type of fungus in patients (92%).

Figure 1 shows that 18% of patients died during treatment of mucormycosis.

Table 6 demonstrates a statistically significant correlation between the outcome of patients with COVID-19-related mucormycosis and steroid use at admission, as well as between blood sugar levels at admission, CT/MRI abnormalities, and DKA presentations (p-value < 0.05). The choice of antifungal medication taken and patient mortality do not differ in a statistically meaningful way.

Table 4: Distribution of patients according to use of therapy

Variable	*No. of patients (%) N = 100*
Supplementary oxygen use	
Room air	28
Nasal cannula/VM	16
NRBM	33
BIPAP	20
Intubated	3
Use of steroid	
Yes	69
No	31
Use of antiviral drug	
Yes	65
No	35
Use of tocilizumab	
Yes	3
No	97

Table 5: Distribution of patients according to laboratory profile

Variable	*No. of patients (%) N = 100*
Blood sugar at admission (mg/dL)	
≤150	69
151–300	19
>300	12
HbA1c levels	
≤5.6	35
5.7–6.4	40
≥6.5	25
Serum ferritin levels	
Normal (<198)	54
High (≥198)	46
NLR	
Normal (<3.5)	11
High (≥3.5)	89
Species of the fungus in patients	
Rhizopus	92
Mucor	8

Discussion

The new SARS-CoV-2 virus that causes the COVID-19 infection has been linked to a variety of illness patterns, from a little cough to potentially lethal pneumonia. As we learn more about this peculiar COVID-19 outbreak, a number of symptoms and problems have been documented; also, new ones are appearing and being reported.

Mucormycosis is an uncommon and severe fungal disease that mostly affects those with weakened immune systems. It is also referred to as zygomycosis or phycomycosis. The most prevalent symptom of this fatal fungal illness is rhinocerebral. Despite having a low incidence rate of between 0.005 and 1.7 cases per million people, there has been a notable increase in its occurrence recently due to the ongoing coronavirus pandemic.[7,8]

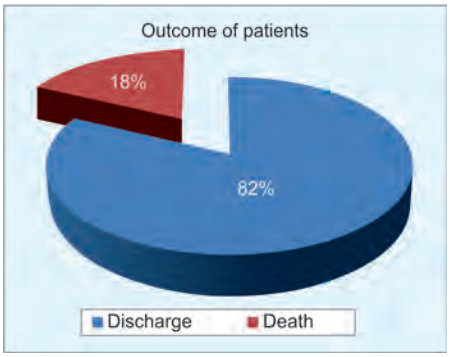

Fig. 1: Distribution of patients according to outcome

A group of 100 patients of mucormycosis following COVID-19 infection admitted to a civil hospital in Rajkot between April 2021 and March 2022 were included in the study using hospital case data.

The clinical features and demographics of our patients matched those seen in other studies. The study's 100 post-COVID mucormycosis patients had a mean age of 57.4, which is similar to the findings of Farghly Youssif et al.'s investigation.[9] Similarly, 57.0% of cases are male patients, while 43.0% are female patients, which is comparable to the data of Farghly Youssif et al. study[9] with 60.6 and 39.4%, respectively. In our study, 38.0% of patients had tobacco smoking as an addiction, which is comparable to Shabana et al.[10] study, where 41.3% of patients had a history of smoking. In our study, 30.0% of patients are known case of DM, which is comparable to the data of Bhattacharyya et al.[11] study, which had 34.6% with DM. About 21.0% of patients had a history of hypertension in our study, which is similar to the data from John et al.[12] study with 22.0% hypertensive patients.

Similar to Mahalaxmi et al.'s[13] work, ours discovered that mucormycosis symptoms initially manifested 30 days following a positive COVID-19 pneumonitis test, which found that 73.7% of symptoms appeared within the 1st month of COVID-19 infection.

In the present study, 72.0% of patients had maxillary sinus involvement and 7.0% had sphenoid sinus involvement, similar to the data from Sharma et al. study,[6] which

Table 6: Comparison of outcome and different variable among COVID-19 infected patients

Variable	*Death (n = 18)*	*Survived (n = 82)*	*χ^2 value*	*p-value*
Steroid used				
Yes	16 (30.2%)	53 (69.8%)	4.059	0.043
No	2 (6.5%)	29 (93.5%)		
Patient presented with DKA				
Yes	11 (75.3%)	4 (24.7%)	36.607	0.000
No	7 (8.2%)	78 (91.8%)		
Blood sugar at admission (mg/dL)				
≤150	2 (2.9%)	67 (97.1%)	47.737	0.000
151–300	6 (68.4%)	13 (31.6%)		
>300	10 (83.3%)	2 (16.7%)		
CT/MRI finding				
Chronic sinusitis	0 (0%)	10 (100%)	23.706	0.000
Fungal sinusitis	11 (13.5%)	71 (86.5%)		
Invasive fungal sinusitis	7 (87.5%)	1 (12.5%)		
Drug used as treatment				
Liposomal amphotericin B	16 (19.7%)	65 (80.3%)	0.372	0.541
Lyophilized amphotericin B	2 (10.5%)	17 (89.5%)		

shows 52.17% maxillary sinus involvement and 21.73% sphenoid sinus involvement.

There were 72% of patients who required oxygen support during COVID infection, which is comparable to Shabana et al.[10] study, which had 73.3% of patients with a history of oxygen support during COVID infection. In our study, 69% of patients had a history of steroid use during COVID pneumonitis, which is comparable to 71% of patients who took steroids as a treatment for COVID in Singh et al.'s study.[3] Three of the study's patients received interleukin-6 (IL-6) inhibitors, such as tocilizumab, which is associated with an increased risk when used to treat people with severe COVID-19. Through a number of different routes, it interferes with innate and adaptive immune responses, causing immunological dysregulation and increasing the susceptibility of patients to invasive fungal infections.

Elevated amounts of free iron are caused by the increased glycosylation of ferritin and transferrin, which decreases their ability to bind iron. By promoting ferritin production, high doses of IL-6 in COVID-19 increase the amounts of free iron. Additionally, endothelial cells are expressing more of the fungal ligand spore coat homolog protein (CotH) and glucose-regulated protein 78 (GRP78), which permits fungal angioinvasion, hematogenous dissemination, and tissue necrosis.[3,14]

In our study, 15% of patients had DKA on presentation, which is similar to 15.9% of DKA patients in the Bhattacharyya et al.[11] study. About 75% of the patients in our study had altered HbA1c levels, which is almost similar to the 70.9% of patients in the Bhattacharyya et al.[11] study who also had altered HbA1c values. 46.0% of patients had a significantly high blood ferritin level, which is almost identical to the findings from the Bhadania et al.[15] study, which indicates that 41.4% of patients have a high ferritin level. Similar to the findings of the Bhadania et al.[15] study, which indicate that 85.0% of patients had a high NLR, indicating a substantial link with mucormycosis, our study's 89.0% of patients had a high NLR.

Jeong et al. conducted a recent comprehensive study of mucormycosis patients in India and around the world and found a 30.7% fatality rate.[16] In our study, 82% of patients survived, and 18% died despite all possible treatments. This data is comparable with Farghly Youssif et al.'s study[9] which shows a 77.2% survival rate and 22.8% deaths in cases of post-COVID mucormycosis.

Opportunistic fungal infections have been associated with a higher likelihood of long-term corticosteroid use. Several immune cells, such as T cells, monocytes, macrophages, polymorph nuclear leukocytes, and T cells, are inhibited by corticosteroids in their function. 46% of patients in the European Confederation of Medical Mycology study had used steroids 1 month prior to receiving a diagnosis of mucormycosis.[17] This was also evident in our study, where 69.0% of patients received steroids in the form of methylprednisolone or dexamethasone.

Conclusion

A rare, dangerous, and frequently fatal infection is mucormycosis. Cases of mucormycosis increased in correlation with immune dysregulation due to COVID-19 and comorbidities, including smoking and DM. Uncontrolled DM was the main risk factor, and using glucocorticoids while treating COVID-19 made it worse. Therefore, this medication should be used carefully throughout the pandemic. The fatality ratio in DKA indicates that high ferritin levels and an acidic environment are also important determinants in the development of fungal angioinvasion. Patients with invasive fungal infections have a worse prognosis than those with chronic sinusitis, suggesting the severity of the infection. Unfortunately, even though there are treatments available, including medication and surgery like FESS, people with mucormycosis still have a high death rate. Due to the high death rate, prompt diagnosis, and appropriate treatment for high-risk patients necessitate a strong index of suspicion.

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ORIGINAL ARTICLE

Prevalence of Celiac Disease in Patients with Nutritional Anemia in Western Part of India

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Abstract

Background: Around 1.6 billion people worldwide are affected by nutritional anemia. A small percentage of nutritional anemia cases are attributed to celiac disease (CeD). However, data on the prevalence of CeD among individuals with nutritional anemia in the Western part of India is scarce.

Patients and methods: Individuals with nutritional anemia were prospectively investigated for the presence of CeD through the detection of immunoglobulin A (IgA) antitissue transglutaminase antibodies (anti-tTG Ab). Those who had a positive antibody result proceeded to have an upper gastrointestinal endoscopy, accompanied by a duodenal biopsy. The diagnosis of CeD was confirmed following Indian guidelines.

Results: A total of 116 patients, including 96 females, were screened, with a mean age of 37 ± 17.8 years. Among them, 19 patients (16.3%) were positive for IgA anti-tTG antibodies. Fifteen of these antibody-positive patients agreed to undergo a duodenal biopsy, which showed villous abnormalities of modified Marsh grade 2 or higher in 11 cases. The overall seroprevalence of CeD was 16.3%, while the biopsy-confirmed prevalence stood at 9.3%. Moreover, an additional four patients (3.4%) were identified as having potential CeD. Chronic diarrhea and short stature emerged as significant predictors of CeD among patients with nutritional anemia.

Conclusion: Even in the Western part of India, approximately one in 10 patients with nutritional anemia have CeD, reflecting similar findings across the country. Consequently, we should screen all patients with nutritional anemia for CeD through antitissue transglutaminase antibody testing. This is especially crucial for those with unexplained, persistent nutritional anemia that does not respond to oral iron therapy.

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Introduction

Celiac disease (CeD) is an immune-mediated disorder that affects the small intestine, triggered by the ingestion of gluten—a protein found in wheat, barley, and rye—in people who are genetically susceptible.[1] Although once thought to be uncommon, CeD exhibits a wide spectrum of clinical manifestations, from cases with no symptoms at all to those with symptoms.[2,3] "classical CeD," characterized by gastrointestinal symptoms, comprises 50–60% of cases, whereas "nonclassical CeD," marked by nongastrointestinal symptoms, makes up 40–50% of these cases.[4] Anemia, short stature, dyspepsia, infertility, or hypertransaminasemia, which are not the usual presentations, can be the sole indicators of CeD, even in the absence of gastrointestinal symptoms, making the clinical diagnosis challenging.[1,4] Due to its varied manifestations, patients with CeD may seek medical attention from healthcare professionals across various specialties other than gastroenterologists or pediatricians. For example, patients may seek care from hematologists (for anemia), endocrinologists for short stature or type I diabetes, or gynecologists for concerns related to infertility.[5] Consequently patients with atypical features without gastrointestinal symptoms are often not screened for CeD.[6]

In 2013, approximately 1.9 billion individuals, representing 27% of the world's population, were affected by anemia.[7] According to the National Family Health Survey released in November 2021, anemia is prevalent among both women and men across all age-groups in India.[8]

Anemia is a common manifestation of CeD. Around 12–69% of individuals with CeD have anemia in Western countries, while as many as 85–90% of patients with CeD have anemia in India.[8–10] In certain instances, iron deficiency might be the sole sign of CeD, even in the absence of diarrhea, making it the most common type of anemia associated with the condition.[4,8–10] A meta-analysis that included 2,998 individuals with iron deficiency anemia, determined that 3.2% (95% CI 2.6–3.9%) of these patients—roughly 1 in 31—were diagnosed with CeD.[11] In a study conducted in India by Kavimandan et al., which included 96 patients with nutritional anemia, 80 patients had iron deficiency anemia, 11 were diagnosed with megaloblastic anemia, and 5 presented with dimorphic anemia. It was further found that 10 patients had CeD. Of these, nine had iron deficiency anemia and one had vitamin B12 deficiency.[12] In another study conducted in Kashmir, which included 161 consecutive patients with iron-deficiency anemia of unclear origin, 13 individuals (8%) were found to have evidence of CeD.[13]

Given the limited data from Western India, our study sought to assess the prevalence of CeD among patients with nutritional anemia at a tertiary care center in this region.

Patients and Methods

We conducted a prospective, cross-sectional study at a tertiary care hospital between January and December 2021. Patients, >12 years of age, with nutritional anemia were recruited. Criteria for anemia was taken as per the World Health Organization (WHO) criteria as males having hemoglobin <13 gm/dL and females having hemoglobin <12 gm/dL.

Patients with other hematological diseases (such as aplastic anemia, thalassemia, hemolytic anemia, and myelodysplasia), advanced malignancies, and chronic conditions (including chronic infectious diseases, chronic renal failure, severe cardiac and respiratory diseases, chronic liver disease, and collagen vascular disease), as well as pregnant patients and those with obvious blood loss (including menorrhagia), were excluded from the study. All of them underwent a complete evaluation for demographics, clinical manifestations, and dietary history. Patients underwent a comprehensive hematological workup, which included complete blood counts, peripheral blood smear analysis, RBC indices, serum iron studies, serum B12 levels, and additional investigations based on clinical indications.

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Screening for Celiac Disease

All patients recruited for this study underwent testing for CeD using the immunoglobulin A (IgA) antitissue transglutaminase antibodies (anti-tTG Ab) conducted by a local commercial laboratory. The anti-tTG Ab value was recorded along with the cutoff value prescribed by the manufacturer.

Upper Gastrointestinal Endoscopy and Duodenal Mucosal Biopsies

Patients with positive IgA anti-tTG antibodies were subsequently asked to undergo an upper gastrointestinal endoscopic examination. During the endoscopy, all findings in the esophagus, stomach, and duodenum were recorded on a case record form. Between four and six biopsy samples were collected from the second portion of the duodenum. Features indicative of CeD, such as scalloping of folds, absence of mucosal folds, a mosaic pattern, and nodular mucosa were noted. Duodenal biopsies were preserved in 10% formalin, and villous abnormalities were graded according to the modified Marsh criteria.[14]

Criteria for the Diagnosis of Celiac Disease

Celiac disease was identified in accordance with the guidelines provided by the Indian Council of Medical Research, which included a combination of clinical manifestations, positive serological findings, along with villous abnormalities classified as modified Marsh grade 2 or 3 (3a, 3b, 3c).[15] Clinical phenotypes of CeD were defined as per Oslo definition, summarized in Table 1.

Treatment

All patients diagnosed with CeD were counseled regarding a gluten-free diet (GFD). All patients were also given hematinic supplements. All necessary diagnostic and therapeutic care was given irrespective of this study.

Statistical Analysis

Data was entered in MS Excel Office 2019 and imported to STATA v12 (College Station, Texas, United States). Laboratory values were classified as normal, high, and low according to normative values. Data with a normal distribution were shown as the mean (±SD), whereas nonnormally distributed data were presented as the median (interquartile range). Categorical variables were described using frequency and percentage. The Chi-squared test and Fisher's exact test were employed to analyze differences in proportions across various sex/CeD categories as suitable. For parametric data, a *t*-test was used, while the rank sum test was applied to nonparametric data to assess statistical significance. Bivariable logistic regression was done for association and to study the predictors of the disease. Penalized logistic regression was employed to calculate the odds ratio for variables excluded from the bivariable regression due to collinearity (where one stratifying group had 0 participants). The association between predictors and CeD was represented as a crude odds ratio. A *p*-value below 0.05 was considered indicative of statistical significance.

Results

Demographic Characteristics

Our study included 116 patients with nutritional anemia, with a mean age of 37.01 ± 17.85 years, and 96 of these patients were women. The most common clinical manifestations among these patients were easy fatigability, weakness, and loss of appetite (Table 2).

Severity of Anemia

Most of the patients, 97 (83.6%) had severe anemia. Majority of the patients (86.2%), both males and females, had a microcytic type of anemia. Macrocytic anemia was seen in 11/116 patients. Normocytic anemia was seen in five patients. Iron deficiency anemia (IDA) was more prevalent than vitamin B12 deficiency anemia (Table 3).

Screening Test for Celiac Disease Using Antitissue Transglutaminase Antibody

We screened all patients for CeD using the IgA anti-tTG antibody test. Among them, 19 patients (16.3%) were positive for IgA anti-tTG antibody, indicating a seroprevalence

Table 1: Clinical phenotypes and terminologies in CeD

Asymptomatic CeD	Often detected on screening of high-risk groups Absence of symptoms at diagnosis
Typical/classical CeD	Symptomatic patients having signs and symptoms of malabsorption
Atypical/nonclassical CeD	Symptomatic patients, with predominant symptoms/signs of other organ involvement and absence of symptoms of malabsorption
Refractory CeD	Persistent or recurrent signs/symptoms of CeD and villous atrophy despite strict adherence to GFD for >12 months
Potential CeD	Subjects mostly detected on screening of high-risk groups Have a positive celiac specific serology with normal small intestinal histology (modified Marsh grade: 0–1)
CeD autoimmunity	Positive anti-tTG or anti-EMA on at least two occasions and small intestinal biopsy have not been done

Table 2: Clinical manifestations

Clinical symptoms	*Female (n = 96)*	*Male (n = 20)*	*Total (n = 116)*
Easy fatiguability	90 (93.75%)	16 (84.21%)	106 (91.38%)
Weakness	87 (90.63%)	16 (84.21%)	103 (88.79%)
Loss of appetite	53 (55.21%)	9 (47.37%)	62 (53.45%)
Heart burn	26 (27.08%)	2 (10.53%)	28 (24.14%)
Abdominal pain	25 (26.04%)	1 (5.26%)	26 (22.41%)
Nausea	21 (21.88%)	3 (15.79%)	24 (20.69%)
Chest pain	21 (21.88%)	1 (5.26%)	22 (18.97%)
Oral ulcer	12 (12.50%)	4 (21.05%)	16 (13.79%)
Short stature	8 (8.33%)	2 (10.53%)	10 (8.62%)
Weight loss	6 (6.25%)	2 (10.53%)	8 (6.90%)
Bleeding manifestation	6 (6.25%)	1 (5.26%)	7 (6.03%)
Chronic diarrhea	4 (4.17%)	2 (10.53%)	6 (5.17%)
Fever	2 (2.08%)	1 (5.26%)	3 (2.59%)

Table 3: Type of anemia

Type of anemia	*Female*	*Male*	*Total*
Iron deficiency anemia	64 (66.7%)	14 (70%)	96 (82.7%)
Vitamin B12 deficiency	12 (12.5%)	1 (5%)	13 (11.21%)
Mixed deficiency	4 (4.2%)	3 (15%)	7 (6.03%)
Total	96	20	116 (100%)

of CeD in patients with nutritional anemia at 16.3%. The anti-tTG Ab levels were mildly positive (2–5 times the upper limit of normal) in 15 patients and strongly positive (>10 times the upper limit of normal) in four patients (Table 4).

Upper Gastrointestinal Endoscopy in Patients Who were Seropositive for Celiac Disease

All 19 serological-positive patients were requested to undergo an upper gastrointestinal endoscopic examination, and 15 of them complied. Among these 15 patients, 7 had normal duodenal folds, 6 exhibited scalloping of the duodenal folds, 1 had atrophic folds in the second part of the duodenum (D2), and 1 displayed nodularity of the duodenal folds. Duodenal biopsies were obtained from all 15 patients.

Histological Evaluation of the Duodenal Biopsies

Eleven patients exhibited villous abnormalities, with 1 patient with Marsh grade 2 and 10 patients with Marsh grade 3 abnormalities (Marsh 3a: three patients, Marsh 3b: six patients, Marsh 3c: one patient). Additionally, four patients (3.4%) had villous abnormalities classified as modified Marsh grade 1, and none had Marsh grade 0.

Prevalence of Celiac Disease in Patients with Nutritional Anemia

Among the 116 patients with nutritional anemia who were screened for CeD, 19 were positive for anti-tTG Ab, indicating a seroprevalence of 16.3%. Eleven patients exhibited villous abnormalities classified as modified Marsh grade 2 or higher, meeting the criteria for CeD, which suggests a prevalence of 9.4%. Additionally, in four patients (3.4%) with anemia and a positive anti-tTG Ab, intestinal biopsies revealed villous abnormalities of modified Marsh grade 1, indicating a diagnosis of potential CeD, resulting in a prevalence of 3.4% for potential CeD in this cohort. Four patients with anemia had a positive anti-tTG Ab but were unable to undergo endoscopic examination. These patients were labeled as having CeD autoimmunity and are very likely to have CeD, given their symptomatic anemia (Fig. 1).

Predictors of Celiac Disease

A significant association was observed between chronic diarrhea and short stature with CeD (*p*-value 0.011 and 0.007, respectively). Chronic diarrhea and short stature can be significant predictors of CeD. The severity and type of anemia were not found to have a significant association with CeD (Table 5).

Hematological Parameters in Patients with Positive Anti-tTG Ab

The mean hemoglobin in patients with positive anti-tTG was 6.2 gm/dL. About 15/19 (78.9%) patients had iron deficiency anemia, 2 (10.5%) had vitamin B12 deficiency, and 2 (10.53%) had a mixed deficiency, suggesting that iron deficiency is the predominant type of anemia in CeD. Majority of the patients in this group (16/19, 84.2%) had severe anemia. In patients with IDA, we normally see thrombocytosis, but in 5/19 (26.3%) patients, thrombocytopenia was seen.

Discussion

In our study, the seroprevalence of CeD among the 116 patients with nutritional anemia was 16.3%, whereas the biopsy-confirmed prevalence stood at 9.3%. Chronic diarrhea and short stature were identified as key predictors of CeD in these patients. The prevalence of CeD in anemic patients observed in this study is consistent with

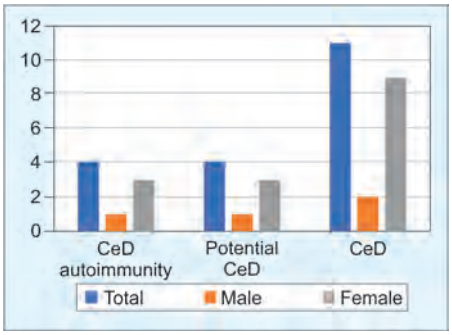

Fig. 1: Prevalence of CeD in patients with nutritional anemia

Table 4: Screening test for CeD, antitissue transglutaminase antibody

		Male n (%)	*Female n (%)*	*Total n (%)*
Anti-tTG Ab	Negative	16 (80%)	81 (84.4%)	97 (83.6%)
	Positive	4 (20%)	15 (15.6%)	19 (16.4%)
Fold rise of IgA anti-tTG Ab				
	Mean fold rise			
	1–2	2 (10.5%)	6 (6.3%)	8 (6.96%)
	2–5	1 (5.3%)	6 (6.3%)	7 (6.09%)
	5–10	0 (0%)	0 (0%)	0 (0%)
	>10	1 (5.3%)	3 (3.1%)	4 (3.48%)

Table 5: Predictors of CeD

Variables		*Crude or (95% CI)*	*p-value*
Age		0.971 (0.926–1.019)	0.232
Smoker		2.250 (0.536–9.450)	0.268
Alcohol consumption		0.600 (0.072–5.034)	0.638
Symptoms	Abdominal pain	1.337 (0.328–5.450)	0.685
	Chronic diarrhea	12.75 (2.205–73.714)	0.004
	Loss of appetite	1.591 (0.439–5.761)	0.479
	Heartburn	0.675 (0.137–3.328)	0.629
	Chest pain	0.944 (0.189–4.714)	0.944
	Easy fatigability	0.937 (0.107–8.180)	0.953
	Nausea	1.500 (0.366–6.147)	0.573
	Fever*	1.273 (0.062–26.228)	0.876
	Weight loss	3.667 (0.644–20.884)	0.143
	Oral ulcer	1.444 (0.282–7.389)	0.659
	Short stature	**9.429 (2.148–41.388)**	**0.003**
Severity of anemia*			
	Normal	Reference	
	Mild	0.818 (0.021–32.266)	0.915
	Moderate	0.263 (0.008–8.305)	0.448
	Severe	0.357 (0.013–9.465)	0.538
Type of anemia*	Microcytic hypochromic	Reference	
	Macrocytic	0.338 (0.019–6.133)	0.464
	NCNC	0.708 (0.037–13.646)	0.819

*Penalized logistic regression performed; NCNC, normocytic normochromic anemia; bold signifies statistical significance

previously published data from other regions globally.[10,11]

Varma et al. from Chandigarh found that 58% (11/19) of patients with refractory iron deficiency anemia were diagnosed with CeD.[16] In a separate study by Mandal et al., 9 of 504 (1.8%) patients with iron deficiency anemia, Mandal et al. were diagnosed with CeD based on duodenal biopsy results.[17] Research conducted by Unsworth et al., which included 483 patients with IDA, reported a CeD prevalence rate of 4.5%.[18] Similarly, Ransford et al. studied 484 patients with IDA and found a CeD prevalence rate of 9%.[19]

Although 50 percent of the patients with CeD in this study had a history of diarrhea, anemia emerged as the primary symptom that led them to seek medical attention, rather than diarrhea. If attending physicians do not recognize that CeD can present as anemia without the classical symptoms, the diagnosis may be overlooked. Studies suggest that about 10% of cases of unexplained nutritional anemia are due to CeD. Our findings align with this, as 11 out of 116 patients (9.4%) with nutritional anemia were diagnosed with CeD. Therefore, CeD should be considered a potential cause of unexplained nutritional anemia. This raises the question of why these individuals went for such long periods even after consulting numerous physicians. Several factors contribute to the underrecognition of CeD, including the misconception that it is a rare condition mainly affecting children, along with the absence of classic symptoms in adults.

Anemia is a significant public health issue, affecting approximately 27% of the global population.[7] The proportion of people with anemia remains significantly higher in India, with the National Family Health Survey reporting that 57% of women and 25% of men are affected.[20]

In an ideal scenario, every patient with anemia would undergo serological screening for CeD. However, given the large population and the high prevalence of anemia in resource-limited countries like ours, screening every individual with anemia may not be economically feasible. In this study, independent predictors of CeD included a younger age at anemia onset, an extended duration of the condition, and the occurrence of diarrhea. The area beneath the receiver operating characteristic (ROC) curve measured 0.86, indicating that these three characteristics could reliably predict CeD in 86% of patients with nutritional anemia. Therefore, screening for CeD should be considered in patients with these predictive factors and in those with unexplained, long-standing nutritional anemia that is unresponsive to oral iron therapy.

This is the first study to explore the prevalence of CeD in patients with anemia in the Western part of India. The diagnosis of CeD was made using standard criteria, with the majority of patients undergoing upper gastrointestinal endoscopy and biopsy. We encompassed the full spectrum of CeD, including patients with anemia exhibiting CeD autoimmunity, potential CeD, and confirmed CeD.

While our initial aim was to include 160 patients with anemia, we managed to recruit only 116 due to the COVID-19 pandemic and the resulting diversion of healthcare resources to COVID-19 patient care. Furthermore, the response to a GFD could not be assessed in all patients because of the ongoing pandemic.

In conclusion, approximately 1 in 10 patients with nutritional anemia has CeD even in the Western part of India, as seen elsewhere in India. Therefore, all patients with nutritional anemia should be screened for CeD using antitissue transglutaminase antibody, especially those with unexplained long-standing nutritional anemia unresponsive to oral iron therapy.

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ORIGINAL ARTICLE

Prescribing Pattern and Effectiveness of Antihypertensives in Patients Suffering from Hypertension to Diabetes Mellitus with and without Compelling Indications in Tertiary Care Hospital

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Abstract

Aim: The prevalence of hypertension (HTN) and diabetes mellitus (DM) is increasing worldwide, and their coexistence is well-documented. Managing both conditions is challenging due to shared pathophysiological mechanisms and the need to balance blood pressure (BP) control with glycemic management. The objective of this protocol was to consider the prescribing pattern and effectiveness of antihypertensive agents in hypertensive and diabetic patients, with and without compelling indications, at tertiary care hospital.

Materials and methods: A prospective, observational study was conducted over 6 months in total 226 diabetic hypertensive patients from a tertiary care hospital. Demographic and medication history data were collected using a self-designed patient profile form. Descriptive statistics were used to analyze the data, and the results were expressed as percentages or means with standard deviations.

Results: A total of 226 patients were included in the study, with 62% males and 38% females. 73% of patients were classified as stage 1 and 27% as stage 2 HTN. Among the prescribed antihypertensive agents, β-blockers (BBs) were the most prescribed, followed by angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), diuretics, and other classes. Combination therapy was predominantly used, with dual-drug therapy being the most common. Compelling indications for antihypertensive treatment included ischemic heart disease (IHD) (38.49%), chronic kidney disease (CKD) (12.38%), and stroke (6.63%). The choice of antihypertensive agents varied based on the presence of compelling indications, with BBs and ARBs being frequently prescribed. BP control was achieved in 93% of the patients, with 85.96% of patients with HTN + DM, and 82.84% of patients with additional compelling indications having controlled BP.

Conclusion: Therefore, it can be concluded that the antihypertensive medications prescribed to the study adhered to guidelines and that long-term use of these combinations proved to be more effective, safe, and well-tolerated for patients with HTN and DM with or without convincing indications. Adopting the best approach to managing HTN in people with diabetes is crucial for ameliorating patient outcomes and enhancing overall quality of life.

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Introduction

Diabetes mellitus (DM) and hypertension (HTN) appear as key global health concerns, with both conditions serving as significant risk factors for cardiovascular diseases (CVD) and cerebrovascular diseases. The incidence of DM is rising rapidly across the globe. The World Health Organization (WHO) reports that the global occurrence of DM in adults was approximately 4.0% in 1995 and is expected to grow to 5.4% by 2025. This increasing trend suggests that the individuals with DM worldwide are anticipated to grow from 135 million in 1995 to 300 million by 2025.[1] Moreover, HTN is a widespread condition, impacting approximately one billion individuals globally. Furthermore, projections suggest that by the year 2025, the number of hypertensive adults worldwide could reach as high as 1.56 billion.[2]

The coexistence of DM and HTN is well-documented. There is a clear correlation between lifestyle changes and the rising prevalence of both conditions. The etiology behind this association can be attributed to shared pathophysiological mechanisms, including insulin resistance, oxidative stress, and endothelial dysfunction. Effectively managing DM and HTN presents challenges at multiple levels, including the patient, healthcare provider, and healthcare system. Addressing these challenges is crucial for improving the overall management and outcomes of individuals with both DM and HTN.[3]

Antihypertensive medications are pivotal in the treatment of HTN, aiming to lower blood pressure (BP) and lessen the threat of CVD. However, the choice of antihypertensive agent in diabetic hypertensive patients should be guided by its efficacy in BP reduction without adversely affecting glycemic control. The selection of appropriate antihypertensives becomes a delicate balance, as some medications may worsen glucose levels, potentially leading to suboptimal diabetes management.[4]

Various antihypertensive medications, such as angiotensin-converting enzyme inhibitors (ACEIs), diuretics, β-blockers (BBs), calcium channel blockers (CCBs), and angiotensin receptor blockers (ARBs) are available for the management of HTN.[5] The choice of drugs should always include an ACE inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) if ACEI cannot be tolerated and should usually include a diuretic. If additional therapy is needed, a CCB, BB, or α-blocker may be used. The first-line approach in managing high BP in diabetic hypertensive individuals involves the use of ACEIs. While ACEIs can be used alone to lower BP, their effectiveness is significantly enhanced when combined with a thiazide-type diuretic or other antihypertensive medications.[6]

For diabetic hypertensive individuals, β-1 selective BBs offer benefits as part of a multidrug therapy regimen. These medications have fewer adverse effects such as hypoglycemic unawareness and decreased sensitivity compared to their nonselective counterparts. In the context of controlling BP, CCBs can be particularly

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useful for diabetic hypertensive patients, especially when used in combination therapy. They were shown to reduce CVD events in diabetics.[7,8]

Understanding the prime therapy of HTN in individuals with diabetes is vital for improving patient outcomes, reducing the burden of complications, and enhancing overall quality of life. Thus, in this regard, the current study was carried out with the objective to study prescribing pattern and effectiveness of antihypertensives in patients suffering from HTN with DM, with and without compelling indications in a tertiary care hospital. This study will also aid the physician in realizing the effectiveness of various antihypertensives, making a faster decision related to therapy, to provide better treatment to the patients, and thereby restore their health.

Materials and Methods

Study Design and Ethical Approval

A prospective, observational study was conducted for a duration of 6 months (from January 2023 to June 2023) in the diabetic hypertensive patients, enrolled from inpatient department (IPD) of medicine in Aditya Birla Memorial Hospital, Pune, Maharashtra, India. The study protocol was approved by the ethics committee of the hospital. The demographic and medication history of the diabetic hypertensive patients was collected through a self-designed patient profile form to study the influence of various antihypertensives on BP and glucose level, to evaluate which therapy (mono/dual/triple therapy/poly-drug therapy) is more effective in controlling BP and to evaluate the effectiveness of antihypertensive agents in patients with or without other compelling indications like diabetes/stroke/myocardial infarction (MI)/chronic kidney disease (CKD).

Inclusion Criteria

- Patients between the age of 18 and 80 years.
- Patients having HTN with diabetes.
- Diabetic hypertensive patients having other comorbidities like ischemic heart disease (IHD)/stroke/CKD/HFrEF.
- Patients willing to participate in the study and those who have signed the informed consent form.[9–11]

Exclusion Criteria

- Patients below 18 years of age and above 80 years of age.
- Pregnant and lactating women.
- Patients on chemotherapy.
- Patients with sepsis.

Data Collection, Assessment, and Analysis

Descriptive statistics was used to summarize the data which included demographic characteristics (like age at onset, gender, etc.), antihypertensive agents used with their dose, frequency, duration, and different etiologic factors. Microsoft Excel was used to calculate and interpret the data, all the values were expressed in percentages, mean, and standard deviation.

Results

The study included 226 patients to evaluate the efficacy of antihypertensive treatments in diabetic hypertensive patients. Out of 226 patients included, 62% of patients were males and 38% were females. The majority of patients were in the 60–80 years of age-group, followed by 45–60 years, 30–45 years, and only 1% of patients belong to the age-group of 18–30 years (Table 1).

The social history of the patients was analyzed. It was observed that although most of the patients were found to be nonalcoholic, nonsmokers, and nontobacco chewers, their sedentary lifestyle was responsible for the diabetic hypertensive condition. Similarly, diet restrictions analysis revealed that most patients were on salt and sugar-restricted diets, followed by salt-restricted diets, sugar-restricted diets, mixed diets, soft diets, and only 1% of patients were consuming a normal diet (Fig. 1).

As per American Heart Association, the enrolled patients were classified as suffering from stage 1 and stage 2 HTN. Out of 226 patients, 73% patients were suffering from stage 1 HTN and 27% patients were suffering from stage 2 HTN.

It was observed that BBs were found to be most prescribed antihypertensives followed by ARBs, CCBs, ACEIs, diuretics and α-1 blockers, and centrally acting α-2 agonists, while direct arterial vasodilators were least prescribed. Among ACEIs, the most prescribed drug was ramipril followed by enalapril. Among ARBs, telmisartan was the most frequently used drug followed by valsartan, losartan, and olmesartan. Amlodipine was the most widely prescribed drug among CCBs followed by cilnidipine, nifedipine, and nicardipine, and azelnidipine was least prescribed. Among the BBs, metoprolol was the most frequently prescribed antihypertensive drug followed by bisoprolol, while labetalol and nebivolol, atenolol, carvedilol, and propranolol were least prescribed. Hydrochlorothiazide was the most frequently used thiazide diuretic followed by chlorthalidone. The results are depicted in Figure 2.

Combination therapy provides greater antihypertensive effectiveness. Hence, we

Table 1: Demographic profile of the study population

Age range (years)	*Males*	*Females*	*Total*	*Percentage (%)*
18–30	2	0	2	1
30–45	5	5	10	5
45–60	34	21	55	24
60–80	99	60	159	70
Total	140	86	226	100

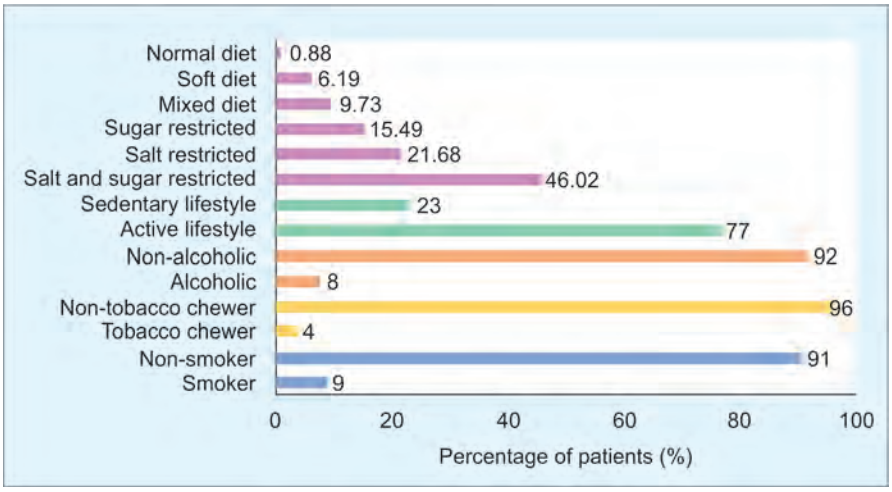

Fig. 1: Social and diet history of patients

analyzed the enrolled patient population for the type of combination drug therapy prescribed. In the present study, it was observed that dual (43.81%) and mono (38.94%) drug therapy was mostly prescribed while triple and poly-drug therapy was prescribed occasionally. Among the 39% of patients who were prescribed with mono-drug therapy, ARBs and BBs were the most prescribed antihypertensive drugs, followed by CCBs. While ACEIs, direct arterial vasodilators and centrally acting α-2 agonist were prescribed intermittently. Among the 44% of patients prescribed with dual-drug therapy, the most prescribed drug combination was ARB + BB (28.28%) and ARB + CCB (26.26%), followed by CCB + BB (21.21%), ACEI + BB (8.08%), BB + α-1 blockers (7.07%). ACEI + CCB, ARB + diuretics, ARB + α-1 blockers, and BB + diuretics were prescribed occasionally. Among the 15% of patients prescribed with triple-drug therapy, ARB + BB + CCB (47.06%) was the single most frequently prescribed triple-drug combination followed by ARB + BB + diuretics (17.65%). Among the 2% of patients prescribed with poly-drug (>3 drugs) therapy, ARB + CCB + BB + diuretics (60%) was the single most prescribed combination drug therapy (Fig. 3).

Hypertension may occur in association with many other pathological conditions, namely HF, IHD, CKD, recurrent stroke, etc., in which there are convincing symptoms for use of a particular treatment. In the present study, we investigated patients diagnosed with HTN with DM for such associated compelling indications. Among the patient population with HTN + DM, the most common compelling indication was IHD, followed by CKD, stroke, and CKD–IHD (Fig. 4).

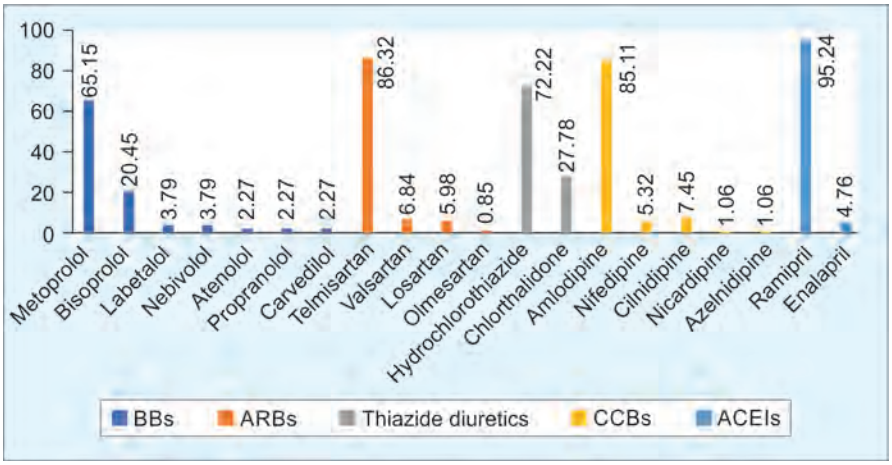

Fig. 2: Most prescribed antihypertensive agents

Drug treatment in such patients with compelling indications should be focused on tailored drug management strategies for specific compelling indications as well as HTN. It was observed that among the 25% of patients diagnosed with only HTN + DM, ARBs (57.89%) were the commonly used drugs followed by BBs (54.39%), CCBs (36.84%), ACEIs (10.53%). Diuretics (7.02%) and α-1 blockers (3.51%) were prescribed very occasionally. Among the 38% of patients diagnosed with HTN + DM + IHD, BBs (68.96%) and ARBs (51.72%) were the most prescribed drugs, followed by CCBs (31.03%) and ACEIs (16.09%). Diuretics (10.34%), α-1 blockers (3.45%), and direct arterial vasodilators (1.15%) were prescribed less frequently. Among the 12% of patients diagnosed with HTN + DM + CKD, BBs (64.29%) were the most frequently used drugs followed by CCB (46.43%), ARB and α-1 blockers (28.57%), centrally acting α-2 agonist (17.85%), and ACEI (7.14%). Among the 6.6% of patients diagnosed with HTN + DM + stroke, ARBs and CCBs (73.73%) were the most frequently used drugs followed by BB (46.66%) and diuretics (13.33%). The results are depicted in Figure 5.

With the main aim to study effectiveness of antihypertensives in patients suffering from HTN + DM with and without compelling indications, control of HTN was defined as per standard treatment guidelines.[9] It was observed that, out of 226 patients, BP was found to be controlled in most patients with HTN + DM, as well as HTN + DM with additional compelling indications. Further, it was revealed that, among patients receiving mono-drug therapy or dual-drug therapy, better BP control was observed as compared

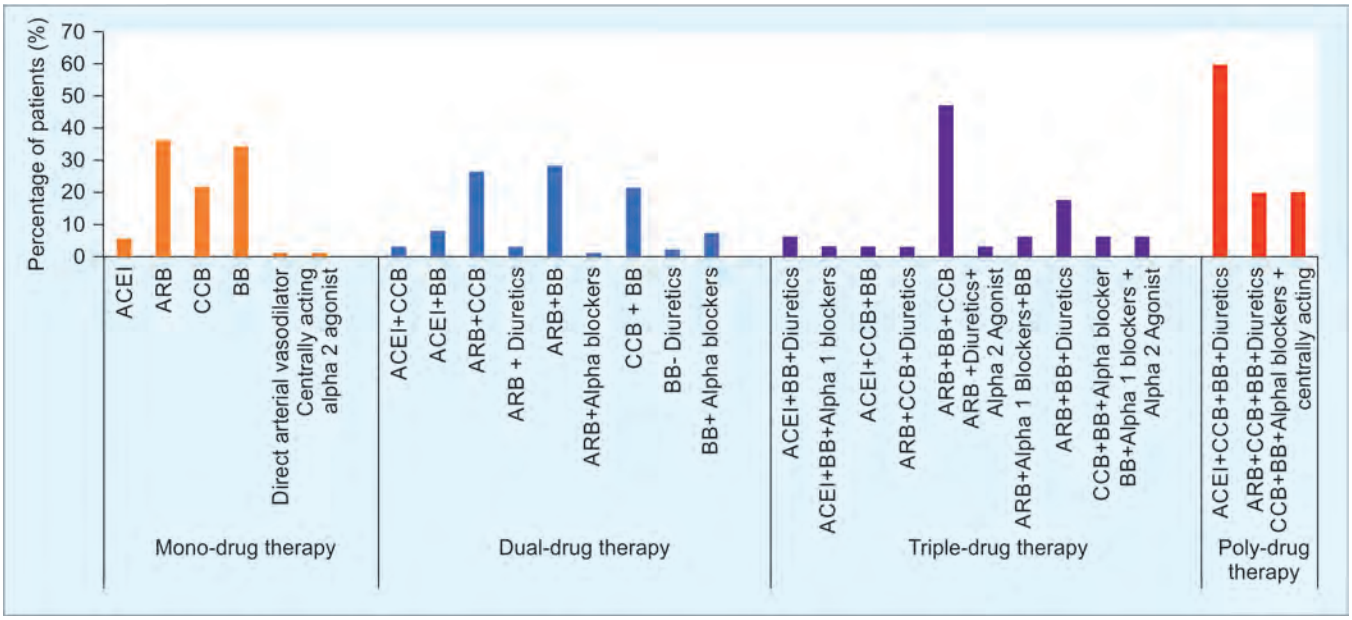

Fig. 3: Most prescribed drug combination therapy

to triple-drug therapy or multi-drug therapy. Furthermore, all patients in the 18–30 years age-group had their BP under control. For other age-groups, >80% of patients had controlled BP. These results indicate that BP control rates varied across different age-groups, with generally higher rates of control observed in younger age-groups (Fig. 6).

The choice of antihypertensive agent in diabetic hypertensive patients should lower BP without loss of blood glucose control. Hence, we evaluated 226 patients overall for blood glucose control and it was found to be controlled in 80% of patients and uncontrolled in 20% of patients.

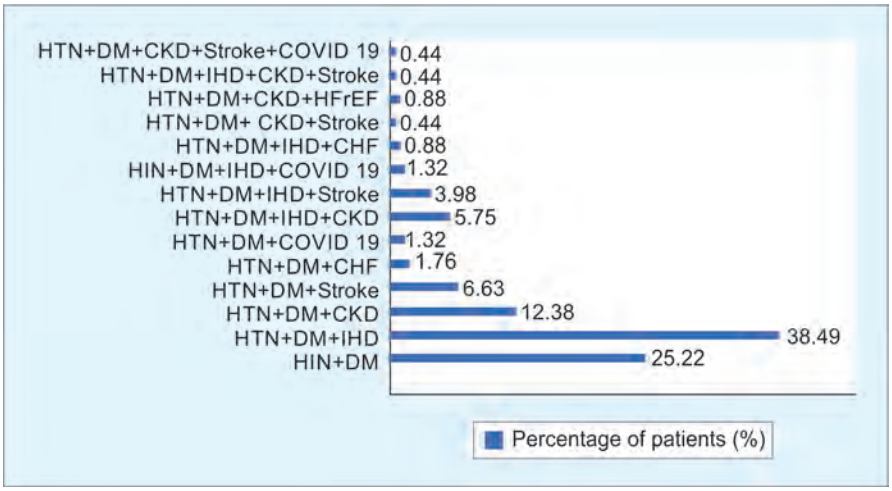

Fig. 4: Compelling indications in patients with HTN + DM

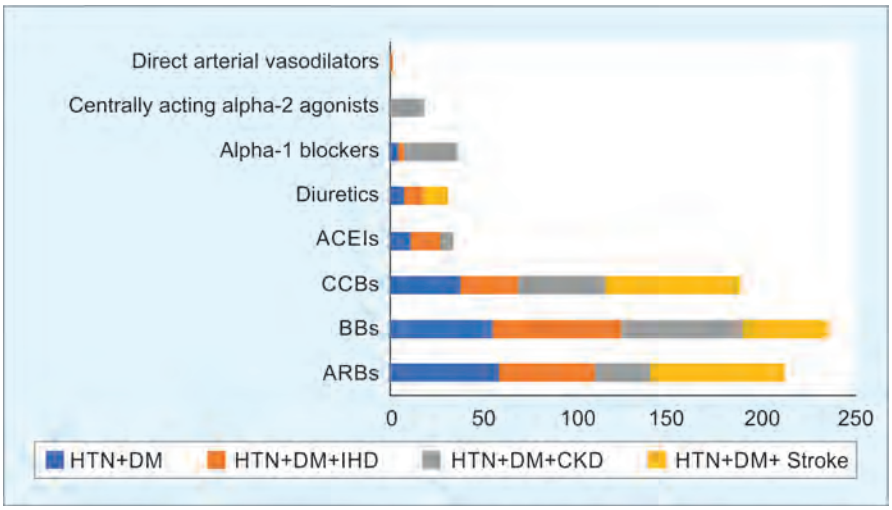

Fig. 5: Drug therapy in compelling indications in patients with HTN + DM

Discussion

The aim of current study was to explore the prescribing pattern and efficacy of antihypertensive medications in patients with both HTN and DM, with and without compelling indications. The study included a diverse population of patients diagnosed with both HTN and DM. The prescribing pattern of antihypertensive medications was assessed, focusing on the utilization of different drug classes. Additionally, the effectiveness of these medications was evaluated by observing BP and blood glucose control.

The findings of this study provide valuable insights into the demographic characteristics of the patients enrolled to assess the effectiveness of antihypertensive therapy in diabetic hypertensive individuals. Numerous studies consistently indicate that males experience a higher occurrence of HTN compared to females, at least until the age of 60. A rise in BP with aging is commonly associated with alterations in arterial and arteriolar stiffness. The higher prevalence rates of HTN in males compared to females can be attributed to several factors including biological, genetic, hormonal, behavioral, and sociocultural influences.[12,13] The results of current study were aligned with the incidence rates of HTN, which tend to be higher in males compared to females.

Strong evidence demonstrates that modifiable risk factors, including alcohol consumption, body mass index (BMI), cigarette smoking, poor diet, and physical inactivity, contribute to over two-thirds of

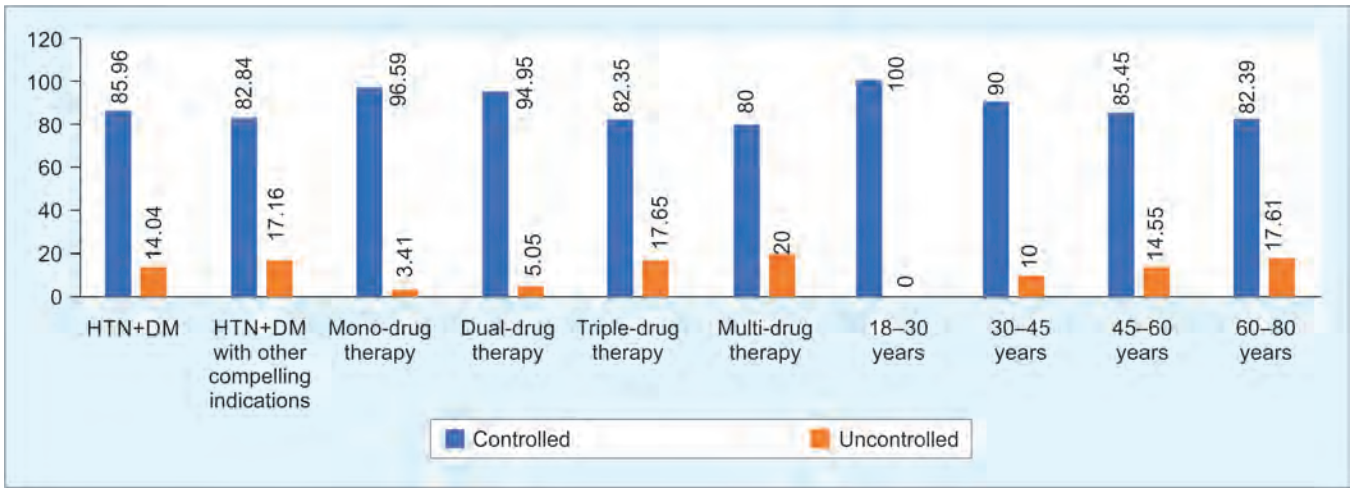

Fig. 6: Blood pressure control in patients suffering from HTN + DM with and without compelling indications with respect to age-group and combination drug therapy

the incidence of cancer, CVD like HTN, chronic respiratory diseases, and diabetes.[14] Lifestyle analysis of the patients included in the present investigation is aligned with the evidence till date as revealed by more hypertensive patients having a sedentary lifestyle. Diet analysis revealed most patients on salt and sugar-restricted diets. However, social history of the patients appeared controversial as more patients were nonalcoholic, nonsmokers, and nontobacco chewers. Thus, it can be concluded that most diabetic hypertensive patients in the present study are associated with physical inactivity and unhealthy diet, which are modifiable risk factors to prevent complications.

The three main preferences for antihypertensive treatment in most patients are an ACEI (or ARB), a calcium channel blocker (CCB), or a thiazide diuretic (preferably a thiazide-like diuretic).[15] In the current study patient population, BBs were found to be the most prescribed class, followed by ARBs, CCBs, ACEIs, diuretics, α-1 blockers, centrally acting α-2 agonists, and direct arterial vasodilators. It has been suggested that BBs should not be used as first drug of choice in patients above 60 years if there are no compelling indications.[16] However, BBs are recommended for patients who have experienced an MI within the past 3 years.[15] In the study population with HTN + DM, the most common compelling indication was IHD, which rationalizes BBs as the most prescribed drug in study population.

All classes of drugs, namely CCBs, ACEIs/ARBs, diuretics, BBs are roughly equivalent in their effectiveness at lowering BP and improving results. However, BBs have been linked to a lower level of protection against strokes. Considering factors such as availability and affordability, the recommended antihypertensive options include amlodipine (a long-acting calcium channel blocker), enalapril or lisinopril (ACEIs), low-dose hydrochlorothiazide (a thiazide diuretic), and if necessary, losartan (a cost-effective ARB).[17]

Among ACEIs, ramipril was the most prescribed drug, followed by enalapril. This finding is supported by clinical evidence demonstrating the efficacy of ramipril. Amlodipine was the most widely prescribed CCB, consistent with its status as a first-line agent for HTN management due to its efficacy and tolerability. Hydrochlorothiazide emerged as the most frequently used thiazide diuretic, reflecting its established role in BP control. Telmisartan was found to be the most frequently used medication among ARBs. These results align with the effectiveness and safety profiles of telmisartan as mentioned in the 2019 Indian guidelines for hypertension-IV (IGH-IV) guidelines,[18] which recommend telmisartan to be used as antihypertensive agent to manage high BP in patients with HTN, DM, and metabolic syndrome.

Poor regulation of BP with mono-drug therapy, with an initial low dose necessitates combining additional drug to existing therapy.[19] Combination therapy is better than mono-drug therapy to achieve target BP. Besides, combination drug therapy helps to achieve expected BP reduction, that too at lower doses of each drug reducing dose-dependent adverse effects. Monotherapy typically targets one or, at most, two mechanisms involved in HTN. In contrast, using a combination of drugs enables the treatment to address multiple hypertensive mechanisms simultaneously providing an antihypertensive effect of 2–5-folds more than that achieved by monotherapy. Combining ACEIs or ARBs with CCBs is another commonly used combination in patients with HTN and DM. This combination provides additional BP-lowering effects and may have benefits for cardiovascular and renal protection.[15,20–22] In the present study, it was observed that dual-drug therapy was mostly prescribed than mono-drug therapy resulted in controlled BP. The results are consistent with the guidelines led by American College of Cardiology (ACC) and European Society of Cardiology (ESC).

Most hypertensive patients receiving mono-drug therapy initially need combination therapy in future for BP regulation. Therefore, beginning treatment with a medication that is part of an optimal two-drug combination is a more straightforward approach than starting with a thiazide diuretic alone. This initial strategy avoids the need to discontinue the thiazide and later add a calcium channel blocker along with an ACEI (or ARB) when a two-drug regimen becomes necessary.[19] Accordingly in the present study population, the most prescribed two drug combinations were ARB + BB, ARB + CCB, and CCB + BB and triple-drug combination was ARB + BB + CCB, of which ARB and CCB were the main choices for antihypertensive drug therapy in most patients and BBs are indicated in patients with IHD.

The coexistence of HTN and DM greatly elevates the chance of CVDs, such as MI, strokes, and congestive heart failure. The combination of these conditions leads to accelerated atherosclerosis and damage to blood vessels. These conditions have a synergistic effect, leading to increased morbidity and mortality. Several studies have highlighted the strong association between HTN, diabetes, and CVD.[23,24] HTN and DM are the foremost reasons for CKD and end-stage renal disease (ESRD). The combination of these conditions accelerates the progression of renal dysfunction. Numerous studies have demonstrated the high prevalence and adverse impact of CKD and ESRD in individuals with HTN and diabetes.[25] Diabetic retinopathy and other eye disorders, such as glaucoma, are commonly seen in patients with HTN and DM. These conditions can lead to visual impairment and blindness. Research has consistently reported the association between HTN, diabetes, and retinopathy or other ocular complications.[26] HTN and diabetes are significant contributors to stroke and other CVDs. The combination of these conditions increases the likelihood of cerebrovascular events and has a negative impact on patient outcomes.[27] These comorbidities significantly affect the management and prognosis of individuals with HTN and diabetes. It is essential for healthcare providers to consider and effectively manage these comorbidities to provide comprehensive care to patients with HTN and diabetes. The findings from the current study population are coherent with these previous reports. The most common compelling indication was found to be IHD, followed by CKD, stroke, and CKD–IHD.

β-blockers have proven benefits in the management of IHD, including stable angina and after MI (heart attack). They help decrease myocardial oxygen mandate by diminishing heart rate and contractility, thereby improving myocardial perfusion and reducing the frequency and severity of angina episodes. BBs also have antiarrhythmic properties and can prevent abnormal heart rhythms associated with IHD. BBs have been demonstrated to lower the risk of cardiovascular complications, in patients with HTN, diabetes, and IHD.[15] ARBs have demonstrated cardioprotective effects in patients with IHD. They help reduce the workload on the heart by decreasing systemic vascular resistance and improving coronary blood flow. ARBs have been shown to decrease the threat of heart attack, stroke, and heart failure, in patients with HTN, DM, and IHD.[28] Individuals suffering with HTN and DM are at higher risk of developing CKD. ARBs have been shown to have renoprotective effects by reducing intraglomerular pressure, decreasing proteinuria, and reducing the advancement of CKD. They are mainly beneficial in patients with both HTN and diabetic nephropathy.[29] In the current study, in relation to coexisting compelling indication, BBs were the most prescribed drugs in patients diagnosed with HTN + DM + IHD. BBs were the most frequently used drugs followed by CCBs and ARBs in patients diagnosed with HTN + DM + CKD and in patients diagnosed with HTN + DM + stroke, ARBs and CCBs were the most frequently used drugs followed by BBs.

Overall, >80% of the total patient population had controlled BP, and only <20% had uncontrolled BP with the prescribed antihypertensive therapies, which were as per guidelines. In addition, overall blood glucose was found to be controlled in 80% of patients and uncontrolled in 20% of patients.[15,17] In conclusion, the antihypertensive medications prescribed to the study group adhered to established guidelines. Long-term use of these drug combinations was found to be more effective, safe, and well-tolerated for patients with HTN and DM, whether or not there were additional compelling indications.

Conclusion

Diabetes mellitus and HTN are significant global health concerns and important risk factors for CVD. The incidence of both DM and HTN is growing globally. Managing these conditions are challenging due to common pathophysiological mechanisms and the need to balance BP control along with glycemic control.

The main objective of this study is to estimate the prescribing pattern and effectiveness of antihypertensive medications in diabetic hypertensive patients with and without compelling indications. The results showed that the most prescribed antihypertensive agents were BBs, followed by ARBs, CCBs, ACEIs, diuretics, and other classes of drugs. Among ACEIs, ramipril was the most prescribed, and among ARBs, telmisartan was the most frequently used. Amlodipine was the most prescribed CCB, and metoprolol was the most frequently prescribed BB. Hydrochlorothiazide was the most used diuretic. Combination therapy was common, with dual-drug therapy being the most prescribed.

Ischemic heart disease, CKD, and stroke were the most common compelling indications for treatment in a significant number of patients. The choice of antihypertensive agents varied depending on the compelling indication. ARBs and BBs were commonly prescribed in patients with HTN + DM, while BBs and ARBs were frequently prescribed in patients with HTN + DM + IHD. BBs and CCBs were commonly used in patients with HTN + DM + CKD, and ARBs and CCBs were frequently prescribed in patients with HTN + DM + stroke.

Overall, 83.62% of the patients had controlled BP, while 16.37% had uncontrolled BP. The study suggested that the selection of antihypertensive agents must be tailored to the individual needs, considering the presence of diabetes, compelling indications, and the impact on BP and glycemic control.

The results highlight the importance of individualized treatment approaches in managing HTN in diabetic patients. The findings suggest that a combination therapy approach, including BBs and ARBs, is commonly employed and can successfully regulate BP in this patient population. However, further research is needed to evaluate the long-term effects and safety of these medications in diabetic patients. Understanding the ideal therapy of HTN in individuals with DM is crucial for refining patient follow-up, decreasing problems, and augmenting overall quality of life.

Acknowledgments

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ORIGINAL ARTICLE

Renal Biopsy Registry from a Single Center in India: 20-year Experience

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Abstract

Background: There is a geographical variation in pattern of kidney diseases due to multiple factors. Renal biopsy is being performed to establish diagnosis of renal diseases. There are only a few biopsy registries which leads to paucity of information. This study was done to evaluate the spectrum of biopsy-proven renal diseases in a tertiary care hospital in southern India.

Materials and methods: Renal biopsy records over 2 decades (2000–2020) performed in the Department of Nephrology in a tertiary care hospital in India were analyzed, and clinicopathological correlation was made.

Results: Total of 4,532 renal biopsies were evaluated in our study after excluding inadequate biopsy samples. Of which males were 58 and 48% were females. Mean age in our study was 38.6 ± 31.4 years. The most common clinical presentation in our study was nephrotic syndrome (37.2%). On histology, the most common diagnosis was primary glomerulonephritis (49.9%), followed by secondary glomerular diseases (22%), tubulointerstitial (20.8%), and vascular diseases (3.3%). Minimal change disease (12.8%), diabetic nephropathy (11.3%), and acute tubulointerstitial diseases (11.2%) were the three most common histological diagnoses in our study.

Conclusion: Nephrotic syndrome was the most common clinical presentation in our study. Minimal change disease was the most common histological diagnosis in our study. There is a need for a uniform nationwide renal biopsy registry in India and even regional renal biopsy registries to analyze the changing trends of renal diseases over time frame and to analyze regional differences in trends of renal diseases.

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Background

There is paucity of data about the epidemiology and prevalence of renal parenchymal diseases in the world.[1] There exist a regional, socioeconomic, racial, and age-related variations in prevalence and incidence of renal parenchymal diseases.[2–5] Renal biopsy has a cardinal role in the management of kidney diseases. Biopsy-proven kidney diseases impart valuable information about incidence, distribution, and possible control of disease with effective and directed treatment and even play an important role in patient guidance for explaining the risk of recurrence after renal transplantation. But renal biopsy is an invasive procedure with potential risks. So, it must be recommended when kidney tissue is required to make a definitive diagnosis that might affect treatment or provide information about disease progression or prognosis. Renal biopsy should be avoided if potential risks outweigh the benefits for the patient. Renal biopsy registries from different countries have provided information about the spectrum of renal parenchymal diseases and patient demographics in their populations. There is no nationwide renal biopsy registry in the Indian subcontinent; hence, information from centers with high volume renal biopsies is useful to understand the pattern and prevalence of renal parenchymal diseases in this region.

Materials and Methods

It is a single-center retrospective analytical study. Native kidney biopsies done in the Department of Nephrology in a tertiary care center in India from 2000 to 2020 were evaluated. The clinical and renal biopsy records of the patients were reviewed. Inadequate sampled biopsies and graft biopsies were excluded from the analysis. Demographical details, clinical presentation, and existence of other comorbidities were noted. Relevant information about clinical presentation like presence of hematuria, presence of systemic features, fever, and laboratory investigations including serum creatinine, serum albumin, lupus serology, complement levels, 24-hour urine protein, or urine protein creatinine ratio were collected from records.

The indications of biopsy were classified as nephrotic syndrome, acute nephritic syndrome, acute kidney injury, rapidly progressive renal failure, chronic kidney disease of undetermined origin (CKD-U), asymptomatic urinary abnormalities like subnephrotic proteinuria and/or microscopic hematuria and gross hematuria.

Renal biopsies were performed under local anesthesia using 2% lignocaine and an 18-gauge automated disposable gun. Two cores were taken. The tissue was placed in 10% formalin for light microscopic examination and in 0.9% saline for immunofluorescence studies. For light microscopy, multiple-step serials from renal core were stained and studied using hematoxylin and eosin, periodic acid–Schiff, Masson trichrome, and Jones' silver methenamine stains. For immunofluorescence, the biopsy specimens were washed in phosphate-buffered saline (PBS) thrice followed by embedding the tissue for frozen section in optimum cutting temperature medium. Once the tissue was frozen, 2–3-μ-thin sections were cut. Two to three sections were layered on each slide and were labeled as immunoglobulin (Ig) G, IgA, IgM, C3, C1q, κ, and λ. The slides were then stained with fluorescein isothiocyanate-labeled antihuman antibodies of IgG, IgA, IgM, C3, C1q, κ, and λ light chains, respectively. The slides were then incubated for an hour at 37°C. After incubation, the slides were again washed thrice with PBS, mounted with glycerin, and viewed under immunofluorescent microscope. Electron microscope was done if required, but not in all cases due to logistical constraints.

The histological diagnoses were classified into four major categories, namely primary glomerular disease, secondary glomerular disease, tubulointerstitial disease, and vascular disease. The glomerular diseases were classified according to the Renal Pathology Society

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Consensus Report.[6] Tubulointerstitial group comprised tubulointerstitial nephritis (TIN)-including both acute and chronic interstitial nephritis, pyelonephritis, acute tubular necrosis, acute tubular injury, and acute tubulointerstitial nephritis. Vascular causes include cases of thrombotic microangiopathy and renal cortical necrosis. Approval was taken from the Institutional Ethics Committee.

Statistical Analysis

Results were analyzed for differences in proportion using Chi-square by the Statistical Package for Social Sciences (SPSS) version 19.0 (SPSS Inc., Chicago, Illinois, United States). The quantitative variables were expressed as the mean ± standard deviation and qualitative variables were expressed as numbers and percentages.

Results

Total 4,532 renal biopsies were performed from 2000 to 2020 of which males were 58% and females were 42%. Mean age was 38.6 ± 31.4 years. Majority of the patients were of first 3 decades (61%). Basic demographic features are shown in Table 1 and age distribution in our analysis is shown in Figure 1. Majority of the patients who underwent renal biopsy were in 1st–3rd decade (62%). 4% cases were of neonates and infants. Elderly age-group (≥60 years) accounted for 2.4% of the cases.

Table 1: Demographic features of our study

Total patients	4,532
Mean age	38.6 ± 31.4 years
Lowest age	26 days
Highest	82 years
Males/females	2,613/1,919 (58%/42%)

Clinical Description

Figure 2 shows the clinical indications for renal biopsy. Nephrotic syndrome accounted for majority of clinical indication for renal biopsy in our analysis (1689/4,532, 37.2%), followed by nephritic–nephrotic illness (956/4,532, 21%), acute nephritic illness (677/4,532, 14.9%), rapidly progressive renal failure (RPRF) presentation (616/4,532, 13.6%), unexplained acute kidney injury (AKI) (438/4,532, 9.7%), chronic kidney disease (CKD) of undetermined origin (96/4,532, 2.1%), asymptomatic urine abnormalities (60/4,532, 1.3%).

Figure 3 summarizes the broad histopathological groups in our registry. Primary glomerular diseases account for majority in our registry (2,260/4,532, 49.9%), followed by secondary glomerular diseases (999/4,532, 22%), tubulointerstitial diseases of kidney (944/4,532, 20.8%), vascular diseases of kidney (149/4,532, 3.3%), in order and 180 renal biopsies were unremarkable accounting for 4%. Figure 4 summarizes the detailed histological presentation in our registry. Minimal change disease (582/4,532, 12.8%) followed by diabetic nephropathy (513/4,532, 11.3%), and focal segmental glomerulosclerosis (372/4,532, 8.2%) were the three most common histological diagnoses in our registry.

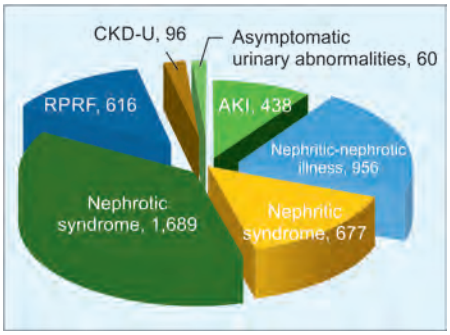

Fig. 2: Major categories of renal biopsy indications in our study population

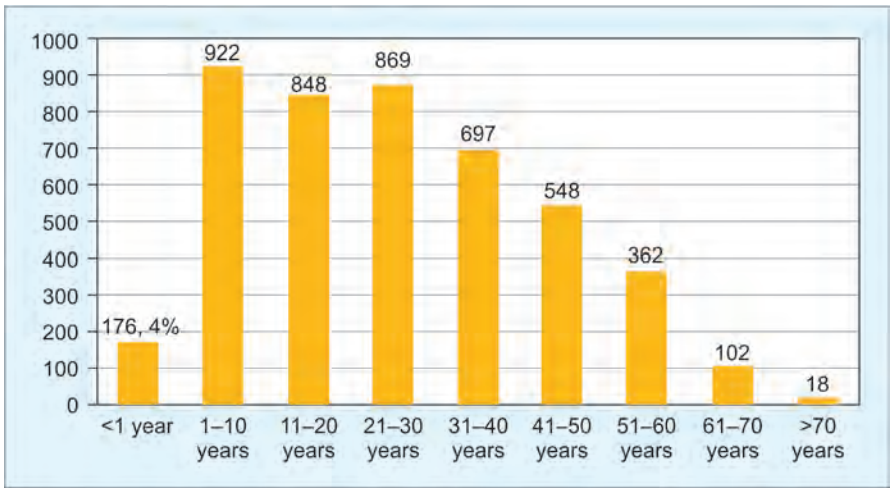

Fig. 1: Age distribution of our study population

Table 2 shows the results of primary glomerular diseases in our registry. Minimal change disease followed by focal segmental glomerulosclerosis and IgA nephropathy were the three most common primary glomerular diseases in our registry.

Table 3 shows the results of secondary glomerular diseases in our registry. Diabetic nephropathy was the most common histological pattern among secondary glomerular diseases.

Table 4 shows the results of tubulointerstitial diseases in our registry. Acute tubulointerstitial diseases [acute tubulointerstitial nephritis (ATIN), acute tubular injury (ATI), acute interstitial nephritis (AIN), acute tubular necrosis (ATN)] account for 53.7% (507/944) followed by chronic TIN (255/944, 27%).

Table 5 shows the results of vascular diseases in our registry. Thrombotic microangiopathy was seen in 79 cases during our analysis accounting for 1.7% of total study population. Cortical necrosis is seen in 70 cases accounting for 1.5% of total study population, of which the majority were females.

Incidence of histopathological lesions to age is shown in Table 6. Primary glomerular diseases were predominant histopathological lesions in first 4 decades, whereas secondary glomerular diseases were predominant histopathological lesions from 5th decade. Tubulointerstitial diseases accounts for maximum histopathological renal lesions in 5–6 decades. Minimal change disease followed by focal segmental glomerulosclerosis and diffuse proliferative glomerulonephritis were top 3 histopathological lesions in 1–2 decades. Whereas in 3–4 decades, acute tubulointerstitial diseases followed by diabetic nephropathy and minimal change disease were the top 3 histopathological lesions. Diabetic nephropathy followed by tubulointerstitial diseases were the leading histopathological lesions after 4th decade.

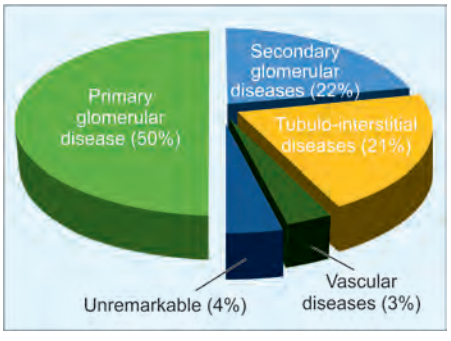

Fig. 3: Broad histological classification in our study population

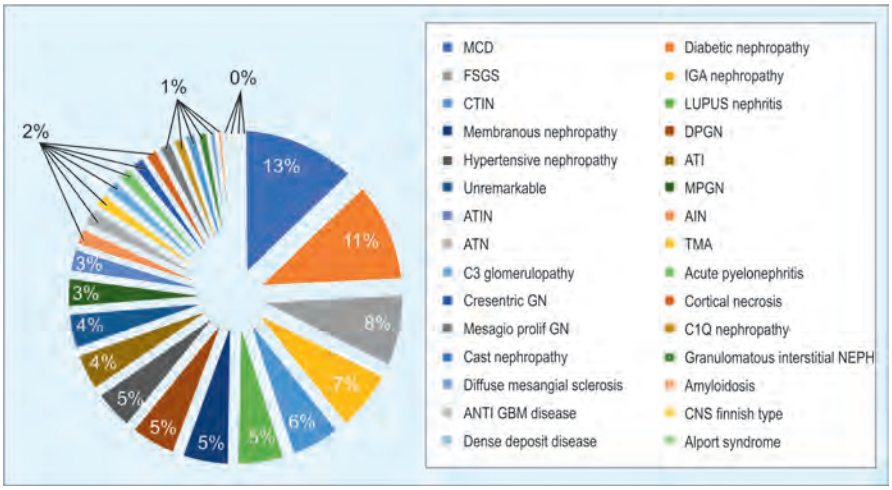

Fig. 4: Detailed histological classification in our study population

Table 2: Incidence of primary glomerular diseases in our study population

Primary glomerular diseases (2,260/4,532)		*Males*	*Females*
MCD	582	286	296
FSGS	372	275	97
IGA nephropathy	313	205	108
Membranous nephropathy	242	156	86
DPGN	232	166	66
MPGN	155	62	93
C3 glomerulopathy	78	46	32
Crescentic GN	70	40	30
Mesagio prolif GN	67	30	37
C1Q nephropathy	59	36	23
Diffuse mesangial sclerosis	34	19	15
Anti-GBM disease	19	11	8
CNS Finnish type	17	8	9
Dense deposit disease	14	9	5
Alport syndrome	6	4	2

DPGN, diffuse proliferative glomerulonephritis

Table 3: Incidence of secondary glomerular diseases in our study population

Secondary glomerular diseases (999/4,532)		*Males*	*Females*
Diabetic nephropathy	513	305	208
Lupus nephritis	245	22	223
Hypertensive nephropathy	208	125	83
Amyloidosis	33	23	10

Table 4: Incidence of tubulointerstitial diseases in our study population

Tubulointerstitial diseases (944/4,532)		*Males*	*Females*
CTIN	255	184	71
ATI	196	134	62
ATIN	122	70	52
AIN	95	56	39
ATN	94	68	26
Acute pyelonephritis	78	50	28
Cast nephropathy	52	42	10
Granulomatous interstitial nephritis	52	22	30

Discussion

Renal biopsies give us definitive diagnoses as well as prognostic information required for deciding therapeutic strategies. The profile of renal disorders varies across the world with changes in population demographics, lifestyles, geographical influence, and socioeconomic status. The present analysis provides information about the renal diseases diagnosed by renal biopsy in our center over a 20-year period. There are only a few nationwide biopsy registries (Table 7),[2–5,7] majority are single center biopsy registries,[8–14] while others are multicenter analyses.[15,16]

Males outnumbered females in our study, which has been demonstrated in all other biopsy registries except European[16] and Czech[5] registries. Though mean age in our study population is comparable to other registries, majority of our study populations were young (52% were in first 2 decades) and only 2.4% were elderly. The elderly population in low and middle-income countries accounts for 2–10% of the total study population,[6,8–11,13,14] whereas the elderly study population in high-income countries was of higher proportions accounting for 14–29%.[2–5,16] This variation in elderly study population may be attributable to limitations of geriatric health care in rural areas and even financial constraints leading to inaccessibility to specialist healthcare for elderly.

Nephrotic syndrome was the most common presentation in our study, and same in the majority of nationwide and single-center registries except Italian registry[2] where urinary abnormalities were the most common presentation. and in Japan registry[15] where chronic nephritic syndrome was the most common presentation. Though the typical nephrotic syndrome presentation was only 37.2% in our study, which was less when compared to other Indian registries[8–10,14]; study population presented with nephrotic range proteinuria were 51.2%. Study population who underwent renal biopsy for nephritic illness in our registry was like other nationwide and single-center registries except Japan registry, where nephritic illness accounted for 49.7%.[15] There was wide variation in study population who underwent renal biopsy for asymptomatic urinary abnormalities in both nationwide and single-center registries which may be due to individual departmental policy in considering these patients for renal biopsy. 13.6% of our study population presented with RPRF which was similar to other single-center registries from India (Table 8).[9–11] Around 10% of our study population underwent renal biopsy for unexplained AKI, which was similar to Spanish[3] and Romanian[4] registry and study

Table 5: Incidence of vascular diseases in our study population

Vascular causes (149/4,532)		*Males*	*Females*
TMA	79	45	34
Cortical necrosis	70	8	62

Table 6: Incidence of histopathological lesions to age in our study population

Biopsy registry		*1–2 decades*	*3–4 decades*	*5–6 decades*	*7 decades and more*
		1,946/4,532, 43%	*1,566/4,532, 34.5%*	*910/4,532, 20.1%*	*110/4,532, 2.4%*
Primary glomerular diseases (2,260/4,532, 49.9%)		72.8%	43.8%	16.4	3.6
MCD	582, 12.9%	20.3	9.3	4.4	0
FSGS	372, 8.2%	14.4	4.2	2.8	0
IGA nephropathy	313, 6.9%	9.2	7.9	1.1	0
Membranous nephropathy	242, 5.3%	3.7	9.2	2.8	0
DPGN	232, 5.1%	10	1.7	1.3	0
MPGN	155, 3.4%	1.8	6.6	1.7	0
C3 glomerulopathy	78, 1.7%	2.9	1.0	0.7	0
Crescentic GN	70, 1.5%	2.5	0.5	1.1	3.6
Mesagio prolif GN	67, 1.5%	0.8	2.9	0.5	0
C1Q nephropathy	59, 1.3%	2.8	0.3	0	0
Diffuse mesangial sclerosis	34, 0.75%	1.7	0	0	0
Anti-GBM disease	19, 0.4%	0.8	0.2	0	0
CNS Finnish type	17, 0.37%	0.9	0	0	0
Dense deposit disease	14, 0.3%	0.7	0	0	0
Alport syndrome	6, 0.1%	0.3	0	0	0
Secondary glomerular diseases (999/4,532)		6.5%	24.3	45.3	72.7
Diabetic nephropathy	513, 11.3%	1.2	11.4	27	59.1
Lupus nephritis	245, 5.4%	4.9	8.0	2.6	0
Hypertensive nephropathy	208, 4.6%	0.3	4.7	12.7	10.9
Amyloidosis	33, 0.73%	0	0.2	3.0	2.7
Tubulointerstitial diseases (944/4,532)		10.6%	25.4	34.9	23.7
ATID (ATIN, AIN, ATI, ATN)	507, 11.2%	7.1	15.3	14.3	0
CTIN	255, 5.6%	2.7	6.1	10.2	12.7
ACUTE pyelonephritis	78, 1.7%	0.4	1.7	4.2	5.5
Cast nephropathy	52, 1.1%	0	0.5	4.4	5.5
Granulomatous interstitial nephritis	52, 1.1%	0.4	1.8	1.8	0
Vascular causes (149/4,532)		3.6%	3.7	2.3	0
TMA	79, 1.7%	2.8	0.8	1.4	0
Cortical necrosis	70, 1.5%	0.8	2.9	0.9	0
Unremarkable (180/4,532)		6.5%	2.8	1.1	0

by Manjunath et al.[13] But, the percentage of study population who underwent renal biopsy for AKI was higher in more recent studies by Kumar et al.[10] and Wilfred et al.,[11] indicating there is an increase in performing renal biopsies for AKI. There is a variation in study population who underwent renal biopsy for CKD in our study (2.1%) vs other nationwide and single-center registries (5.6–18.7%), which might be due to lack of availability of baseline renal function tests and late presentation with kidneys not amenable for renal biopsy in our study population.

Primary (49.9%) and secondary (22%) glomerular diseases were the most common histological diagnoses in our study and consistent with other nationwide and single-center registries. Minimal change disease was the most common histological diagnosis in our study similar to studies done by Das et al.,[9] Wilfred et al.,[11] and Manjunath et al.[13] However, in Western world registries[2,5,6,16] IgA nephropathy was the most common histological diagnosis. Minimal change disease (MCD) was the second common histological diagnosis in Spanish[3] and Czech registry.[5] Focal segmental glomerular sclerosis (FSGS) was the second most common histological diagnosis among primary glomerular diseases in our study accounting for 16.5% of primary glomerular diseases. Similar incidence was seen in studies done by Das et al.[9] and Manjunath et al.[13] Majority of the primary glomerular diseases were common in males in our study except for MCD, membranoproliferative glomerulonephritis (MPGN) and Mesangial proliferative glomerulonephritis pattern. MCD had female preponderance in study done by Kumar et al.,[10] whereas MPGN had an equal gender distribution.

Diabetic nephropathy followed by lupus nephritis were the two most common histological diagnoses among secondary glomerular diseases in our study, which is comparable to majority of Indian registries[8–11,13,15] and some of the nationwide registries.[6,12,14,15] Immune-mediated glomerulo nephritis was the

Table 7: Comparison with nationwide and regional renal biopsy registries across the world

	Our study India	*Italian registry*[2]	*Spain registry*[3]	*Czech registry*[5]	*Romanian database*[4]	*China database*[7]	*Japan registry*[15]	*Serbian registry*[12]	*Adél Molnár et al.*[16] *Europe*
	2000–2020	*1996–2000*	*1994–2001*	*1994–2000 (28 centers)*	*1995–2004*	*1994–2014 (10 hospitals)*	*2007–2008 (23 centers)*	*1987–2006 (single center)*	*2006–2020*
Total biopsies	4,532	13,132 (native kidney)	9,378	4,004	635	4,931	2,126 (native kidneys)	2,362 adult renal biopsies	2,140 native biopsies
Mean age	38.6 ± 31.4 years (1 month–82 years)			38.8 years	38.5 ± 15.2, range 18–80 years	35.2 ± 12.5 years (10–76)	44.9 ± 21.5	39.1 ± 13.8 years (16–79)	44.2 ± 21.9 years
Sex (M:F)	58/42		60/40	48.7/51.3	51.5/48.5		53.1/46.9	51.2/48.8	49.8/50.2
Nephrotic presentation	37.2	32.8	35.5	39.3	52.3		16.5	53.6	
Nephritic illness	14.9	3.8	4.5	19.1	21.9		49.7 Chronic—48.2 Acute—1.5	7.4	
AUA	1.3	38.5	25.9		3.3			24.3	
AKI	9.7		13.5		12.4		0.8	0.6	
CKD	2.1		12.1		10.1			8.6	
RPRF	13.6						4.7		
Primary glomerular	49.9	53.2		59.8	66.2	81.55%	51.9	64%	I
Secondary glomerular	22	17.9		25.6	26.4	13.02%		24%	
Tubulointerstitial	20.8	1.8		4.4	1.5	1.09%		3.7	
Vascular	3.3	2.4			2.3			5.7	
Most common PGN	MCD (25.7) FSGS (16.5) IGAN (13.8)	IGAN	MN (22.9) MCD (17.1) FSGS (14.1)	IGAN (34.5) MCD (12.5) MesPGN (11.3)	MPGN (29.4) MesPGN (incl IgAN) (28.9) FSGS (11.9)	IGAN (43.45) FGN (16.79) MsPGN (14.35)	IGAN	MN (18.9) FSGS (18.9) MPGN (10)	IGAN FSGS MN
Most common SGN	DN (51.3) LN (24.5)	Immune-mediated GN	Amyloid	Immune-mediated GN (48.6) Heriditary GN (27.7) LN (23)	Immune-mediated GN (55.6) Infectious diseases ASS GN (25) Dysgammaglobinemia ASS GN (14.4)	LN (47.3) HSPN (18.8) DN (4.8)	DN	LN (75) amyloid DN	LN

AUA, asymptomatic urinary abnormalities; DN, diabetic nephropathy; LN, lupus nephritis; IGAN, IgA nephropathy; MesPGN, mesangial proliferative glomerulonephritis

most common histological diagnosis in Italian,[2] Czech[5] and Romanian database[4]; amyloid was the most common diagnosis in Spanish registry.[3] The incidence of diabetic nephropathy in our study is 15.7% among all glomerular diseases which is higher than the other nationwide registries and single-center studies from India, where it ranges from 0.15 to 5%.[2–5,8–11,15] This might be due to more liberalized approach in considering diabetic patients for renal biopsy in our center. Renal biopsy is considered in diabetic patients when there is unexplained rapidly worsening renal function, suddenly increasing proteinuria, microhematuria, absence of diabetic retinopathy and/or other evidence of a nondiabetic renal disease such as lupus nephritis, vasculitis, and paraproteinaemia. The incidence of amyloid in our study is lower than other registries[3,4,8,9,12] comprising only 3.3% of total secondary glomerular diseases. This might be because of the confirmation of disease in suspected cases by gingival or abdominal fat pad biopsies rather than renal biopsy in our center.

Tubulointerstitial diseases accounted for 20.8% of overall renal biopsies in our study similar to studies done by Kumar et al.[10] and Wilfred et al.[11] However, the incidence of tubulointerstitial diseases is higher than other nationwide registries[2–6,12,14,16] and Indian single-center registries.[8,9,13,14] This might be due to more liberal approach in performing renal biopsies in patients with acute renal failure and unexplained CKD in our center, high incidence of tropical AKI, more consumption of over-the-counter drugs and indigenous medicines in our geographical area. Among tubulointerstitial diseases, acute tubulointerstitial diseases (ATIN, ATI, AIN, ATN) accounts for major cause with maximum incidence in 3rd and 4th decade followed by chronic TIN with incidence increasing with age.

Thrombotic microangiopathy (TMA) accounts for 1.7% of overall biopsy-proven renal diseases in our study, similar to other Indian single-center registries.[8,10] Cortical necrosis accounts for 1.5% of biopsy-proven renal diseases in our study, of which majority are females of reproductive age-group. This is due to obstetric complications in view of irregular access to antenatal monitoring and dependence on unhygienic home delivery practices.

Conclusion

This large renal biopsy data from a tertiary care center in South India shows that primary glomerulonephritis (GN) constitutes up to 50% of glomerulonephritis with MCD and FSGS being the most common in contradistinction to the developed world where IgA nephropathy predominates. Diabetic nephropathy and lupus nephritis

Table 8: Comparison with Indian single-center renal biopsy registries

	Our study	*Balakrishnan et al.*[14]	*Mittal et al.*[8]	*Das et al.*[9]	*Kumar et al.*[10]	*Wilfred et al.*[11]	*Manjunath et al.*[13]
	2000–2020	*1990–2001*	*2006–2016*	*1990–2008*	*2016–2018*	*2008–2013*	*2005–2013*
Total biopsies	4,532	4,035	3,275	1,849 (biopsies included)	106	661 native kidney biopsies	1,113
Mean age	38.6 ± 31.4 years	>15 years	33.2 ± 14.2 years	32.27 ± 18.38 (10–80)	41.3 ± 18.39 years	42.8 years (8 months–78 years)	35.2 ± 12.5 years (10–76)
Sex (M:F)	1.4:1		1.62:1	1.44:1	1.7:1	1.66	1.74:1
Nephrotic presentation	37.2	65.4	60.3	49	40.5	29	38.8
Nephritic illness	14.9	15.7	11	9	26.4	6.1	16.1
AUA	1.3	1.7	5.6	9		13.3	11.7
RPRF	13.6	3.4	8.2	12	10.3	10.6	5.2
AKI	9.7	1.8	4.3	6.5	16.9	14.9	11.3
CKD	2.1	10.7	9	13.6	5.6	18.2	16.7
Primary glomerular	49.9		73	69.1	57.5	42.3	81.55%
Secondary glomerular	22		15.5	18.2	21.6	21.6	13.02%
Tubulointerstitial	20.8		5.3	6.7	18.8	20	1.09%
Vascular	3.3		3.7	3.2	1.8	6	
Most common PGN	MCD (25.7) FSGS (16.5) IgAN (13.8)	FSGS PIGN MCD	FSGS (22.1) MCD (20.4) MN (19.4)	MCD (21.8) FSGS (15.2) MN (10.1)	MN (22.9) MPGN (18) MCD (16.3)	MCD (33.6) MN (15.7) FSGS (12.6)	MCD (24.9) PIGN (16.4) FSGS (16)
Most common SGN	DN (51.3) LN (24.5) Hypertensive nephropathy (20.8) Amyloid (3.3)	LN DN	LN (60.6) Amyloid (21.1) DN (9)	LN (80.1) Amyloid (10.1) DN (6.5)	DN (43.4) LN (30.4)	DN (76.9) LN (14.7) Amyloid (1.2)	LN DN

are the most common secondary GN. CIN due to undetermined causes is higher in our country which may indicate nephrotoxin or environmental exposure. These differences may be explained by differing policies for biopsy, later presentation of patients to hospitals in India and a presumed high exposure to environmental toxins.

There are certain limitations in our study. The most important is the lack of readily available electron microscopic interpretation of renal biopsies due to logistic constraints. This study represents certain geographical areas of India. This study summarizes pattern of renal diseases who underwent renal biopsies only and may not represent the epidemiology of kidney disease in the general population. Despite these limitations, our study is one of the largest single-center registries in India.

Conclusion

Our study concludes that primary glomerular diseases are the major histological pattern among biopsy-proven renal diseases. The distribution pattern of biopsy-proven renal diseases varies across the world depending on multiple factors like age and sex, geographical mapping, lifestyle of the general population and prevalence of lifestyle diseases. Minimal change disease, diabetic nephropathy, acute tubulointerstitial diseases are the topmost histological patterns observed in our study. There is a need for uniform nationwide renal biopsy registry in India and even regional renal biopsy registries to analyze the changing trends of renal diseases over time frame and to analyze regional differences in trends of renal diseases.

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ORIGINAL ARTICLE

Achievement of ABC Goals in Type 2 Diabetes in Real-life

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Abstract

Introduction: This real-life observational study from a diabetes centre in Western India reports the status of A1C (glycated hemoglobin), blood pressure, and cholesterol levels (ABC goals) currently achieved in type 2 diabetic patients.

Research design and methods: A cohort of 497 patients of type 2 diabetes first seen at the Diabetes Endocrine Nutrition Management and Research Centre from the years 2014 to 2017 were followed for a median [interquartile range (IQR)] duration of 21.5 (7, 33) months. A minimum of two follow-up clinical evaluations and investigations were analyzed.

Results: Hemoglobin A1C (HbA1c) dropped significantly in the whole cohort (HbA1c, Percent: initial 9.0 ± 1.98, follow-up 7.66 ± 1.73; $p < 0.0001$). Increasing duration of diabetes showed a significantly poorer achievement of HbA1c targets on follow-up (HbA1c 0–5 years vs 5.1–10 years and >10 years, $p < 0.001$). Pretreatment HbA1c of <6, 6.1–7, 7.1–7.5, 7.6–8, 8.1–9, and >9% was seen in 2, 15, 11, 8, 20, and 44%, respectively. The corresponding HbA1c values on follow-up were 5, 30, 14, 11, 17, and 23%, respectively. Sodium-glucose transport protein 2 inhibitor (SGLT2i) group was in poorer control (HbA1c 8.20 ± 1.71) at follow-up than non-SGLT2i group (HbA1c 7.55 ± 1.72), $p < 0.001$) probably due to significantly greater use of sulphonylurea as background therapy in SGLT2i group (SGLT2i group 72.2%, non-SGLT2i group 58.7%, $p < 0.02$). Initial ABC targets were at goal for HbA1c, high blood pressure, and low-density lipoprotein (LDL) cholesterol in 17, 40, and 33% of patients, respectively. On follow-up, percent of patients at goal were HbA1c 35%, hypertension 95.77%, and LDL cholesterol 75.85%.

Conclusion: The study brings out the difficulties in achieving HbA1c goals as compared to blood pressure and LDL cholesterol goals. Additionally, it brings out the efficacy of sulphonylureas as a treatment modality. Longer duration of diabetes resulted in lower achievement of glycemic targets.

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Introduction

Achievement of glycemic targets is an important strategy in the prevention of cardiovascular, renal, retinal, and neuropathic complications of diabetes.[1–5] Although the hemoglobin A1C (HbA1c) targets recommended for each diabetic needs to be individualized, HbA1c of <7% has been recommended as a target in most diabetics.[6] The targets prescribed by American Diabetes Association (ADA) for type 1 and type 2 diabetics were same until 2002[7] although it was suggested in the same year that they should be different.[8] The HbA1c targets depend upon the type of diabetes, duration of disease, age of patient, macrovascular and microvascular complications, psychosocial and economic factors, and support systems available for diabetes care.[9]

Achievability of targets, HbA1c (A) as well as blood pressure (B) and LDL cholesterol (C) has been very disappointing.[10] Currently, in most clinics mean HbA1c is around 7.7 and only 36.3% of patients achieve the target of <7%.[11] The blood pressure and LDL cholesterol goals have a better success rate of 48.8 and 41.5%, successively.[12] Considering the fact that multifactorial intervention can reduce albuminuria and mortality, it is important to improve ABC goals.[13]

As the incidence of macrovascular and microvascular complications continues to be high even if the 7% HbA1c is reached, efforts are being made to lower the HbA1c to 6.5 or 6%. This was attempted in several studies where deleterious effects of excessive and rapid lowering of blood glucose were observed.[14–16] However, subanalysis of data in these studies have brought out positive benefits of tight glycemic control.[17,18] Hypoglycemia has been identified as injurious to cardiovascular system[19] hence exploration of treatment modalities causing a very low incidence of hypoglycemia is considered desirable. In this regard, the introduction of dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-RA)'s and sodium-glucose cotransporter 2 (SGLT-2) inhibitors have offered the possibility of achieving stringent HbA1c targets without significant hypoglycemia. Furthermore, GLP-RA's have shown benefits in atherosclerotic vascular disease[20] and SGLT-2 Inhibitors in cardiovascular disease, heart failure and renal disease.[21–24]

HbA1c is considered an accurate parameter to assess mean blood glucose of the past 3 months. It has limitations in a few circumstances, primarily where the erythrokinetics have changed.[25] It is also postulated that there can be differences in the rate of glycation.[26] Another important drawback in relying on HbA1c alone in assessing glycemic status is that it does not give information on glycemic excursions[27] and hence it has to be supplemented by either self-monitoring of blood glucose (SMBG) or continuous glucose monitoring system (CGMS). Yet HbA1c continues to be a gold standard in assessing average glycemia in the past 2–3 months.

This is a retrospective observational study reporting data on a cohort of type 2 diabetic patients managed at the Diabetes Endocrine Nutrition Management and Research Centre (DENMARC) in Western India.

Patients and Methods

Patients

Patients of type 2 diabetes ($n = 497$), first seen at DENMARC in the years 2014–2017 were followed up for their glycemic control. They were selected on the basis of the regularity of their visits and full availability of data. Type 1 diabetics were excluded in this study. All patients were assessed initially and at every follow-up visit by diabetes educators and the senior author (HB Chandalia). In April 2015, SGLT-2 inhibitors were introduced in India. This offered a unique opportunity to compare the attainment of HbA1c targets in patients under treatment with SGLT-2i as compared to the non-SGLT2i groups.

Methods

HbA1c was done using high-performance liquid chromatography (HPLC) standardized to National Glycohemoglobin Standardization Program (NGSP) criteria.[28]

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The patient characteristics are shown in Table 1. They were put on antidiabetic regime as per standard clinical guidelines.[29,30] Most of them were on oral glucose-lowering regime and insulin. Ninety patients received SGLT-2i besides other OADs and insulin. HbA1c was done initially and at >3-month intervals. Each patient had an initial HbA1c and two or more HbA1c during follow-up (total follow-up HbA1c values: 1246); mean of follow-up HbA1c values was used for statistical analysis and compared with the initial value. Overall, initial and follow-up HbA1c in the SGLT-2i and non-SGLT-2i inhibitor groups were compared. The HbA1c data of whole cohort were stratified in six groups depending upon HbA1c percentage: <6, 6.1–7, 7.1–7.5, 7.6–8, 8.1–9, and >9%. The percentage of patients in each HbA1c category was determined before and after treatment. The HbA1c targets achieved in patients with shorter (<5 years) vs those with longer duration of diabetes (5–10, >10 years) were compared.

Data were entered in Microsoft Excel and analyzed using Stata Version 17 (© StataCorp, College Station, Texas, United States). For the linear variables, means and standard deviations (SD), and for categorical variables, proportions were calculated. The means between two groups were compared using the unpaired and paired *t*-test (for different groups and pre and post-treatment mean values). The proportions were compared using the Chi-squared test or Fisher's exact test (for low expected cell counts). In order to adjust for potential confounders, regression models for multivariate analysis were used. A *p*-value of <0.05 was considered to be statistically significant.

Table 1: Profile of patients studied and mean Hb1Ac pre- and post-treatment

Characteristics	*Baseline clinical profile*	*HbA1c at baseline and follow-up*		
	n (%)	*Baseline*	*Follow-up*	*p-value*
		Mean (SD)	*Mean (SD)*	
Total	497 (100)	9.00 (1.98)	7.66 (1.73)	<0.0001
Age				
20–39	45 (9.1)	9.60 (2.08)	7.71 (1.76)	<0.0001
40–49	147 (29.6)	8.99 (1.93)	7.59 (1.54)	<0.0001
50–59	166 (33.4)	8.96 (1.97)	7.80 (1.79)	<0.0001
60–69	105 (21.1)	8.82 (1.90)	7.58 (1.84)	<0.0001
≥70	34 (6.8)	9.03 (2.31)	7.53 (1.92)	0.001
Gender				
Male	318 (63.9)	8.95 (2.02)	7.64 (1.72)	<0.0001
Female	179 (36.1)	9.08 (1.92)	7.71 (1.76)	<0.0001
Duration of diabetes				
0–5 years	225 (45.3)	8.82 (2.08)	7.13 (1.46)	<0.0001
5.01–10 years	125 (25.2)	9.09 (1.97)	8.20 (1.79)	<0.0001
>10 years	147 (29.6)	9.20 (1.82)	8.03 (1.85)	<0.0001
BMI categories				
Normal/underweight	58 (11.7)	8.91 (2.04)	7.40 (1.50)	<0.0001
Overweight	191 (38.7)	9.05 (2.03)	7.69 (1.78)	<0.0001
Obese	245 (49.6)	9.00 (1.94)	7.70 (1.74)	<0.0001
Comorbidities/complications				
Hypertension	291 (44.1)	9.03 (2.03)	7.52 (1.75)	<0.0001
CVS	52 (10.5)	8.95 (1.95)	7.72 (1.84)	0.0003
Renal disorders	23 (4.6)	8.57 (2.13)	7.37 (2.06)	0.008
Neurological disorders	4 (0.8)	7.90 (1.42)	8.88 (2.19)	0.31
Retinopathy	7 (1.4)	9.67 (1.87)	7.19 (1.45)	0.01
Treatment given				
Metformin	452 (90.9)	9.04 (1.99)	7.67 (1.69)	<0.0001
Sulphonylureas	304 (61.2)	9.41 (1.92)	7.92 (1.75)	<0.0001
DPP4	450 (90.5)	9.04 (1.97)	7.69 (1.72)	<0.0001
Repaglnidine	17 (3.4)	9.06 (2.29)	8.43 (2.35)	0.32
Piogltа	19 (3.8)	9.85 (2.79)	8.13 (1.97)	0.02
Insulin	104 (20.9)	9.76 (1.93)	8.17 (1.62)	<0.0001
SGLT2	90 (18.1)	9.09 (1.76)	8.20 (1.71)	<0.0001

Results

Baseline clinical profile of the population studied (n = 497) is presented in Table 1. The age stratification showed that the majority of patients were ages 40–49, 50–59, and 60–69 years. Notably, 9.1% were in a young age group of 20–39 years. There was preponderance of male gender. Duration of diabetes was stratified in 0–5, 5.01–10, and >10 years. 88.3% of patients were overweight or obese by the body mass index (BMI) criteria proposed for Asians. Duration of follow-up was median [interquartile range (IQR)] of 21.5 (7, 33) months.

In the whole cohort, HbA1c dropped significantly at follow-up as compared to the initial value (initial HbA1c: 9.0 ± 1.98, follow-up HbA1c: 7.66 ± 1.73; $p < 0.0001$). Table 1 shows the HbA1c at initial and follow-up visits, with multiple regression analysis of various factors that could have influenced the HbA1c outcome. HbA1c was reduced significantly in all categories of ages, gender, duration of diabetes, and BMI. Presence of comorbidities, like hypertension, cardiovascular disease, and renal complications did not change the outcome, but HbA1c was not reduced in patients with neurological diseases. The treatment modality used did not alter the outcome except for the fact that repaglinide and pioglitazone did not lower the HbA1c significantly. Furthermore, statistical analysis was done to bring out the factors that contributed to the attainment of HbA1c level of <7% did not show interaction of age, gender, BMI categories, obesity, and comorbidities (Table 2). However, poor achievability of glycemic targets was seen with longer duration of diabetes. Other exception was presence of neurological diseases and use of repaglinide as treatment modalities. In these categories, the number of patients treated was very small. Addition of SGLT2i in patients undergoing background therapy with a veritable combination of oral drugs (metformin, DPP4i, and sulphonylureas) and insulin did not show further improvement in glycemic control.

As per the real-world algorithms these patients received lifestyle therapy, metformin, DPP-4 inhibitors, sulphonylureas, insulin, and rarely glinides. All drugs were used either as monotherapy or more frequently as dual or triple combination therapy. Most frequently employed modality of treatment in our patients were metformin, DPP4i, and sulphonylurea. Sulphonylureas were used in 61.2% of whole cohort and significantly more ($p < 0.02$) number of SGLT2i treated group (72.22%) as compared to non-SGLT2i treated group (58.72%). There were no patients on

Table 2: Proportion of patients with Hb1Ac <7 and ≥7% at baseline and follow-up and logistic regression models for factors associated with post-treatment Hb1Ac levels of <7%

Characteristics	*Total*	*Proportion of maintenance to <7*		*Adjusted logistic regression models*			*Odds ratio (95% CI)*	*p-value*
		Baseline		*Follow-up*		*p-value*		
		<7	*≥7*	*<7*	*≥7*			
	N (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*			
Total	497 (100)	79 (15.9)	418 (84.1)	207 (41.7)	290 (58.3)	<0.0001		
Age								
20–39	45 (9.1)	6 (13.3)	39 (86.7)	20 (44.4)	25 (55.6)	0.003	Reference	
40–49	147 (29.6)	24 (16.3)	123 (83.7)	60 (40.8)	87 (59.2)	<0.0001	0.85 (0.41, 1.80)	0.68
50–59	166 (33.4)	22 (13.3)	144 (86.7)	66 (39.8)	100 (60.2)	<0.0001	1.06 (0.50, 2.25)	0.89
60–69	105 (21.1)	17 (16.2)	88 (83.8)	46 (43.8)	59 (56.2)	<0.0001	1.30 (0.58, 2.93)	0.53
≥70	34 (6.8)	10 (29.4)	24 (70.6)	15 (44.1)	19 (55.9)	0.10	1.14 (0.39, 3.33)	0.81
Gender								
Male	318 (63.9)	55 (17.3)	263 (82.7)	135 (42.5)	183 (57.5)	<0.0001	Reference	
Female	179 (36.1)	24 (13.4)	155 (86.6)	72 (40.2)	107 (59.8)	<0.0001	0.88 (0.57, 1.36)	0.57
Duration of diabetes								
0–5 years	225 (45.3)	46 (20.4)	179 (79.6)	122 (54.2)	103 (45.8)	<0.0001	Reference	
5.01–10 years	125 (25.2)	15 (12.0)	110 (88.0)	40 (32.0)	85 (68.0)	0.0001	0.44 (0.26, 0.74)	0.002
> 10 years	147 (29.6)	18 (12.2)	129 (87.8)	45 (30.6)	102 (69.4)	<0.0001	0.41 (0.23, 0.74)	0.003
BMI categories								
Normal/underweight	58 (11.7)	8 (13.8)	50 (86.2)	28 (48.3)	30 (51.7)	<0.0001	Reference	
Overweight	191 (38.7)	32 (16.8)	159 (83.2)	81 (42.4)	110 (57.6)	<0.0001	0.75 (0.38, 1.45)	0.39
Obese	245 (49.6)	38 (15.5)	207 (84.5)	96 (39.2)	149 (68.8)	<0.0001	0.74 (0.38, 1.45)	0.38
Comorbidities/complications*								
Hypertension	219 (44.1)	36 (16.4)	183 (83.6)	100 (45.7)	119 (54.3)	<0.0001	1.85 (1.20, 2.85)	0.005
CVS	52 (10.5)	7 (13.5)	45 (86.5)	18 (34.6)	34 (65.4)	0.008	0.86 (0.42, 1.76)	0.69
Renal disorders	23 (4.6)	7 (30.4)	16 (69.6)	14 (60.9)	9 (39.1)	0.02	3.32 (1.00, 11.02)	0.05
Neurological dis	4 (0.8)	1 (25.0)	3 (75.0)	1 (25.0)	3 (75.0)	>0.99	0.48 (0.04, 5.18)	0.55
Retinopathy	7 (1.4)	0 (0)	7 (100)	4 (57.1)	3 (42.9)	0.05	1.89 (0.34, 10.45)	0.47
Treatment given*								
Metformin	452 (90.9)	69 (15.3)	383 (84.7)	184 (40.7)	268 (59.3)	<0.0001	0.68 (0.28, 1.67)	0.404
Sulphonylureas	304 (61.2)	29 (9.5)	275 (90.5)	101 (33.2)	203 (66.8)	<0.0001	0.55 (0.35, 0.86)	0.008
DPP4	450 (90.5)	71 (15.8)	379 (84.2)	183 (40.7)	267 (59.3)	<0.0001	0.54 (0.27, 1.08)	0.084
Repaglnidine	17 (3.4)	2 (23.5)	13 (76.5)	6 (35.3)	11 (64.7)	0.41	0.33 (0.08, 1.31)	0.116
Piglitazone	19 (3.8)	4 (21.1)	15 (78.9)	6 (31.6)	13 (68.4)	0.41	0.58 (0.16, 2.11)	0.409
Insulin	104 (20.9)	5 (4.8)	99 (95.2)	26 (25.0)	78 (75.0)	<0.0001	0.40 (0.22, 0.75)	0.004
SGLT2	90 (18.1)	11 (12.2)	79 (87.8)	26 (28.9)	64 (71.1)	0.004	0.52 (0.29, 0.91)	0.023

CI, confidence intervals; *Reference for these categories is no for these variables

GLP-RA therapy in this cohort. Ninety patients received additional therapy with SGLT2 inhibitors. Our data were analyzed to elucidate the efficacy of SGLT2 inhibitors when added to the background therapy of triple oral drugs and insulin. In our cohort, 407 subjects not on SGLT2i achieved a follow-up HbA1c of 7.55% ± 1.72 from initial HbA1c of 8.98% ± 2.03. The SGLT2i group had initial HbA1c of 9.09 ± 1.76 and follow-up HbA1c of 8.20% ± 1.71 (SGLT2i group vs non-SGLT2i group at follow-up, $p < 0.001$).

In a multivariate regression model, odds ratio of HbA1c outcome of <7% at follow-up as related to multiple variables was examined (Table 2). Those with a duration of 5–10 years as well as >10 years of diabetes had significantly poorer control at follow-up than those with <5 years of diabetes (0–5 vs >5.1–10 years, $p < 0.001$; 0–5 vs >10 years, $p < 0.001$). However, poor glycemic control seen in those 5.1–10 years of diabetes vs those with >10-year duration was not significantly different ($p = 0.411$).

Figure 1 shows the percent of patients having HbA1c levels <6.0, 6.1–7, 7.1–7.5, 7.6–8, 8.1–9, and above 9% initially (A) and at follow-up (B). Categories of <7–7.5 and >7.6–8% were created by us so as to assess our patient population more realistically as a large number of our patients had long duration (>5 years, $n = 125$; >10 years, $n = 147$) of diabetes and were on complex therapies, including triple combinations of oral hypoglycemic agent (OHA) with insulin. The HbA1c of whole cohort dropped from 9.0 ± 1.98 to 7.66 ± 1.73% ($p < 0.01$). HbA1c of <7 and <7.5% was seen initially in a total of 17 and 28% of patients, respectively. On follow-up, a total of 35 and 49%, respectively, achieved the HbA1c of <7 and <7.5% (Fig. 1).

Table 2 shows result of multiple regression regarding factors associated with post-treatment HbA1c of <7%. Shorter

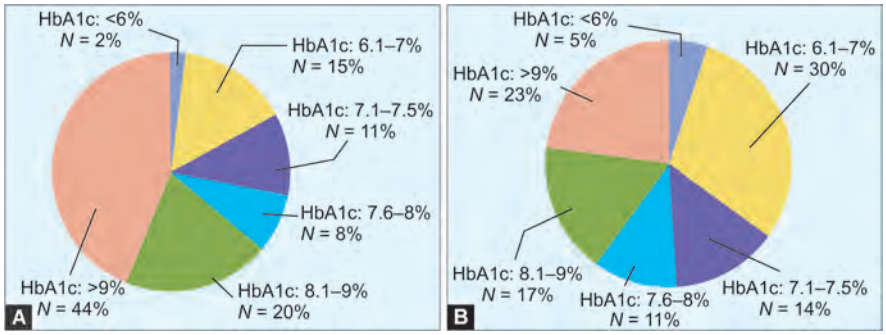
duration of diabetes (<5 years) and longer duration of follow-up (>25 months) produced significantly better HbA1c outcomes. Among the drugs used, sulphonylureas, insulin, and SGLT2 inhibitors produced significantly better glycemic outcome.

In a multiple logistic regression model, Table 3 compares patients treated with SGLT2i vs those not given SGLT2i. Duration of diabetes was significantly longer [median, IQR 8 (4, 13) years] in SGLT2i-treated group as compared to non-SGLT2i group [median IQR 6 (1.5, 12) years, $p < 0.002$].

Discussion

Optimum glycemic control is one of the most important aspects of diabetes management. Good glycemic control relieves symptoms of a catabolic state to that of an anabolic state, relieves osmotic symptoms, mycotic genital infections, and most importantly creates a sense of well-being and improved quality of life. Above all it reduces the incidence and/or severity of cardiovascular, renal, retinal, and neuropathic complications of diabetes, thus reducing morbidity and mortality.

Besides targeting glycemic control, management of diabetes includes control of lipids and BP levels. Achievement of ABC targets has been studied in many centers. In our cohort at goal ABC targets were as follows: Initial data: HbA1c <7 in 17%, normotensive (blood pressure <140/90 mg/dL) in 40%, and normal LDL (directly estimated <100 mg/dL) in 33%. On follow-up of whole cohort at goal HbA1c, blood pressure, and LDL cholesterol were seen in 35, 95.77, and 75.85%, respectively. Blood pressure and LDL cholesterol were at goal in 93 and 64%, respectively, of patients showing abnormality at baseline. Thus, glycemic control continues to be the most difficult out of the three parameters. World over, the best results have been attainment of HbA1c goal in 55%, blood pressure goals in 25% and LDL cholesterol goals in 40% of diabetic patients.[31] Population-based studies report single cross-sectional data[12] while the present study reports follow-up data. On follow-up, high attainment of lipid and blood pressure goals in this study can probably be attributed to the fact that at all visits these patients were seen by the same healthcare team and each patient had at least two follow-up consultations offering an opportunity to optimize results. Additionally, our center has a system of chart reviews of BP and SMBG by email or phone, especially in the titration phase of treatment. However, this strategy was not able to improve the achievability of HbA1c goals. Our results report a success rate of the same degree as most diabetes centers, provided HbA1c of 7.5% is considered the goal because of the complex risk profile of our study population. It is well accepted that target of 7–7.5 or even 7.6–8% is optimum in such patients.[29] This study achieved HbA1c target of <7 in 35% and <7.5 in 49% of patients. As compared to other studies[31] our group achieved the glycemic target in 49% of patients only when the target goal was shifted to 7.5%. Shifting our patients from 7.5 to <7% HbA1c was difficult, probably due to high prandial blood glucose[32] resulting from high carbohydrate diets. This suggests that serious efforts must be made to lower the carbohydrate content of diets prescribed to our patients from 55–65 to <50% of total calories.[33] In an earlier study published in the year 2015, we



Figs 1A and B: HbA1c percentage at initial and follow-up visits. (A) HbA1c percentage at initial visit; (B) HbA1c percentage at follow-up visits (mean of >2 values)

Table 3: Comparison of patients in the SGLT2i group vs non-SGLT2i group

Variables	*Total*	*SGLT2 given*	*Not given*	*p-value*
All	497 (100)	90 (18.1)	407 (81.9)	
Age				
Mean (SD)	53.1 (10.7)	52.7 (9.6)	53.1 (11.0)	0.73
Gender				
Male	318 (63.9)	66 (73.3)	252 (61.9)	0.04
Female	24 (36.0)	24 (26.7)	155 (38.1)	
Duration of diabetes (years)				
Median (IQR)	6 (2, 13)	8 (4, 13)	6 (1.5, 12)	0.02
BMI categories				
Normal/underweight	58 (11.7)	2 (2.3)	56 (13.8)	<0.001
Overweight	191 (38.7)	27 (30.3)	164 (40.5)	
Obese	245 (49.6)	60 (67.4)	185 (45.7)	
Comorbidities/complications				
Hypertension	291 (44.1)	35 (38.9)	184 (45.2)	0.27
CVS	52 (10.5)	7 (7.8)	45 (11.1)	0.35
Renal disorders	23 (4.6)	4 (4.4)	19 (4.7)	>0.99
Neurological disorders	4 (0.8)	0 (0.0)	4 (1.0)	>0.99
Retinopathy	7 (1.4)	2 (2.2)	5 (1.2)	0.62
Other medications				
Metformin	452 (90.9)	81 (90.0)	371 (91.2)	0.69
Suphonylureas	304 (61.2)	65 (72.2)	239 (58.7)	0.02
DPP4 inhibitors	450 (90.5)	78 (86.7)	372 (91.4)	0.17
Repaglnidine	17 (3.4)	3 (3.3)	14 (3.4)	>0.99
Pioglitazone	19 (3.8)	5 (5.6)	14 (3.4)	0.34
Insulin	104 (20.9)	22 (24.4)	82 (20.2)	0.36
Duration of follow-up (months)				
Median (IQR)	21.5 (7, 33)	24 (12, 39)	18 (7, 30)	0.0008

reported attainment of <7% HbA1c in 28% of patients.[34] In the present study, 35% achieved goal of 7.0% HbA1c. This reflects insignificant ($p = 0.08$) improvement in the attainment of HbA1c targets in the present study. Tavakoli et al. showed significant improvement in the attainment of glycemic goals in two studies conducted by them in the years 2010–2014 and 2015–2019.[35]

In the basic regulatory trials of empagliflozin (Empa-Reg study) <43% of subjects in the whole study population received sulphonylureas.[21] In our study, the sulphonylureas were received by 61.2% of patients. Furthermore, a significantly greater number ($p = 0.02$) of patients in SGLT2i-treated groups received sulphonylureas as compared to non-SGLT2i-treated group. We only used glicliazide (in most cases immediate release type, three times a day, in divided dosage of 20–80 mg, premeal) which was found to be effective and not attended by any episodes of severe hypoglycemia during the study period.

It can be postulated that use of newer therapeutic agents like DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-RA will lead to an improvement in HbA1c outcomes. In this cohort, no GLP-RA's were used and SGLT2 inhibitor were introduced only in a subgroup. Yet in many centers where all drugs have been fully deployed, the attainment of HbA1c targets has been disappointing. Of all the ABC targets, HbA1c outcomes are more dependent on lifestyle. Thus some other tools like education, continuity of care, and lifestyle interventions need to be intensified to improve glycemic outcomes. A renewed focus on these aspects may improve glycemic outcomes. It can also be postulated that the pharmacotherapy and other means of treatment available to us are inadequate.

Use of SGLT2i was introduced in India in 2015 and hence was a newer agent in our present study. We looked at differences in SGLT2i-treated patients vs those treated with other modalities of treatment on the background of standard oral glucose-lowering agents and insulin. In our cohort, the baseline HbA1c in SGLT2i group (9.09 ± 1.96%) and non-SGLT2i group 8.98 ± 2.03 was not significantly different ($p = 0.69$). However, during follow-up HbA1c was significantly higher in SGLT2i group (SGLT2i group: 8.2 ± 1.71%, non-SGLT2i group: 7.55 ± 1.72%, $p < 0.0001$). Our data do not reveal significant improvement in glycemic control in patients receiving SGLT2i along with other standard therapies vs those who did not receive a SGLT2i. Use of sulphonylurea compounds was high (61.2%) in our cohort and significantly more in SGLT2i-treated patients as compared to non-SGLT2i treated group (SGLT2i group 72.2%, non-SGLT2i group 58.7%, $p < 0.02$). Number of patients receiving insulin was not significantly different in SGLT2i-treated and non-SGLT2i-treated groups (24.44 vs 20.14%). Duration of diabetes was significantly longer in the SGLT2i-treated group ($p < 0.02$) (Table 3). These factors could have contributed to poorer glycemic control in this group. SGLT2i did not produce additional improvement in glycemia once insulin and/or sulphonylureas had been exhibited. Combination of insulin and sulphonylureas is likely to lead to a higher incidence of hypoglycemia, however, multiple doses (basal-bolus most of the time) insulin therapies with fractional doses of sulphonylurea (unmodified gliclazide) produced an optimum response in our patients without any incident of serious hypoglycemia. Currently, sulphonylureas are forgotten while listing insulin-sensitizer drugs but they are known to be highly effective in this regard.[36] ADA/European Association for the Study of Diabetes (EASD) recommended in the year 2018 that patients of diabetes with multiple cardiovascular or renal disease must receive SGLT2i or GLP-RA as a protective therapy.[37] These organizations further suggested that if HbA1c is <6.5 or <6%, other therapy be de-escalated and SGLT2i or GLP-RA given. However, these recommendations emerged later than this study period and hence were not followed in the treatment algorithm. Presently use of SGLT2i is considered before a sulphonylurea where indications like cardiovascular and renal complications[37] or long-duration of type 2 diabetes are present.[38] The above discussion should not lead to the conclusion that SGLT2i was shown to be ineffective in our patients. In the multiple regression model (Table 2) they were shown to have a significant glucose-lowering effect. Only when added on the background therapy with sulphonylureas and/or insulin, the efficacy of SGLT2i probably got masked. There is no obvious explanation for the same but it can be postulated that background therapy could downregulate SGLT2 receptors in the renal tubules thus rendering the addition of SGLT2i relatively ineffective.

Our data show that difficulty in achieving HbA1c goal starts as early as 5 years after the diagnosis of diabetes. In a large real-world study,[38] the cardiovascular disease has been shown to significantly increase at 5 years postdiagnosis of diabetes and progresses to a coronary artery disease risk equivalence after 10 years of diabetes. This affirms the need to target control of glycemia and control of comorbidities early on, ideally at the diagnosis of diabetes or before or certainly in the first 5 years of diabetes. The difficulty in controlling glycemia with increased duration of diabetes must be recognized and addressed without any inertia. First 5 years of diabetes offer the best opportunity for improving cardiovascular outcomes through meticulous glycemic control which in turn will influence the long-term outcomes by the glucose memory effect.

The limitation of this study is that it was a real-life retrospective observational study. The results reported in the SGLT2i-treated group need to be confirmed by a prospective controlled study designed to examine the performance of SGLT2i added on to various background therapies. The strength of the study lies in the fact that it was a cohort study where at least two follow-up observations were available additionally supported by titration of medications as required. Patients were seen by the same team of healthcare workers during the entire duration of the study.

Conclusion

In this study, HbA1c target of <7 was achieved in 35% and <7.5 in 49% of patients. Amongst ABC targets, achievement of HbA1c targets has been the poorest. As good glycemic control necessitates suitable changes in lifestyle it is necessary to improve our strategies in this regard. Long duration of diabetes affects the achievement of HbA1c targets adversely.

Use of third-generation sulphonylureas, especially unmodified gliclazide in divided dosage can safely improve glycemic control. Those not under control on a combination of metformin, gliclazide, and a DPP4 inhibitor with or without insulin do not significantly improve their glycemic control further with the addition of a SGLT2 inhibitor. While using combination therapy with various drugs in diabetes, the sequential order in which they are exhibited may show a varied degree of efficacy. This question deserves further studies.

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ORIGINAL ARTICLE

Fixed-dose Combination Therapy of Paracetamol, Phenylephrine, and Chlorpheniramine Maleate for the Symptomatic Treatment of Common Cold in Indian Adults

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Abstract

Background: Common cold is a highly prevalent acute upper respiratory tract infection (URTI) leading to at least 4–6 episodes in adults annually. Persistent common cold infections can have a significant economic impact. Very few studies assess the efficacy of fixed-dose combination (FDC) therapies for the symptomatic treatment of common cold in Indian adults. This study assesses the efficacy and safety of FDC of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg for treating Indian adults with common cold symptoms.

Methods: A total of 420 patients aged between 18 and 65 years were recruited for this study. Patients were evaluated for efficacy and safety using an FDC of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg per tablet. The study duration was 5 days, and the patients had to visit the clinical trial site for the baseline visit on the 1st day, the reevaluation visit on the 3rd day, and the conclusion visit on the 5th day. Efficacy was measured by total symptom score (TSS), and safety assessments were made using adverse events reported by patients.

Results: A total of 318 out of 420 patients completed the study. On the first visit, the mean TSS was 9.016, which reduced to 5.011 and 0.495 on the second and third visits, respectively. By the third visit, 268 (84.276%) patients had no symptoms of common cold. The one-way ANOVA test showed a statistically significant reduction in TSS from the 1st to the 5th day of treatment ($p < 0.0001$). Additionally, there were no severe adverse drug reactions reported during the study; only 13 nonserious adverse events were reported, including hyperacidity and drowsiness.

Conclusion: The FDC of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg was efficacious and safe for symptomatic treatment of common cold in adults.

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Introduction

Common cold is an acute and self-limiting condition affecting the upper respiratory tract, often accompanied by symptoms such as fever, nasal congestion, rhinorrhea, sore throat, coughing, sneezing, and headaches.[1] Typically, adults might experience 4–6 episodes of common cold annually, with the infection lasting an average of 5–7 days.[2,3]

Acute upper respiratory tract infections (URTIs) were reported to be the most common illness worldwide in 2019, accounting for 42.83% of all cases.[4] In India, the National Health Portal reported that common cold affected over 4 million people in 2018.[5] Rhinovirus is the leading cause of URTIs, responsible for approximately 35% of global cases and 10% of cases in India.[6] Additionally, as of September 2023, there were over 770 million confirmed cases of Coronavirus, which also presents with common cold symptoms.[7]

Immunocompromised individuals and chronic obstructive pulmonary disease (COPD) patients may develop severe complications or experience exacerbations due to a common cold infection.[2,8] These infections can cause significant economic impacts, including absenteeism and decreased work productivity.[9] According to a survey, 44% of the workforce reported absenteeism due to these infections, resulting in a 26% decrease in work productivity. Additionally, many people reported a lack of sleep due to nasal congestion.[10]

Despite the availability of numerous treatment options, antibiotics continue to be the most prescribed medication for acute URTI. In India, there is a high consumption of antibiotics for the treatment of common cold which led to an increase in antibiotic resistance in India.[11] Given that common cold is mainly caused by a viral infection, antibiotics are ineffective unless there is a secondary bacterial infection. Thus, early symptomatic treatment is crucial to prevent subsequent URTI complications.[12] De Sutter et al.'s review emphasizes the practical benefits of combination therapy for treating common cold symptoms. Their analysis suggests that integrating antihistamines, decongestants, and analgesics provides greater relief compared to using any one drug alone.[13] This highlights the potential advantage of a comprehensive approach to managing cold symptoms effectively. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in alleviating various symptoms such as headache, pain from sore throat, and fever.[14] Paracetamol is a widely used NSAID due to its exceptional safety, which results in the least amount of gastrointestinal toxicity compared to other NSAIDs.[15] Phenylephrine and other oral decongestants work by targeting adrenergic receptors and causing vasoconstriction of the small blood vessels in the nasal mucosa, which reduces nasal swelling and alleviates nasal congestion.[16] Decongestants can be used for a short period when combined with antitussive or antihistamine to provide symptomatic relief from cough that occurs with rhinitis or cold.[17] Chlorphenamine, a first-generation antihistaminic drug, treats common cold by acting on H1 receptors with an antimuscarinic action, alleviating symptoms such as rhinorrhea and nasal irritation.[18]

Limited research exists on the symptomatic treatments for adults experiencing common cold symptoms. Therefore, this study seeks to address this gap by examining the efficacy of the fixed-dose combination (FDC) of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg in relieving common cold symptoms among adult patients.

Methodology

This was an active postmarketing surveillance study conducted in India on adult patients suffering from common cold. This study was carried out in seven ear, nose, and throat (ENT) specialist hospitals and

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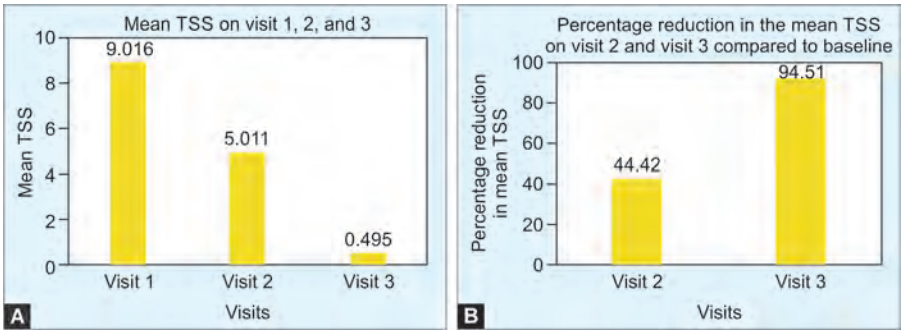
outpatient departments (OPDs) located in Maharashtra, Bihar, Chhattisgarh, and Uttar Pradesh. The Central Drugs Standard Control Organization (CDSCO) suggests a sample size exceeding 200 patients for clinical trials. Our study referenced a phase III clinical trial conducted by Picon et al., which employed a comparable combination treatment and included 146 patients.[19] To achieve a statistical power of 80%, a sample size of 300 patients was determined. Accounting for potential dropouts, we opted to enroll 420 patients to ensure obtaining over 300 evaluable patients. Patients were administered a 5-day treatment plan. The study involved both male and female adult patients aged 18–65 years who were diagnosed with common cold based on symptoms such as fever, nasal congestion, rhinorrhea, sore throat, coughing, sneezing, and headache. Only patients who could adhere to the protocol for 5 days were selected. The study excluded patients with hypersensitivity to paracetamol, phenylephrine, and chlorpheniramine maleate and patients with hepatic or renal dysfunction. Additionally, patients who could not adhere to the study protocol due to psychological illness were excluded from the study.

The investigational product was comprised of FDC that included paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg per tablet. The investigational product was supplied to patients at no cost, consisting of 15 tablets to be taken orally three times daily for 5 days, with an interval of 8 hours in between. The formulation had been approved by the Indian regulatory authority, that is, CDSCO for the treatment of common cold.[20]

During the 5-day treatment regimen, patients visited the clinical trial site three times for evaluations of efficacy and safety. On the 1st day, a baseline assessment was conducted, while the 3rd day featured a reevaluation visit and the 5th day marked the conclusion of the study. Before enrolment, patients were informed of the procedure and their consent was obtained. Medical histories were obtained, and clinical evaluations were conducted on the first visit. Throughout the 5 days, patients were instructed to record any symptoms they experienced. In the event of major adverse events, patients may be withdrawn from the study and treated accordingly. Patients were advised against taking any other medications during the study, but home remedies like steam inhalation and saltwater gargling were permitted to alleviate nasal congestion and sore throat.

The severity of the patient's symptoms was evaluated using the total symptom score (TSS), which is an 11-point scale where patients rated their symptoms from 0 to 10, with 0 indicating no symptoms and 10 indicating the most intense symptoms. The TSS was then converted into a Likert-type symptom severity scale that assigned scores of 0 for no symptoms, 1–3 for mild symptoms, 4–6 for moderate symptoms, and 7–10 for severe symptoms. The patient's symptoms, including fever, nasal congestion, rhinorrhea, sore throat, coughing, sneezing, and headaches, were recorded using the same scale throughout the 5-day treatment period. The mean values for TSS and the percentage of mean TSS were calculated for the three visits and compared to the baseline values. Adverse events were reported by patients to the investigator of the respective clinical trial site and were evaluated using the World Health Organization Uppsala Monitoring Centre (UMC) scale. Investigators provided proper medical care if a major adverse event occurred.

This study adhered to the "New Drugs and Clinical Trial Rules 2019," "National Ethical Guidelines for Biomedical and Health Research involving Human Participants," "Good Clinical Practices Guidelines," and other relevant regulations. This clinical trial was registered with both the Indian regulatory authority, the CDSCO, and the Clinical Trials Registry of India (CTRI), with the registration number provided CTRI/2021/11/037857. Additionally, ethics committee approval has been obtained from all the local ethics committees that are within a 50 km radius of each trial site.



Figs 1A and B: (A) Mean TSS on visit first, second, and third; (B) Percentage reduction in the mean TSS on visit second and third compared to baseline

Results

Efficacy Assessment

A total of 318 out of the 420 enrolled patients completed the study, while 102 were lost to follow-up. The mean TSS score was determined for the first, second, and third visits and compared with the baseline values. During the first visit, the mean TSS score was 9.016, which subsequently decreased to 5.011 and 0.495 on the second and third visits, respectively. This data is illustrated in Figure 1A. Notably, the mean TSS score steadily improved over 5 days after administering the investigational product. The percentage reduction in the mean TSS was 44.42% on the second visit, and 94.51% on the third visit compared to the baseline (Fig. 1B). The outcomes of the one-way ANOVA test demonstrated a statistically significant difference in the TSS value between the first visit and the third visit.

Among the 318 patients in this study, 315 exhibited severe-intensity symptoms, and three patients experienced moderate-intensity symptoms of common cold on their baseline visits, as assessed using the Likert-type symptom severity scale. The severity of these symptoms reduced progressively, such that on the 3rd day of treatment (second visit), only 19 patients had severe symptoms, while 270 experienced moderate symptoms and 29 had mild symptoms. On the 5th day of treatment (third visit), none of the patients had severe symptoms, two patients had moderate symptoms, 48 patients had mild symptoms, and 268 patients had no symptoms of common cold. The intensity of symptoms across the three visits is visually represented in Figure 2.

Safety Assessment

During the study, a total of 13 patients encountered mild adverse effects. Specifically, four (30.7%) patients mentioned experiencing hyperacidity, while nine (69.3%) patients reported feelings of drowsiness following the administration of the investigational product. The potential explanation for these outcomes could be the presence of chlorpheniramine and paracetamol in the investigational drug. Notably, all these adverse events were deemed nonserious, requiring no medical intervention during the study. No additional complications were observed among the participants. The summary of the reported adverse events is mentioned in Table 1.

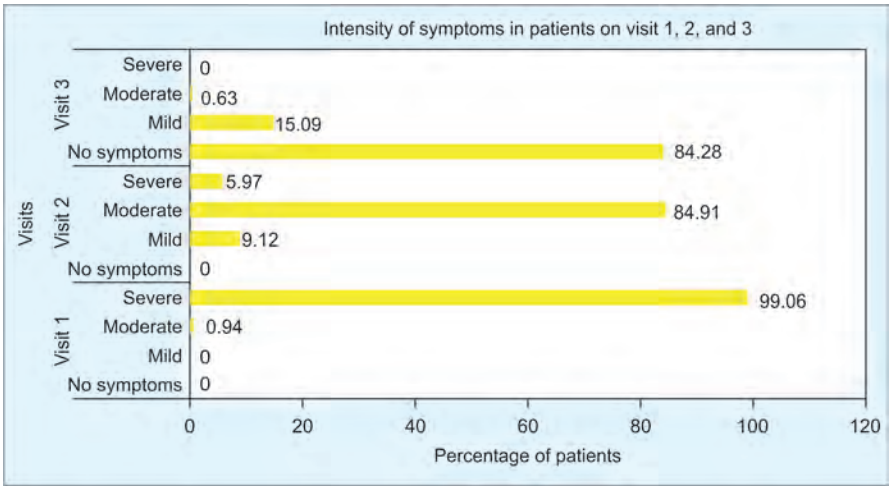


Fig. 2: Intensity of the symptoms on visits first, second, and third

Table 1: Summary of reported adverse events

All adverse events (AEs)	*No. of cases*	*Percentage of patients*	*Intensity of adverse events*
Drowsiness	4	30.7%	Mild
Hyperacidity	9	69.3%	Mild
Serious AEs	0	0	–
AEs leading to discontinuation	0	0	–
AEs leading to death	0	0	–

Discussion

In this study, we investigated the efficacy and safety of the FDC therapy comprising paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg for managing common cold symptoms in adult patients. Below, we discuss our results in comparison with previous research, highlighting both the strengths and limitations of the study.

Our study analyzed data from 318 adults diagnosed with common cold. Over 5 days, we assessed the mean TSS and percentage reduction. On the first visit, the mean TSS value was 9.016, which decreased to 5.011 and 0.495 on the second and third visits, respectively. The percentage reduction in the mean TSS was 44.42% on the second visit and 94.51% on the third visit compared to the baseline value. Additionally, the severity of symptoms was calculated over the 5 days, and by the 5th day of treatment, 268 (84.276%) were completely free of common cold symptoms. During the study, no serious adverse events were reported. The only adverse events reported were hyperacidity and drowsiness, which resolved on their own and did not require any medical intervention. The one-way ANOVA test results indicated a statistically significant difference in TSS values between the 1st and 5th days of treatment.

A phase III clinical trial was conducted by Picon et al. on individuals aged 18–60 with moderate to severe flu-like symptoms or a common cold. The study evaluated the FDC of paracetamol (400 mg), chlorpheniramine maleate (4 mg), and phenylephrine (4 mg) for efficacy and safety over 10 days. 146 patients were randomly assigned to a treatment group (n = 73) or a placebo group (n = 73), with 138 participants completing the study. The outcome measure was the TSS on a 4-point scale, where patients rated their symptoms from 1 (mild) to 4 (severe). Both groups received rescue medication (500 mg paracetamol), and the number of participants using rescue medication was documented. The treatment group experienced a reduction in mean TSS from 14.09 to 3.54, while the placebo group reduced from 14.23 to 4.64. The treatment group showed a significantly greater reduction in symptoms than the placebo group (p = 0.015). The usage of rescue medication was higher in the placebo group (50.7%) than in the treatment group (25%), indicating that the treatment with the investigational product was effective and sufficient for the symptomatic treatment of common cold.[19]

Kiran et al. performed a phase IV clinical trial in India to evaluate the safety and efficacy of the FDC therapy containing paracetamol (500 mg), phenylephrine (10 mg), chlorpheniramine maleate (2 mg), and caffeine (30 mg) for patients with common cold. The study included 18–75-year-old patients who were able to adhere to the study protocol but excluded those with severe renal or hepatic dysfunction or an allergy to any components of the medication. The nonrandomized, noncomparative trial had a treatment duration of 5 days, with patients visiting the clinical trial site three times. The efficacy of the medication was assessed using a TSS on an 11-point scale, ranging from 0 (no symptoms) to 10 (severe symptoms). A total of 280 patients were initially enrolled, with 18 lost to follow-up, leaving 262 patients for analysis. Results showed a significant reduction in the mean TSS, with a 50.72% decrease at the second visit and a 91.40% decrease at the third visit compared to the first visit. Adverse drug events were limited to mild sedation and gastritis. The study concluded that the combination of antihistamine, decongestant, and analgesic in the FDC was effective and safe for symptomatically treating common cold.[21]

In a phase IV clinical trial by Kiran et al., infants with common cold were treated with paracetamol, phenylephrine, and chlorpheniramine maleate oral drops. 200 children who met the age requirement of under 1 year and weighed between 2.5 and 11.8 kg from specialized pediatric facilities were enrolled in the study. These children exhibited symptoms such as fever, sneezing, runny nose, nasal congestion, persistent crying, and cough. Infants with hypersensitivity to the investigational product or hypertension due to phenylephrine were excluded from the study. Treatment spanned 5 days, with three clinical visits. TSS was used to assess the efficacy of the treatment. Of 164 completed infants, 95 were symptom-free by the 5th day. The mean TSS was 5.914 on the first visit, 3.579 on the second visit, and 1.475 on the third visit. The percentage decrease from the baseline was 39.484% during the second and 75.051% during the third. Some parents reported chlorpheniramine-induced drowsiness. The study concluded the paracetamol, phenylephrine, and chlorpheniramine maleate combination was effective and safe for infant cold symptoms, suggesting potential adaptation for adult use.[22]

Our study provides substantial evidence for the efficacy, and safety of the FDC of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg per tablet in managing common cold symptoms in adult patients in India. Moreover, our findings are consistent with earlier studies,

demonstrating the efficacy of FDC therapy in adult populations. Further randomized clinical trials need to be conducted to assess the efficacy and potential adverse effects of this treatment in a larger sample of Indian adults suffering from common cold.

Conclusion

Generally, common cold often resolves by itself within a week, and treatment is usually required only to alleviate the accompanying symptoms. This study shows a significant decrease in the TSS and a high percentage of patients achieving complete relief. Notably, the FDC maintains a favorable safety profile with only a few mild adverse events reported. These results emphasize the significance of the FDC of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg as a treatment option for common cold in Indian patients.

Disclosure

The study was conducted on Indian patients in compliance with all the regulatory guidelines. Dr Devarshi Mhathre, Dr Sanjay Kumar, Dr Nitin Joshi, Dr G N Shirali, Dr Vaishali Sangole, Dr Manya Thakur, and Dr Sharad Bhalekar were investigators for the study. The investigational product used for the conduct of the study is the FDC of paracetamol 500 mg, phenylephrine 10 mg, and chlorpheniramine maleate 2 mg per tablet which is available in the Indian market under the brand name Sinarest New Tablets.

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ORIGINAL ARTICLE

A Retrospective Observational Study to Compare the Clinical and Laboratory Parameters of Patients Requiring Hospitalization during 3rd Wave vs 2nd Wave of Coronavirus Disease 2019

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Abstract

Background: Following the outbreak of coronavirus in Wuhan, China in 2019, there has been multiple waves of different variants of COVID-19 throughout the world in the continuum of a pandemic. This study aims to compare different clinical and laboratory parameters of hospitalized patients in Omicron-driven 3rd wave vs Delta-driven 2nd wave in India.

Materials and methods: This was a retrospective cross-sectional observational study that was done in the Department of General Medicine, Mahatma Gandhi Hospital, Dr S N Medical College, Jodhpur (Rajasthan). It included 100 patients of 3rd wave and 2nd wave respectively who were hospitalized. The primary outcome of the study was patient's survival and condition at discharge and secondary outcomes included length of hospital stay and mode of oxygenation.

Results: The presence of cough, shortness of breath, and loss of taste are more common symptoms in 2nd wave vs 3rd wave with *p*-value being 0.0002, 0.004, and < 0.0001 respectively. The severity of illness, need for intensive care unit (ICU), and outcome in terms of discharge with oxygen or without oxygen were also statistically significant in the 2nd wave vs 3rd wave with *p*-value being < 0.0001 for all three variables. A total of 67% of patients were vaccinated in 3rd wave group compared to 11% in 2nd wave group (*p*-value < 0.0001). Comparison of laboratory parameters also revealed statistically significant results with D-dimer, quantitative C-reactive protein (CRP), normal (NL) ratio, and serum lactate being more deranged in the 2nd wave compared to the 3rd wave with *p*-value being < 0.05. Comparison of involvement of lung parenchyma based on computed tomography (CT) severity score revealed *p*-value < 0.0001 that is statistically relevant.

Conclusion: Omicron-driven 3rd wave was associated with significantly less severity, less inflammatory response, and better outcome compared to Delta-driven 2nd wave. More vaccination and probably less intrinsic virulence during 3rd wave has a major role in the better outcome.

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Introduction

In December 2019, Wuhan, Hubei Province of China, experienced an invasion of atypical acute respiratory disease. This disease later spread rapidly from the city of Wuhan and invaded other parts of the world. Later, it was discovered that the disease was caused by a novel coronavirus. In February 2020, the World Health Organization (WHO) named this disease as "coronavirus disease 2019" (COVID-19). Various variants (like Beta, Alpha, Gamma, Omicron, Delta) of SARS-CoV-2 virus are found to dominate the different pandemic waves. Various COVID variants have varied rates of mortality and prognosis. Till now, COVID-19 has caused three waves in its pandemic; the 1st wave occurred between March 2020 and January 2021.[1] Delta variant started in late 2020 during 2nd wave of COVID infections in India. WHO recognized another variant, that is, Omicron, on November 26, 2021, which was the main variant during the 3rd wave in India. Various emerging COVID-19 variants at the time of different waves not only cause an increase in morbidity, transmissibility, and mortality but also show the capability to dodge identification with the use of various diagnostic tests. They also have the ability of causing a reinfection in already vaccinated and recovered patients.[2] With this background, the present retrospective observational study was planned for the comparison of the clinical and laboratory parameters of patients requiring hospitalization during 3rd wave vs 2nd wave of COVID-19.

Materials and Methods

This was a retrospective cross-sectional observational study that was conducted in the Department of General Medicine, Mahatma Gandhi Hospital (Dr S N Medical College, Jodhpur). 200 patients in total admitted in both general ward and intensive care unit (ICU) from March 1, 2021 to June 30, 2021—2nd COVID wave (Delta variant) and January 1, 2022 to March 31, 2022—3rd COVID wave (Omicron variant) were taken.

Study Design

Retrospective cross-sectional observational study.

Study Location

Department of General Medicine, Mahatma Gandhi Hospital (Dr S N Medical College, Jodhpur).

Sample Size

200 patients.

Sample Size Calculation

The sample size was calculated with alpha error 0.05 and a study power of 80%, using the following formula for hypothesis testing for two independent population proportions:

$$N = \frac{[Z_{1-\alpha/2}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}]^2}{(P_1-P_2)^2}$$

Here, N = sample size, ($Z_{1-\alpha/2}$) = standard normal deviation for type-1 error (taken as 1.96 for 95% confidence level or alpha error 0.05), Z_{1-} = standard normal deviation for type-2 error (taken as 0.84 for 80% study power), P_1 = proportion of complications in group A [taken as 9% (0.09) as per finding in Ward et al.[3]], P_2 = proportion of complications in group B [taken as 2% (0.02) as per finding in Ward et al.[3]], $P = (P_1 + P_2)/2 = 0.05$. The sample size using this formula came to be a minimum of 165 subjects. Considering 10% of attrition rate, the sample size was increased and rounded off to 200.

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Subjects and Selection Method

Systemic sampling was done where every 10th patient was taken from 2nd wave as per the described time frame according to registration number and every 2nd patient in 3rd wave as per registration number of the admitted patients.

Inclusion Criteria

All COVID-19 reverse transcription-polymerase chain reaction (RT-PCR) positive oral throat swab samples or nasopharyngeal swabs above 18 years of age irrespective of gender admitted during the respective time period of 2nd and 3rd waves.

Exclusion Criteria

- Pregnancy.
- Malignancy.

Procedure Methodology

Permission for the study was taken from the Institutional Ethics Committee and also permission from the medical superintendent was taken to access the medical records of admitted COVID-19-positive patients from the medical records room. Relevant information about patients that met the inclusion criteria was collected including clinical parameters, that is, history, detailed examination, vitals at presentation, symptoms, duration of hospital stay, need for mechanical ventilation, oxygen requirement, and mortality. Relevant investigations, that is, arterial blood gas (ABG), complete blood count (CBC), C-reactive protein (CRP), D-Dimer, interleukin-6 (IL-6), international normalized ratio (INR), renal function test (RFT), liver function test (LFT), random blood sugar (RBS), hemoglobin A1c (HBA1c), and imaging of each patient were also recorded. Classification of COVID-19 patients according to clinical severity was divided into three categories, taking into account the presentation on the 1st day of admission. This was based on the guidelines for adult COVID patients given by AIIMS/ICMR-COVID-19 National Task Force/Joint Monitoring Group (MOHFW, Government of India) on May 17, 2021.[4] This is as follows:

Mild: Upper respiratory tract symptoms (and/or fever) but no shortness of breath or hypoxia.

Moderate: Any one of the following:

- Respiratory rate ≥24/minute with breathlessness.
- SpO_2: 90 to ≤ 93% on room air.

Severe: Any one of the following:

- Respiratory rate >30/minute with breathlessness.
- SpO_2: < 90% on room air.

The final outcome of patients was broadly classified as:

- Discharged without domiciliary oxygen therapy.
- Discharged with the requirement of domiciliary oxygen therapy.
- Death during treatment in the hospital.

Statistical Analysis

Quantitative data was compared using student's *t*-test and presented as mean + standard deviation (SD) or median (range). For qualitative variables, Chi-squared test was used and presented as frequency and percentage. All data was analyzed using appropriate software. A *p*-value of < 0.05 was considered statistically significant.

Results

In 2nd wave, mean 54.28 years age was 49.75 years, male:female ratio was 1.85, and percentage of comorbid patients was 51%, while in 3rd wave the mean age was 47.97 years, male:female ratio was 1.5, and 55% patients were comorbid. In 3rd wave group, 67% patients were vaccinated compared to 11% vaccination in 2nd wave group (*p*-value < 0.0001). Regarding symptoms fever was common in both waves (57 vs 64% in 2nd wave and 3rd wave), while cough, shortness of breath, and loss of smell were more common in 2nd wave (*p*-value 0.0002, 0.004, < 0.0001 respectively). In comparison of mode of oxygenation, *p*-value was < 0.0001, that is, significant, suggesting more oxygen demand in 2nd wave compared to 3rd wave. The mean normal (NL) ratio was 4.47 in 2nd wave, while 2.97 in 3rd wave. Mean hospital stay was 10.55 days in 2nd wave and 5.29 days in 3rd wave (*p*-value < 0.0001), mean computed tomography (CT)-score was 15.76 in 2nd wave and 7.82 in 3rd wave (*p*-value < 0.0001). D-dimer was raised in 83% of patients in 2nd wave and 41% in 3rd wave (*p*-value < 0.0001). CRP was raised in 100% of patients in 2nd wave compared to 84% patients in 3rd wave group (*p*-value < 0.0001). Serum lactate was raised in 73% of patients in 2nd wave group, while 35% patients had raised value in 3rd wave group (*p*-value < 0.0001). In 2nd wave group, 67% of patients needed ICU, while 17% needed ICU in 3rd wave (*p*-value < 0.0001). Finally, on comparing outcomes, more deaths occurred in 2nd wave compared to 3rd wave (33 vs 9%) and more patients needed oxygen at the time of discharge (18 vs 8% respectively), with a statistically significant difference suggesting poor outcomes in 2nd wave (*p*-value was < 0.0001) (Table 1). Both the groups had almost

Table 1: Comprehensive table comparing major parameters between both the groups

Variable		*2nd wave*	*3rd wave*	*p-value*
Mean age		54.28	47.97	0.003
M:F ratio		1.85	1.5	0.465
Comorbidity		51 (51%)	55 (55%)	
Symptoms	Fever	57 (57%)	64 (64%)	0.311
	Cough	65 (65%)	39 (39%)	0.0002
	Loss of smell	44 (44%)	2 (2%)	<0.0001
	Malaise	8 (8%)	33 (33%)	<0.0001
	Vomiting	2 (2%)	15 (15%)	0.001
	Shortness of breath	66 (66%)	46 (46%)	0.004
Vaccinated		11 (11%)	67 (67%)	<0.0001
Oxygen requirement	Face mask	14 (14%)	27 (27%)	<0.0001
	High flow mask	26 (26%)	9 (9%)	
	Invasive	24 (24%)	10 (10%)	
	NIV	36 (36%)	2 (2%)	
	Room air	0	52 (52%)	
Mean NL ratio		4.47	2.97	
Mean hospital stay		10.55	5.29	<0.0001
Mean CT score		15.76	7.82	<0.0001
D-dimer (>500 ng/mL)		83 (83%)	41 (41%)	<0.0001
CRP (>10 mg/L)		100 (100%)	84 (84%)	0.0002
Lactate (>1.5 mmol/L)		73 (73%)	35 (35%)	<0.0001
ICU admission		67 (67%)	17 (17%)	<0.0001
Discharge with domiciliary oxygen therapy		18 (18%)	8 (8%)	<0.0001
Death		33 (33%)	9 (9%)	<0.0001

similar numbers of comorbid patients with insignificant *p*-value. In total 51% of patients were comorbid in 2nd wave compared to 55% in 3rd wave (Table 2). In 2nd wave, 14% of patients needed venturi mask, 26% needed high flow mask, 24% needed invasive ventilation, and 36% needed noninvasive ventilation (NIV), while none of the patients were on room air. In 3rd wave, 27% of patients needed venturi mask, 9% needed high flow mask, 10% needed invasive ventilation, 2% needed NIV, and 52% patients maintained saturation on room air. Here, the demand for oxygen showed significant difference, that is, statistically relevant (with *p*-value < 0.0001) showing the increased need for oxygen in 2nd wave compared to 3rd wave (Table 3). In 2nd wave, 14% of patients were in mild category, 32% in moderate, and 54% in severe category, while 3rd wave group had 60% patients in mild category, 23% in moderate category, and 17% in severe, having a statistically significant difference with a *p*-value < 0.0001 (Table 4).

Discussion

In our study of 200 people admitted in our hospital, a comparison was made between 100 patients of 2nd wave (mostly Delta variant) vs 100 patients of 3rd wave (mostly Omicron variant) COVID-19 patients. Among the 2nd wave group, 65% were male and 35% were female, while among the 3rd wave group of patients were 60% men and 40% were women. Male:female ratio was 1.85 in 2nd wave, while 1.5 in 3rd wave; hence both groups were comparable. The mean age was 54.28 ± 13.48 in the 2nd wave and 47.97 ± 16.86 in the 3rd wave. Among 2nd wave group, 51% of patients were comorbid, while 55% were comorbid among 3rd wave group of patients, suggesting almost equal distribution and hence comparable. A comparison of symptoms showed that fever was chief complaint in 57% of patients in 2nd wave as compared to 64% patients in 3rd wave ($p = 0.311$) suggesting that fever was common symptom in both waves. Cough was present in 65% of patients in 2nd wave compared to 39% of patients in 3rd wave ($p = 0.0002$), hence cough was statistically more common complaint in 2nd wave compared to 3rd wave. Similarly, loss of smell was present in 44% of patients in 2nd wave compared to 2% of patients in 3rd wave (*p*-value < 0.0001), hence loss of smell was more common symptom in 2nd wave compared to 3rd wave. Gastrointestinal symptom like vomiting was chief complaint in 2% of patients in 2nd wave, while 15% of patients had vomiting in 3rd wave (*p*-value = 0.001), that is, gastrointestinal symptoms were more common in 3rd wave. Shortness of breath was present in 66% of patients in 2nd wave compared to 46% of patients in 3rd wave (*p*-value = 0.004), suggesting that it was more common symptom in 2nd wave and more involvement of lung parenchyma. The above data suggests that the symptoms that characterize an Omicron infection are different from those of the Delta SARS-CoV-2 variant and have less involvement in the lower respiratory tract. Arslan et al.[5] in their research concluded that the number of asymptomatic patients were significantly higher in the Omicron variant group than in the Delta variant group (34.7 vs 13.7%, respectively, *p*-value < 0.001). Menni et al.[6] in their prospective observational study found that loss of smell was less common in patients infected with Omicron variant than with Delta variant (16.7 vs 52.7%, odds ratio (OR) 0.17; 95% confidence interval (CI) 0.16–0.19, *p*-value < 0.001). Regarding vaccination status, 11% of patients were vaccinated in 2nd wave group compared to 67% vaccination in 3rd wave (*p*-value < 0.0001). Bouzid et al.[7] in their retrospective cohort study found that patients with the Omicron variant were more vaccinated (65 vs 39% for 1 dose and 22 vs

Table 2: Distribution of patients according to comorbidity

Comorbidities	*2nd wave*		*3rd wave*		*p-value*
	N	*%*	*N*	*%*	
Diabetes	31	31.0	29	29.0	0.757
Hypertension	36	36.0	31	31.0	0.453
IHD	6	6.00	9	9.00	0.420
COPD	8	8.00	17	17.0	0.054

Table 3: Distribution of patients according to the mode of oxygenation

Mode of oxygenation	*2nd wave*		*3rd wave*	
	N	*%*	*N*	*%*
Venturi mask	14	14.00	27	27.00
High flow mask	26	26.00	9	9.00
Invasive	24	24.00	10	10.00
NIV	36	36.00	2	2.00
Room air	0	0.00	52	52.00
Total	100	100.00	100	100.00

Chi-square 100.56; *p*-value < 0.0001 (S)

Table 4: Distribution of patients according to the severity

Initial severity	*2nd wave*		*3rd wave*	
	N	*%*	*N*	*%*
Mild	14	14.00	60	60.00
Moderate	32	32.00	23	23.00
Severe	54	54.00	17	17.00
Total	100	100.0	100	100.0

11% for 3 doses). Comparison of severity of illness showed that 86% of patients were moderately to severely affected among 2nd wave group as compared to 40% among 3rd wave group (p-value < 0.0001), hence showing decreased severity among patients of 3rd wave, this might be due to the fact that 67% patients were vaccinated in the 3rd wave compared to 11% in 2nd wave, hence resulting in better immunity and outcome and also decreased virulence of Omicron itself might also have contributed to this. Bouzid et al.[7] in their retrospective cohort study found that as compared to Delta variant, the Omicron variant was independently associated with a lower risk for ICU admission, mechanical ventilation, and inhospital mortality.

When oxygen required was compared, it revealed that among 2nd wave patients, 26% (n = 26) required high flow mask, 24% (n = 24) required invasive ventilation, 36% (n = 36) required NIV, 14% (n = 14) required venturi mask, and 0% (n = 0) maintained SpO_2 on room air, while among 3rd wave patients 9% (n = 9) required high flow mask, 10% (n = 10) required invasive ventilation, 2% (n = 2) required NIV, 27% (n = 27) required venturi mask, and 52% (n = 52) maintained SpO_2 on room air (p-value < 0.0001), showing that the oxygen requirement was more among 2nd wave patients compared to 3rd wave patients, suggesting more involvement of lung parenchyma and more severity.

A comparison of mean hospital stay showed that mean hospital stay was 10.55 days among 2nd wave group patients, while 5.29 days in 3rd wave group of patients. This indicates that 2nd wave was associated with longer duration of stay, slower recovery, and increased morbidity. Mean CT-score was 15.76 in 2nd wave group of patients, while 7.82 in 3rd wave group of patients. Arslan et al.[5] in their study found that the median high-resolution computed tomography (HRCT) thorax score was significantly higher in the Delta variant group than in the Omicron variant group (p = 0.001). This suggests that 2nd wave had more involvement of lung parenchyma and hence more oxygen requirement. The final outcome was also compared which showed that among 2nd wave patients, 18% (n = 18) were discharged with domiciliary oxygen, 49% (n = 49) were discharged without domiciliary oxygen therapy, and 33% (n = 33) were expired, while among 3rd wave patients, 8% (n = 8) were discharged with domiciliary oxygen, 83% (n = 83) discharged without domiciliary oxygen therapy, and 9% (n = 9) were expired (p-value < 0.0001), suggesting that mortality and severity was more in 2nd wave compared to 3rd wave. Bouzid et al.[7] in their study found that patients having the Omicron variant had a higher rate of discharge home from the emergency department (ED) [59 vs 37%; difference, 21. 9% age points (–26.5 to –17.1% age points)]. Also, among 2nd wave patients, 67% (n = 67) needed ICU care, while among 3rd wave patients, 17% (n = 17) needed ICU (p-value < 0.0001), suggesting more severity of illness in 2nd wave. Among laboratory parameters, neutrophil lymphocyte ratio comparison showed that among 2nd wave patients 58% (n = 58) had higher than normal value, that is, >3.5 compared to 33% (n = 33), among nonvaccinated patients (p-value = 0.0004) suggesting NL ratio was more in 2nd wave compared to 3rd wave patients. Serum lactate was >1.5 mmol/L in 73% (n = 73) in 2nd wave patients, while 35% (n = 35) in 3rd wave patients (p-value < 0.0001), suggesting more severity of hypoxia and more lung involvement in 2nd wave. Comparison of serum CRP-values suggested that 100% of patients in 2nd wave group had raised CRP (>10 mg/L) as compared to 84% in 3rd wave group (p-value 0.0002), suggesting more severity of inflammation in 2nd wave. Comparison of D-dimer was also made which revealed that 83% of patients in 2nd wave group had raised D-dimer values compared to 41% in 3rd wave group (p-value 0.0002), this indicates that more patients in 2nd wave had procoagulant state and this might be the reason of more incidence of stroke and myocardial infarct post COVID-19 illness after 2nd wave. Li et al.[8] in their study found that D-dimer levels were lower in Omicron cases [median D-dimer level 0.04 mg/L (0.02–0.09)] than in Delta cases [33.2 s (28.9–37.3); 0.33 mg/L (0.19–0.60)].

Conclusion

Omicron-driven 3rd wave was associated with significantly less severity, less inflammatory response, and better outcome compared to Delta-driven 2nd wave. More vaccination and probably less intrinsic virulence during 3rd wave has a major role in the better outcome.

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ORIGINAL ARTICLE

Effect of a Structured Tele Based Post COVID-19 Rehabilitation Program in the Indian Population

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Abstract

Introduction: The emergence of coronavirus disease of 2019 (COVID-19) and the imperative for social distancing have propelled telehealth to the forefront. Even after discharge, patients may experience lingering symptoms, termed post-COVID-19 syndrome, which impairs functioning. This syndrome persists beyond recovery from COVID-19. Hence, timely implementation and sustained access to pulmonary rehabilitation services are crucial for COVID-19 patients. This study aims to assess the impact of a structured telerehabilitation program on post-COVID-19 recovery in the Indian population.

Methodology: A total of 53 patients, with their informed consent, were included in the study, comprising 71.7% males and 24.3% females, with a mean age of 57.15 years (SD = 11.74, range: 30–81 years). Upon enrollment, comprehensive assessments were conducted, incorporating the visual analog scale (VAS) score for fatigue, 1-minute sit-to-stand test, post-COVID-19 functional status scale, and Depression, Anxiety, and Stress Scale-21 (DASS-21). Treatment interventions were administered remotely *via* WhatsApp video or Zoom calls, consisting of pulmonary rehabilitation protocols encompassing warm-up exercises, breathing exercises, aerobic and strength training, yoga, cooldown exercises, and regular educational sessions tailored to individual patient needs.

Results: There was a significant improvement in outcome measures: VAS score for fatigue ($t = 8.6$, S, $p < 0.001$), 1-minute sit-to-stand (steps: $t = 5.9$, S, $p < 0.001$), and health-related quality of life ($Z = 5.9$, S, $p < 0.001$).

Conclusion: The study shows that a structured tele-based program is not only effective in patients but also an approach that is feasible and should be considered for the delivery of rehabilitation to patients who are unable to participate in center-based rehabilitation.

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Introduction

The coronavirus disease of 2019 (COVID-19) outbreak, first detected in Wuhan, China, in December 2019, rapidly escalated into a global pandemic. It is a highly contagious respiratory disease causing widespread respiratory, physical, and psychological impacts on patients.[1] Post-COVID-19 recovery involves patients experiencing different levels of respiratory, physical, and psychological issues. Both patients treated in hospitals and those managed at home may face ongoing impairments. Developing a targeted rehabilitation program is essential to aid their recovery, highlighting the importance of pulmonary rehabilitation for all affected individuals.

Approximately, 10–20% of individuals who experience symptomatic acute COVID-19 are reported to transition to a persistent phase of clinical manifestations, lasting over a month's duration[2] and characterized by chronic symptoms such as fatigue, dyspnea, headache, neurocognitive conditions, including brain fog, and impaired daily physical functioning[3] with increased risk of developing stress, depression, irritability, insomnia, and frustration.[4] This complex and debilitating phenomenon is commonly referred to as post-COVID-19 syndrome. Also, patients with severe acute respiratory syndrome (SARS), a disease caused by the same taxonomy as that of COVID-19 had similar presentations and the follow-up studies have shown that the physiological and radiological abnormalities persisted even after 6 months.[5]

COVID-19 prompted a public health emergency, emphasizing the equal importance of prevention, treatment, and rehabilitation in the medical response. The pandemic necessitated contact-free methods for safe treatment delivery, underlining the significance of telehealth services like telecoaching, telemonitoring, and telerehabilitation. Telerehabilitation serves the dual purpose of need for rehabilitation and social distancing,[6] hence merits its adoption for post-COVID-19 patients with mild to moderate disabilities requiring frequent monitoring or residing in isolated areas or are not available to participate in standard programs. Telerehabilitation allows patients to access medical care, exercise guidance, and psychological support remotely, reducing the risk of disease transmission and minimizing hospital visits. This method has the potential to replace human interaction without compromising patient satisfaction or effectiveness of treatment delivery and eliminates the stress of contracting the disease to both the patients and treating therapist.[7] This study is aimed at studying the effect of a structured tele-based post-COVID-19 rehabilitation program in the Indian population.

Methodology

This retrospective study, spanning August 2020–May 2021 at the Pratibha Prabhakar Pulmonary Rehabilitation Centre, Mumbai, India, analyzed data from post-COVID-19 survivors enrolled in a telerehabilitation program. Given the pandemic and lockdowns in Mumbai, the 4-week program was delivered *via* WhatsApp/Zoom. Patients were informed at enrollment that their data might be used for research, and voluntary consent was obtained. Patient recruitment for telerehabilitation is detailed in Figure 1.

Following a detailed history and evaluation, treatment goals were set, and a treatment plan was developed. The outcome measures used for the patient assessment were as follows:

- Visual analog scale for fatigue (VAS-F).
- 1-minute sit-to-stand test (1-minute STS test).
- Post-COVID-19 functional status scale (PCFS scale).[8]
- DASS-21 scale.[9]

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The pulmonary rehabilitation program included:

- Warm-up exercises: Breathing, chest expansion, stretching, and range of motion exercises for all joints and muscle groups.
- Aerobic exercises: Walking, spot marching, and stair climbing.
- Strengthening exercises: Utilizing household items (e.g., water bottles, sandbags) or Therabands for upper and lower limbs, shoulder girdle, lunges, squats, dynamic quadriceps, and sit-to-stand exercises.
- Yoga: Asanas for chest expansion (parvatasana, chakrasana), breathing techniques (om chanting), pranayama (anulom-vilom, bhramari).
- Cool down: Stretching, relaxation, meditation techniques.
- Respiratory exercises: Incentive spirometry, expiratory exercises with balloon bladder.
- Education: Regular individual patient education sessions.

Patients were individually monitored for heart rate, oxygen saturation (SpO_2), and rate of perceived exertion (RPE) during exercise sessions. Exercise intensity was progressively adjusted according to each patient's response and capacity. Rehabilitation sessions were conducted remotely, three times weekly over 4 weeks. Postprogram, patients were reassessed to determine discharge or continued rehabilitation needs.

Results

The sample size was determined using SAS 9.2, and data analysis was performed with Statistical Package for the Social Sciences (SPSS) V15.0. Data presentation included mean, standard deviation (SD), and count (*N*) for continuous variables, and frequency and percentage for categorical variables. Normal data comparisons between pre- and postintervention were conducted using student's paired *t*-test, while the Wilcoxon signed-rank test was utilized for nonnormal data. Both tests were applied due to uncertainty about data normality, yielding similar significant results. Statistical tests were two-tailed with an alpha (α) significance level set at $p < 0.05$. The initial sample size calculation, based on literature review, indicated 14 participants were needed; however, for statistical validity, 53 participants were included. The demographic characteristics of the study participants are presented in Table 1, which provides information on gender, comorbidities, treatment location, and ventilation type. The study was retrospective, evaluating pre- and postintervention data.[10] Table 2 summarizes the pre- and postanalysis of results for, VAS-F, 1-minute STS test, and PCFS scale. Figure 2 illustrates the changes in functional capacity measured by the 1-minute STS test pre- and postintervention. Figure 3 illustrates the changes in fatigue measured by VAS F and health-related quality of life measured by (PCFS scale) pre- and postintervention.

Descriptive Statistics: Study Population ($n = 53$)

Discussion

In a study on the effectiveness of a telerehabilitation program for post-COVID-19 recovery in India, 53 patients (71.7% males, 24.3% females, mean age 57.15 ± 11.74, range: 30–81) showed significant improvements in VAS-F score, 1-minute STS test, and PCFS scale.

Visual Analog Scale for Fatigue

Fatigue is a prominent feature of post-COVID-19 syndrome and leads to activity limitation and poor quality of life in post-COVID-19 patients.[10] In this study, the telerehabilitation program resulted in statistically significant improvement in fatigue. The observed improvement can be attributed to several factors, including enhanced muscular strength, increased aerobic capacity, and reduced desaturation.

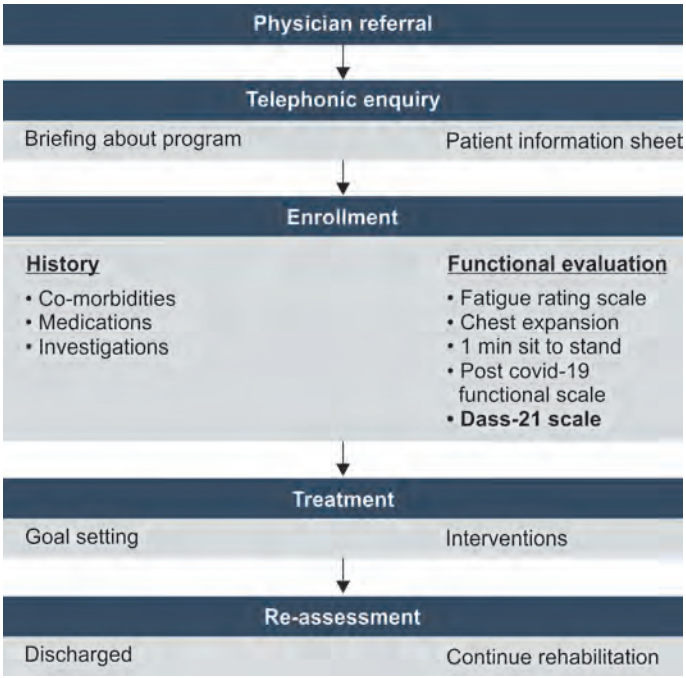

Fig. 1: Process of the patient recruitment into the telerehabilitation program

Table 1: Demographic data

Sr. no.	*Demographic data*	*Variables*	*Percentage (%)*
1	Gender	Males	72
		Females	28
2	Comorbidities	Diabetes mellitus	34
		Hypertension	42
		Ischemic heart disease	19
		Chronic pulmonary disease	9
		Neurological conditions	13
3	Place of treatment	Hospitalized	96
		Home quarantined	4
4	Type of ventilation	Mechanical	0
		Noninvasive ventilation	25
		Nonrebreather mask	21
		Simple face mask	36
		Nasal canula	85

Table 2: Analysis of outcome measures comparing pre- and postvalues

Outcome measure	*Test*	*Pre*	*Post*	*Test value, significance and p-value*
VAS-F	Paired *t*-test	3.08 ± 2.35	0.84 ± 1.31	$t = 8.6$, S, $p < 0.001$
	Wilcoxon signed rank test	3.0 (0.0, 9.0)	0.0 (0.0, 4.0)	$Z = 5.5$, S, $p < 0.001$
1-minute STS test	Paired *t*-test			
Steps		14.30 ± 5.83	18.64 ± 5.42	$t = 5.9$, S, $p < 0.001$
Seconds		57.98 ± 5.91	59.85 ± 1.10	$t = 2.3$, S, $p = 0.024$
RPE		3.23 ± 2.12	1.64 ± 1.46	$t = 6.1$, S, $p < 0.001$
Steps	Wilcoxon signed rank test	15 (3.0, 25.0)	60 (27.0, 60.0)	$Z = 4.8$, S, $p < 0.001$
Seconds		19 (6.0, 32.0)	60 (52.0, 60.0)	$Z = 2.4$, S, $p = 0.02$
RPE		3 (0.0, 10.0)	1.5 (0.0, 5.0)	$Z = 5.1$, S, $p < 0.001$
PCFS scale	Paired *t*-test	2.06 ± 1.25	0.66 ± 1.04	$t = 9.9$, S, $p < 0.001$
	Wilcoxon signed rank test	2.0 (0.0, 4.0)	0.0 (0.0, 4.0)	$Z = 5.9$, S, $p < 0.001$

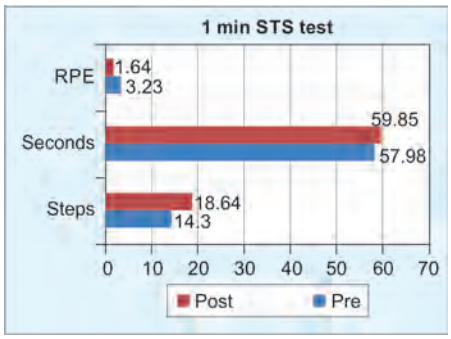

Fig. 2: 1-minute STS test: comparing pre- and postvalues

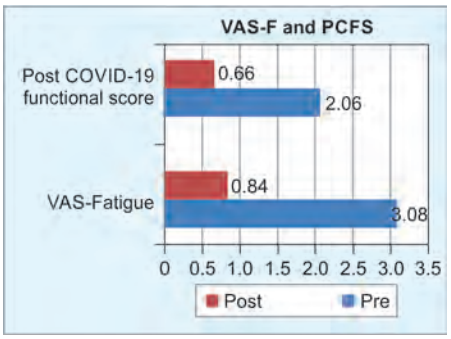

Fig. 3: Fatigue and health-related quality of life: comparing pre- and postvalues

Pulmonary rehabilitation has been shown to alleviate dyspnea and fatigue and enhance self-dependence in patients with chronic respiratory diseases like interstitial lung disease (ILD)[11] and chronic obstructive pulmonary disease (COPD).[12] Strength training, a component of exercise training in pulmonary rehabilitation imparts multisystem benefits. In the musculoskeletal system, it increases the number of sarcomeres and actin and myosin content and alters muscle fiber composition. It modulates neural responses by increasing neuromuscular coordination. Strength training also regulates whole-body metabolism.[13]

Recent evidence suggests that low-load strength training may be more effective than traditional high-load training. Lower volume and fewer repetitions have been shown to significantly improve strength and power output, and lead to muscle hypertrophy. Additionally, low-load training helps to avoid the discomfort, fatigue, and stiffness that often follow more demanding high-load workouts.[14,15] Also, in COPD patients, breathing exercises have been shown to be effective in reducing fatigue.[11] Similarly, in this study, incorporation of breathing exercises might have impacted the fatigue scores. Regular practice of breathing exercises, alters breathing patterns, through more efficient diaphragm recruitment. This leads to a reduction in breathlessness, thereby reducing the fatigue levels.

1-Minute Sit-to-stand Test

In this study, the median number of repetitions for 1-minute STS test during the initial assessment was 15. However, the reference value for 1-minute STS test in age-matched normal individuals is 41 repetitions.[16] Hence, performance of subjects in this study was almost 65% less (below percentile 2.5 of the reference values) than their healthy counterparts in 1-minute STS test. This suggests a significant decrease in functional capacity in post-COVID-19 patients at the time of enrolment. A significant decrease in functional capacity in patients during and after COVID-19 is well documented.[17] Following 4 weeks of telerehabilitation, statistically significant improvement was observed in the number of repetitions in 1-minute STS test ($p < 0.001$). Also, the average improvement of four repetitions on 1-minute STS test following a telerehabilitation program in this study exceeds the minimal important difference (MID) of this test in COPD patients which is three repetitions. This indicates indirectly that the improvement achieved in the functional capacity by telerehabilitation is clinically significant although a direct relation through MID in patients with COVID-19 is not established yet.[18] This significant improvement in functional capacity could be the result of cardiovascular conditioning, oxidative metabolic changes at the muscle level, better ventilation, and lung recruitment brought about by a holistic pulmonary rehabilitation program consisting of aerobic exercises, strength exercises, and breathing exercises. Few additional studies have corroborated the impact of telerehabilitation on functional capacity among post-COVID-19 patients, exhibiting results consistent with the findings presented in this study. A prospective cohort study conducted in New York concluded that virtual outpatient rehabilitation for patients recovering from COVID-19 showed improvement in lower limb strength and cardiopulmonary endurance following 2 weeks of rehabilitation. They also emphasized that virtual rehabilitation is an efficacious method of treatment delivery for recovering COVID-19 patients.[19] A retrospective case series that assessed effects of 8-week pulmonary telerehabilitation on functional capacity using 1-minute STS test in COVID-19 survivors in the Indian population also showed a statistically and clinically significant improvement in functional capacity.[10]

Post-Coronavirus Disease 2019 Functional Status Scale

Reduced levels of physical activity, functional mobility, anxiety, depression, pain, and discomfort were extensively documented in COVID-19 survivors. Shah et al. in a cross-sectional survey established impaired health-related quality of life (HRQOL) in COVID-19 survivors despite other comorbidities. They further documented a greater decline in mobility, self-care, and usual activities in hospitalized compared with those who did not require hospitalization. They further documented that the impact persisted across all the domains of HRQOL even beyond 12 weeks of infection.[20] PCSF scale is a patient-reported scale designed to assess the effects of COVID-19 on functional status. It is an ordinal scale, from grade 0 which indicates "no functional limitation" to grade 4 indicating "severe functional limitation." It is an easy to administer tool and it evaluates both symptom intensity and HRQOL. The developers proposed its use to monitor direct recovery upon discharge from the hospital, at 4 and 8 weeks postdischarge; and to assess functional sequelae at 6 months.[8]

Machado et al. demonstrated the construct validity of the PCFS Scale in patients with COVID-19, 3 months after the onset of symptoms. They also proposed its use to discriminate between subjects with greater impairments in terms of symptoms, HRQOL, and physical activity. They further advocated its use for referring patients to rehabilitation programs and as an outcome in research studies.[21] This study revealed a significant reduction in PCFS scale scores posttelerehabilitation, signifying notable enhancement in the functional status of subjects after the intervention. Gloeckl et al. showed a statistically significant improvement in HRQOL, assessed using 36-question short-form health survey (SF-36) in postacute COVID-19 patients following a pulmonary rehabilitation program.[22] Spielmanns et al. in their prospective cohort study assessed the effects of postacute comprehensive pulmonary rehabilitation on functional status using functional independence measurement (FIM). They found significant clinical and functional improvements and underlined the importance of postacute rehabilitation for COVID-19 recovery.[23] The results of these studies are consistent with the findings of this study. However, this study's assessment of HRQOL using a disease-specific outcome measure enhances the credibility and clinical relevance of the results.

Conclusion

The impairments caused by COVID-19 persist even after the infection is subsided. This warrants rehabilitation as a key during the recovery phase. This study shows that a structured tele-based program is a feasible yet effective approach and should be considered for the delivery of rehabilitation to patients who are unable to participate in center-based rehabilitation. Further studies are required to assess the benefits of tele-based vs center-based rehabilitation and to gauge the cost-effectiveness of the same. This could then benefit patients in areas where accessing a center for rehabilitation is not possible.

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ORIGINAL ARTICLE

Gastrointestinal Tuberculosis: 8-year Experience from a Tertiary Care Hospital in North India

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Abstract

Introduction: Tuberculosis (TB) represents a significant communicable disease on a global scale. The clinical manifestations of abdominal TB frequently resemble those of various gastrointestinal disorders, potentially leading to delays in accurate diagnosis.

Materials and methods: From January 2012 to December 2019, consecutive patients aged 12 years and older, diagnosed with gastrointestinal TB at a tertiary care center in North India, were enrolled. Demographic and clinical data, radiological imaging findings, gastrointestinal endoscopy results, and histopathological findings were meticulously recorded. Antitubercular treatment was administered, and gastrointestinal endoscopy was performed upon the completion of treatment.

Results: During the study period, 234 patients with gastrointestinal tuberculosis were enrolled, of which 151 (64.5%) were male and 83 (35.5%) were female. The most common presenting symptoms included weight loss (94.9%), abdominal pain (85.9%), fever (51.7%), and diarrhea (30.8%). The ileocecal region was the most frequently affected site (76.1%), followed by segmental colonic TB (17.1%). The most common finding on computed tomography (CT) of abdomen was thickening of the bowel wall with/without local or mesenteric lymphadenopathy. The most common endoscopic lesions were ulcerations (82.0%) followed by nodularity (73.9%), deformed cecum and ileocecal valve (41.9%) and strictures (11.1%). Histopathological examination of endoscopic biopsy revealed, well-formed granulomas in 94 (40.2%), collection of epithelioid cells with Langhans giant cells in 66 (28.2%), and chronic nonspecific inflammatory changes in 74 (31.6%). All patients responded to the antitubercular treatment. Follow-up colonoscopy in 171 (73.1%) patients showed regression of lesions.

Conclusion: Gastrointestinal tuberculosis (GiTb) presents with nonspecific symptoms such as weight loss, fever, and abdominal pain, with ileocecal region being most commonly involved. Gastrointestinal endoscopy shows ulceration, nodularity, and strictures as prominent findings. Histopathology and culture were helpful for making diagnosis in almost half of the patients with GiTb. Majority of the patients responded well to antitubercular treatment.

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Introduction

Tuberculosis (TB) remains a critical global health issue, with India accounting for 27% of the world's TB cases.[1] Extrapulmonary TB, which occurs in approximately 20% of TB cases, includes abdominal TB (10% of extrapulmonary TB), which is associated with significant morbidity and mortality.[2,3] Gastrointestinal tuberculosis (GiTb) constitutes about 70–78% of abdominal TB cases, with the ileocecal area being most commonly involved followed by colon and jejunum.[4] Rarely GiTb may also involve stomach, duodenum, and esophagus. The three characteristic intestinal lesions produced in GiTb include (1) ulcerative, (2) hypertrophic, and (3) stricturous or constrictive.[4] The diagnosis of GiTb is often made by combining clinical suspicion, endoscopic or colonoscopic findings with tissue histology including acid-fast bacilli (AFB) staining. GiTb can mimic benign ulcers, malignancy, Crohn's disease (CD), or sarcomas.[5,6]

The study aimed to evaluate the clinical, radiological, endoscopic, and histopathological features of GiTb and to assess the response to antitubercular therapy (ATT).

Materials and Methods

We conducted a prospective cohort study, enrolling consecutive patients aged 12 years and older diagnosed with gastrointestinal tuberculosis (GiTb) based on clinical evaluation, radiological imaging findings, and tissue histology from January 2012 to December 2019. The study was conducted in a tertiary care center in North India.

A diagnosis of GiTb was made in patients with compatible symptoms if one of the following criteria was met:

- Isolation of *Mycobacterium tuberculosis* from biopsy specimens.
- Demonstration of caseating epithelioid cell granuloma and/or AFB on histopathological and AFB staining assessment of biopsy specimens.
- Successful therapeutic trial to antitubercular treatment (ATT) in addition to clinical and radiological evidence of tuberculosis.

Patients with active pulmonary tuberculosis, tubercular ascites, and/or pleural effusion were excluded from the study. Additionally, patients with ulcerative colitis and CD, as well as those with radiological imaging showing lesions limited to the jejunum/proximal ileum (due to the nonavailability of an enteroscope for small bowel visualization), were also excluded. Demographic, clinical data, and radiological imaging findings were recorded. Patients underwent either upper and/or lower gastrointestinal endoscopic examination with biopsies as indicated by clinical and radiological evaluations. Esophagogastroduodenoscopy (EGO) was performed after overnight fasting (or fasting for a minimum of 6 hours) using the Olympus EXERA II GIF-H 180 gastroscope. Ileocolonoscopic examination was conducted using the Olympus EXERA II CF-H180 AL video colonoscope. During EGO and ileocolonoscopy, the location and type of lesions (ulcers, nodules, or strictures) were identified in all patients.

Strictures were defined as luminal narrowing that prevented the passage of the scope through the area of narrowing. When a lesion was identified, a minimum of six biopsy samples were obtained from the edges of the lesion and subjected to histopathology, acid-fast staining, and culture. Biopsy samples were incubated in BACTEC MGIT-960 systems (Becton Dickinson

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Diagnostic, United States). Growth obtained was subjected to Ziehl–Neelsen (ZN) staining. If AFB were present, further confirmation was done by immunochromatography assay (TBcID), which is specific for the MPT64 antigen of the *Mycobacterium tuberculosis* complex.

Patients diagnosed with GiTb were treated with standard antitubercular drugs as per the revised national TB control program (RNTCP) under directly observed treatment, short-course (DOTS). Repeat endoscopy/colonoscopy was performed after the completion of treatment.

Statistical Analysis

The data collected were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version software. Results were expressed as mean ± standard deviation, ranges, median, or percentages. Descriptive statistical methods were employed to analyze the results.

Results

During the study period, 234 patients were diagnosed with gastrointestinal tuberculosis. Of these, 151 (64.5%) were male and 83 (35.5%) were female, resulting in a male-to-female ratio of 1.8:1. The mean age was 40.9 ± 15 years. Most patients (77.8%) had experienced symptoms for a duration ranging from 6 months to 2 years prior to diagnosis (Table 1). The most common presenting symptoms among patients with gastrointestinal TB were weight loss (94.9%), abdominal pain (85.9%), fever (51.7%), and diarrhea (30.8%) (Table 2). A history of ATT for pulmonary TB was present in seven patients (3%).

The most frequently involved site was the ileocecal region (76.1%), followed by segmental colonic TB (17.1%). Isolated ileal TB was observed in 5.1%, duodenal TB in 0.9%, esophageal TB in 0.4%, and gastric TB in 0.4% of patients (Table 2). Among patients with segmental colonic TB, the ascending colon was most commonly affected (12%, *n* = 28), followed by the sigmoid colon (2.1%) (Table 2).

Table 1: Duration of symptoms in study population

Duration of symptoms in years	*Number (%)*
<6 months	20 (8.5%)
6 months–1 year	100 (42.7)
1–1.5 years	32 (13.7%)
1.5–2 years	50 (21.4%)
>2 years	32 (13.7%)

Radiological imaging, specifically CT, revealed thickening of the bowel wall with or without luminal narrowing and local and/or mesenteric lymphadenopathy as the most common findings (Table 2 and Figs 1 to 3). Endoscopic findings included ulcerations (82.1%), nodularity (73.9%), deformed cecum and ileocecal valve (41.9%), and strictures (11.1%) (Table 2 and Figs 1 to 3). Histopathological examination showed well-formed granulomas in 94 patients (40.2%), with focal caseation in 26 patients (Figs 3A to D). Other histopathological findings included collections of loosely arranged epithelioid cells with Langhans giant cells in 66 patients (28.2%) and chronic nonspecific inflammatory changes in 74 patients (31.6%). AFB was detected in 32 patients (13.7%) on ZN staining of endoscopic biopsy specimens. BACTEC-MGIT cultures from biopsy specimens revealed *Mycobacterium tuberculosis* growth in 131 patients (56%).

All patients were treated with ATT according to the revised national TB control program (RNTCP). Follow-up endoscopy in 171 patients (73.1%) demonstrated regression of lesions, with clearance of ulcers, nodularity, and strictures.

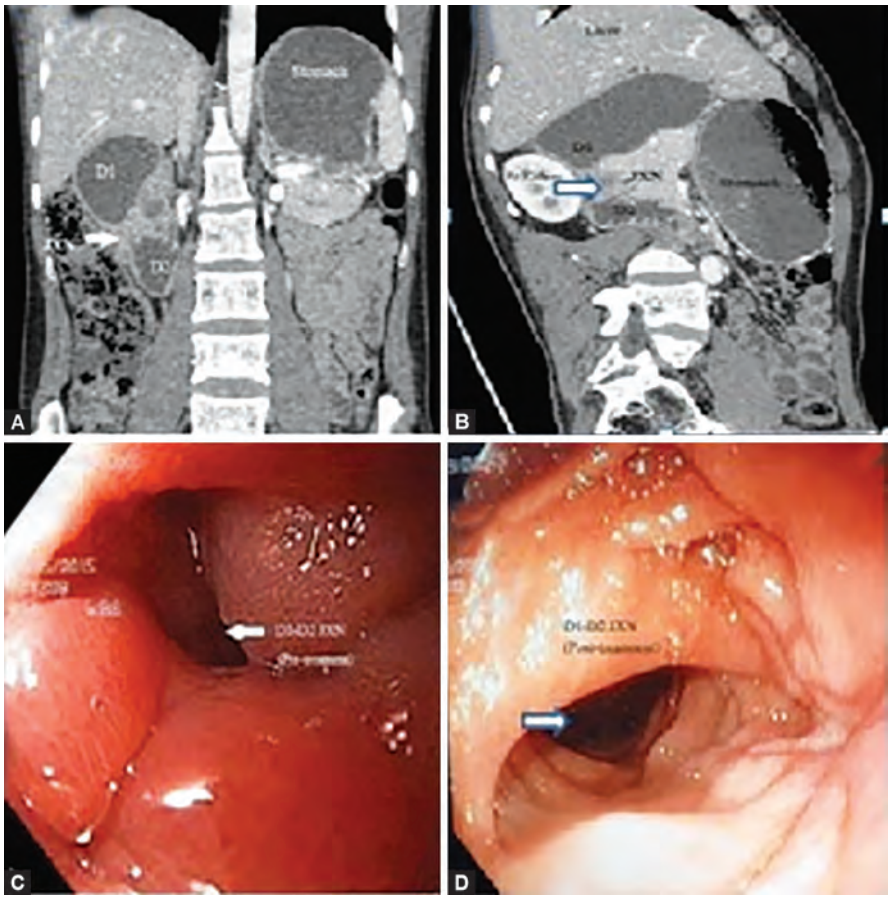
Discussion

This study is a prospective cohort investigation involving patients with gastrointestinal tuberculosis (GiTb). Most patients (77.8%) were diagnosed after a delay of 6 months–2 years from the onset of symptoms. The majority of patients were aged 19–49 years, consistent with previous reports.[4] Our study also revealed a slight male predominance, which aligns with findings from other studies.[7,8] However, a few studies have reported a female predominance in their cohorts.[9]

The clinical presentation of GiTb varies depending on the site and type of involvement.[10,11] In our cohort, the most common site of involvement was the ileocecal region (76.1%), followed by segmental colonic TB (17.1%), isolated ileal TB (5.1%), duodenal TB (0.9%), esophageal TB (0.4%), and gastric

Table 2: Symptomatology, site of involvement, and type of lesion on endoscopy

Symptoms	*Number (%)*
Weight loss	222 (94.9%)
Pain abdomen	201 (85.9%)
Fever	121 (51.7%)
Diarrhea	72 (30.8%)
Constipation	39 (16.7%)
Bleeding per rectum	25 (10.7%)
Vomiting	18 (7.7%)
Odynophagia	1 (0.4%)
Past history of ATT intake	7 (3%)
Site of involvement	Number (%)
Esophagus	1 (0.4%)
Stomach	1 (0.4%)
Duodenum	2 (0.9%)
Isolated ileal involvement	12 (5.1%)
Ileocecal region	178 (76.1%)
Ascending colon	28 (12.0%)
Transverse colon	4 (1.7%)
Descending colon	1 (0.4%)
Sigmoid colon	5 (2.1%)
Rectum	2 (0.9%)
CECT finding	Number (%)
Thickened gut wall with regional lymphadenitis	157 (67.1%)
Thickened gut wall	72 (30.8%)
Thickened gut wall with stricture	5 (2.1%)
Type of lesion on endoscopy	Number (%)
Ulcer	192 (82.1%)
Nodularity	173 (73.9%)
Deformed cecum and ileocecal valve	98 (41.9%)
Stricturous luminal narrowing	26 (11.1%)



Figs 1A to D: (A and B) Coronal and sagittal CECT images showing narrowing at D1/D2 junction; (C) Endoscopic image showing edematous mucosa with narrowing at D1/D2 junction; (D) Endoscopic image after course of antitubercular treatment showing patent duodenal human

TB (0.4%). These findings are consistent with those of other studies, where the ileocecal region is frequently identified as the most common site of involvement.[12–15] The predominant presenting symptoms in our study were weight loss (94.9%), abdominal pain (85.9%), fever (51.7%), and diarrhea (30.8%). Similar symptom profiles have been observed in other studies.[14–17]

In a study by Mukewar et al., among patients with colonic TB, the main clinical manifestations included weight loss (74.6%), loss of appetite (62.7%), fever (40.3%), diarrhea (16.4%), constipation (22.5%), and bleeding per rectum (11.9%).[13] Makharia et al. found that in intestinal TB, the primary clinical manifestations were abdominal pain (90.5%), weight loss (83%), loss of appetite (69.8%), fever (41.5%), diarrhea (37.7%), constipation (49%), and bleeding per rectum (16.9%).[14]

In our study, esophageal TB was observed in one patient (0.4%), which is consistent with the low frequency (0.2%) reported by other studies.[3] One percent of cases of abdominal TB are constituted by stomach and duodenal TB each.[3] Gastric TB was noted in one patient (0.4%) and presented as a nonhealing gastric ulcer. Additionally, two patients had isolated duodenal TB, presenting with symptoms of gastric outlet obstruction.

The most common finding on abdominal CT in our study was thickening of the bowel wall with or without local or mesenteric lymphadenopathy with ileocecal region being the most commonly involved.

In our study, the most common endoscopic lesions were ulcerations (82.1%), followed by nodularity (73.9%), deformed cecum and ileocecal valve (41.9%), and strictures (11.1%). These findings are consistent with a study by Alvares et al., where ulcerations were observed in 70% of patients, nodularity in 56%, deformed cecum and ileocecal valve in 40%, and strictures in 23% of patients with colonic tuberculosis.[16] Similar patterns were reported by Misra et al.[17] and Singh et al[18].

In the current series, histological examination was suggestive of tuberculosis in 160 patients (68.37%), revealing various forms of well-defined and ill-defined granulomas, epithelioid cell granulomas with Langhans giant cells with caseation observed in only 26 patients. A study by Mukewar et al.[13] found that among 69 patients with colonic tuberculosis, histology supported the diagnosis in 50 patients (73%), showing both well-defined and ill-defined granulomas, with caseation present in only two patients. Singh et al.[18] reported that histopathology was suggestive of tuberculosis in 45 out of 62 patients (72.5%), displaying well-formed granulomas and collections of epithelioid cells, with caseation in only five patients.

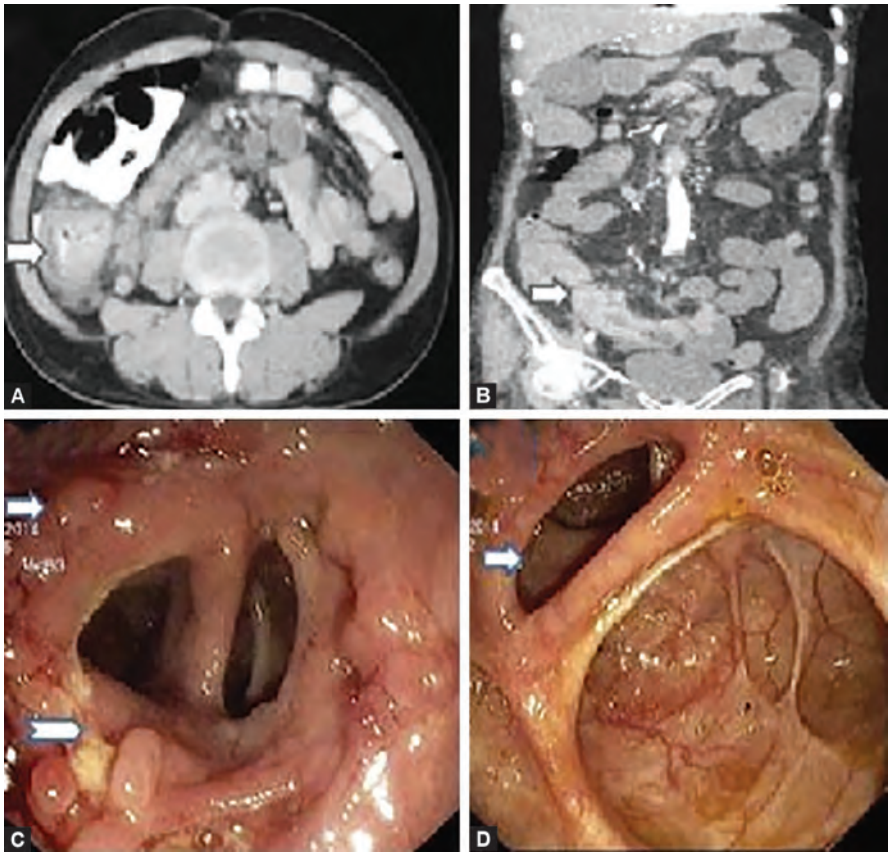
In our study, 74 patients (31.6%) were given a trial of ATT, and all responded positively. Using ATT response as a diagnostic criterion is consistent with other studies.[14] Park et al.[19] emphasized the utility of a 3-month trial of ATT to differentiate between colonic tuberculosis and CD. Mukewar et al.[13] reported significant improvement in patients with intestinal tuberculosis within 4–6 weeks of initiating ATT. The use of 6-month therapy is as effective as traditional 9-month ATT in abdominal TB and offers benefits such as reduced treatment costs and improved patient compliance.[20]

In our cohort, all patients showed significant regression of lesions with ATT. Singh et al.[18] reported improvements in all patients with colonic tuberculosis, with follow-up colonoscopy showing clearance of nodules, polypoid lesions, and ulcers, although strictures resolved only partially. Mukewar et al.[13] also reported significant resolution of tubercular lesions with ATT.

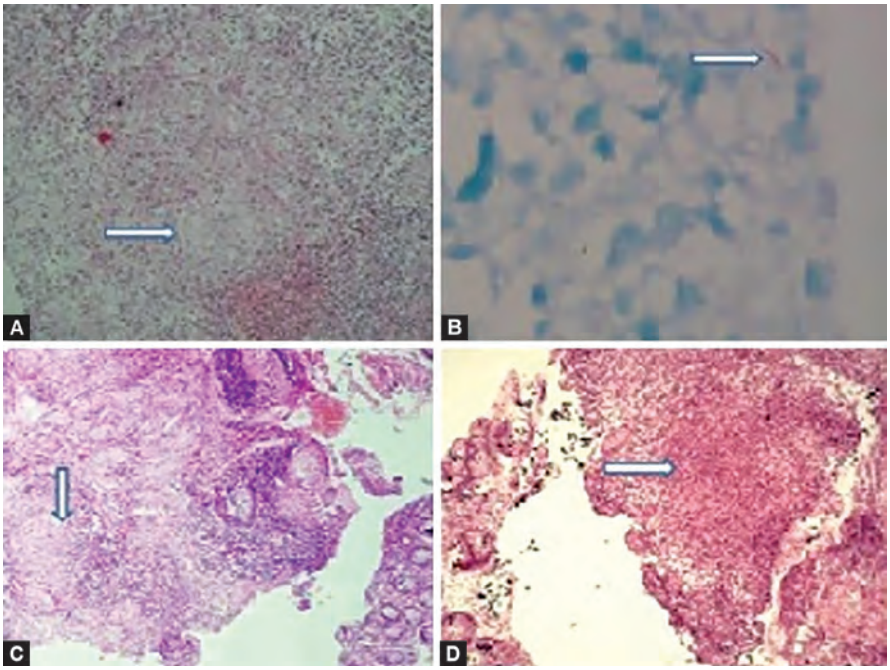
In the current series, AFB on ZN staining was detected in 32 patients (13.7%). The frequency of AFB on ZN staining of biopsy specimens varies across studies, ranging from 5 to 15%.[3] For instance, Mukewar et al.[13] found AFB in only three out of 69 patients with colonic tuberculosis, whereas Singh et al.[18] was unable to demonstrate AFB on staining of biopsy specimens. In our study, BACTEC-MGIT cultures from biopsy specimens revealed growth of *Mycobacterium tuberculosis* in 131 patients (56%).

The yield of *Mycobacterium tuberculosis* on culture is variable and is often low. Singh et al.[18] found no positive cultures among 62 patients, while Shah et al.[21] reported *Mycobacterium tuberculosis* growth in 31 out of 50 intestinal biopsy cultures. Bhargava et al.[22] observed that tissue culture increases diagnostic yield with positive cultures in 40%. The increased culture yield in our study may be attributed to the use of advanced culture techniques and the highly sensitive liquid culture media (BACTEC-MGIT) employed.

This study has several limitations. During follow-up colonoscopy biopsies were not performed, which could have provided additional information on the resolution of lesions. CD though less common in India, can be misdiagnosed as ileo-colonic tuberculosis.



Figs 2A to D: (A and B) Axial and coronal CECT image showing mural thickening of ileocecal region; (C) Colonoscopic image arrow showing nodularity and arrowhead showing ulcerations over ileocecal region with patulous ileocecal valve; (D) Colonoscopic image after course of antitubercular treatment showing regression of ulcerations and nodularity with patulous ileocecal valve



Figs 3A to D: (A) Hematoxylin and Eosin stained duodenal mucosal biopsy (high power view) image-arrow showing epithelioid cell granuloma; (B) ZN stained duodenal biopsy image with arrow showing AFB; (C) Hematoxylin and Eosin stained ileal biopsy (low power view) image with arrow showing epithelioid cell granuloma; (D) Hematoxylin and Eosin stained colonic mucosal biopsy image with arrow showing epithelioid cell granuloma with extensive lymphocytic infiltration

CD may also show partial improvement due to the antiinflammatory effects of ATT. However, the improvement seen will not be significant or long-lasting.[19] Over a long-term follow-up period of 8 years, no patients in our study experienced recurrence of tuberculosis, although a few reported minor complaints of vague abdominal discomfort. None of the patients were human immunodeficiency virus (HIV)-positive or immunocompromised, so the findings may not be applicable to those populations. Additionally, while a minimum of six biopsies were taken in this study, previous research suggests that obtaining at least eight colonoscopic biopsies can improve diagnostic yield.[23] GeneXpert testing was not performed on biopsy specimens due to the unavailability of this facility at the time of the study.

Conclusion

Gastrointestinal tuberculosis often presents with symptoms that mimic various gastrointestinal disorders, which can delay accurate diagnosis. The ileocecal region is the most commonly affected site. Gastrointestinal endoscopy frequently reveals ulceration, nodularity, and strictures as prominent findings. Histological examination and culture are useful diagnostic tools in a significant number of cases. In approximately one-third of cases, the diagnosis is confirmed by observing a positive response to ATT. ATT alone can also lead to notable improvements in symptoms, including the resolution of endoscopic gastrointestinal lesions.

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REVIEW ARTICLE

Cognitive Neurology Continuing Medical Education: History Taking and Bedside Mental Status Examination in a Patient with Dementia

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Abstract

In a patient presenting with forgetfulness, history taking comprises asking questions pertaining to specific cognitive domains namely memory, language, executive function, visuospatial functions, and social cognition to characterize the clinical phenotype. The next step is to administer a standardized screening test for cognitive assessment, namely the Montreal Cognitive Assessment (MoCA)/mini mental status examination (MMSE). These have been validated in five Indian languages. Detailed lobar function tests to assess functions of frontal, temporal, parietal, and occipital lobes namely planning, set-shifting, recent and remote memory, apraxia, agnosia, cortical sensory loss, language, etc., are the final step to identify the possible subtype of dementia. Attention testing with random letter cancellation test must be performed at the outset, as an inattentive patient cannot complete rest of the examination. Clock drawing is a simple bedside test that can assess global cognitive functions by detecting deficits in attention, planning, right-left orientation, constructional ability, visuospatial orientation, and neglect.

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Introduction

Dementia is a common presentation at the neurology outpatient clinic. Based on the results of a nationwide study published in the Lancet global health,[1] Alzheimer's disease and other dementias constitute 4.6% of total neurological disorder disability-adjusted life years in India in 2019. This amounts to an estimated 3.69 million people living with the disease. Given the burden, there is a pressing need for timely and accurate diagnosis, tailored medical therapy, and supportive care. Diagnosis requires thorough history taking and focused neurological examination to narrow down the long list of differential diagnoses. As a student, it is essential to know the simple bedside evaluation of patient with suspected dementia. Students are often enamored by the extensive neuropsychological testing batteries and often omit higher mental functions in assessment of patients. Consultants are often expected to evaluate patients amidst a long queue of patients waiting outside outpatient department (OPD) room; there is need for tests that can be easily performed to narrow down the differential diagnoses. This narrative review, targeted primarily for medicine and neurology residents, attempts to demystify the bedside evaluation of a patient suspected of dementia.

Definition

Diagnostic and Statistical Manual of Mental Disorders (DSM V)[2] defines major neurocognitive disorders as all of the following:

A. Modes/significant cognitive decline in one or more of the cognitive domains based on:
1. Concern about mild/significant decline, expressed by individual or reliable informant or observed by clinician.
2. Modest/substantial impairment, documented by objective cognitive assessment.

B. No interference with independence in everyday activities, although these activities may require more time and effort, accommodation, or compensatory strategies or interference with independence in everyday activities.

C. Not exclusively during delirium.

D. Not better explained by another mental disorder.

Specifiers:

1. Etiology: one or more of the following:

- Alzheimer's disease.
- Cerebrovascular disease (vascular neurocognitive disorder).
- Frontotemporal lobar degeneration (frontotemporal neurocognitive disorder).
- Dementia with Lewy bodies (neurocognitive disorder with Lewy bodies).
- Parkinson's disease.
- Huntington's disease.
- Traumatic brain injury.
- HIV infection.
- Prion disease.
- Substance/medication abuse.

2. Presence or absence of behavioral abnormality.
3. Severity of functional decline (mild, moderate, or severe).

Mild neurocognitive disorder comprises all the above except functional decline [mild noncommunicable disease (NCD) by definition does not impair functional decline to the point of impairing independent living].

The six cognitive domains are perceptual-motor, language, learning and memory, social cognition, executive function, and complex attention.

Delirium,[1] on the other hand, is characterized by disturbance in attention, develops over a short period of time, fluctuates in severity during the day, with an additional disturbance in cognition, which is not explained by other neurocognitive disorders, and not in the context of coma. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

When a patient presents with forgetfulness, the temporal profile (onset, duration, progress) is crucial to differentiate delirium from dementia. Delirium is often acute, there is a characteristic fluctuation in attention, and most importantly, it is treatable.

To diagnose a patient with suspected dementia, history taking, higher mental status examination, focused neurological examination, and relevant investigations are required. Let us understand each of them step by step.

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History Taking

It is essential to take history from a caregiver who stays with the patient as people with dementia will often deny their symptoms. Abrupt onset or stepwise progression may suggest vascular etiology. Leading questions examining individual cognitive domains should be asked.

Memory

For working memory, the patient may be asked whether he knows the way from the examination chamber to main door of the hospital. For anterograde episodic memory, he/she may be asked what the headlines of the day's newspaper were or what he consumed for his last meal. For remote memory, the patient may be asked about important events of his personal past like wedding anniversary, place of birth, first school, etc. They can be probed about problems learning and recalling new information, forgetting conversations, or repeating questions about recent activities. Forgetting to pay bills, paying bills twice, or repeatedly shopping for the same items indicates recent memory impairment.

Language

During the interview, one can observe the vocabulary, fluency, and content of speech output.[3] Word finding difficulty may present with trouble retrieving the name of a family member or a family friend. Some may report substituting words or mispronouncing names. There may be effortful speech, difficulty in comprehension of speech, or reading/writing difficulties. It is important to ascertain whether these symptoms are truly a disorder of language, such as spelling difficulty when writing, or reflect another source of difficulty, such as motor weakness interfering with mechanical aspects of writing.

There may be shorter sentences, circumlocutions (empty speech when describing things or answering a question), or paraphasic errors.

Executive Function

Individuals may describe challenges executing previously familiar multistep activities like cooking a meal, organizing the office bag, or planning a birthday party. Individuals may have difficulty completing an initiated task because of easy distractibility. Driving may be a challenge because of reduced attention and inability to process multiple steps of completing the task.

Visuospatial Functions

There may be difficulty driving and parking as there is loss of direction sense. He may bump into objects while navigating his way around at home. There may be difficulty recognizing familiar faces.

Social Cognition

Family members may note a significant change in the patient's personality, while patients with social difficulties often have limited insight. Disinhibition may be in the form of rude/inappropriate comments, or sharing personal information with strangers. There may be hypersexuality in the form of viewing pornography excessively, sexual jokes, inappropriate touching, or demanding intercourse every night from spouse. There may be disproportionate rage to no apparent provocation. It may also manifest in the form of apathy. Flattened affect may manifest as reduced emotional response to a significant life event of an acquaintance like death of a spouse. There may be inappropriate laughter or crying. There may be ritualistic behavior in the form of unusual and repetitive habits and collections, such as repeatedly cleaning the clothes shelf and checking if the main home door is locked. There may be sudden changes in behavior like excessive spending, excessive indulgence in a form of food like sweets, or stopping religious prayers in a previously spiritual person. Hyperorality may be in the form of shoving the mouth with food or eating on a full stomach. Utilization behavior may be in the form of picking up objects placed on examination table and fidgeting with them. They may have limited insight into the illness. These behavioral changes are most often seen in behavioral variants of frontotemporal dementia (FTD); though they overlap with atypical Parkinson's disease syndrome like progressive supranuclear palsy, corticobasal syndrome is well known.

Each of the above functions helps localize the lesion to areas of the brain as summarized in Table 1.

Table 1: Localization of neurologic symptoms[7]

Symptom analysis	*Localization*
Apathy	Medial prefrontal cortex
Executive dysfunction	Dorsolateral prefrontal cortex
Working memory impairment	Prefrontal cortex
Social disinhibition, emotional lability, anger, aggression, verbal/physical abuse	Orbitofrontal cortex
Planning, judgement, insight	Prefrontal cortex
Formed visual hallucinations (persons, animals)	Temporo-parietal-occipital junction
Unformed visual hallucinations (e.g., flashes of light)	Occipital lobe
Low self-esteem (performance monitoring in respect to anticipated outcome)	Anterior cingulate cortex
Recent memory	Papez circuit
Remote memory	Medial temporal lobe
Neglect	Dominant parietal lobe
Urinary frequency, urgency, incontinence with little embarrassment	Paracentral lobule
Tinnitus, deafness	Lateral temporal lobe

Higher Mental Status Examination

Examination of higher mental functions begins as soon as the subject enters the examination room. One has to look for general appearance, whether obese/averagely or thin built, whether hair and clothes are well kept or tucked in partially (reflecting lack of self-care), vocabulary of the patient (excessive talking or paucity of words), whether he is restless or apathetic, abusive, whether he sits through the interview or tries to run out of the room, whether he laughs or cries inappropriately during the interview.

MMSE and MOCA are internationally validated cognitive screening batteries. The Hindi version of MMSE (HMSE) is also validated and available for use. ICMR-NCTB[4] has validated MoCA in five Indian languages (Hindi, Telugu, Bengali, Kannada, and Malayalam) for use with educated and illiterate patients.

Once a patient has fared poorly in the screening test, a detailed lobar function test needs to be done to identify the subtype of dementia. Following lobar function tests can be performed bedside.

Lobar Function Tests[5]

Frontal Lobe

- *Attention*: At the outset of higher mental status examination, it is vital to start with test of attention.[5] Testing higher mental functions in an inattentive patient may be futile.

Tap A test: Read out a long series of letters and ask the patient to tap once the letter "A" is spoken. No mistake should be made by normal individuals.

- *Random letter cancellation test*: Read out a long series of letters and ask the patient to

tap once the letter "A" is spoken. No mistake should be made by normal individuals.

- *Reitan's trail making test A*

Tests attention, and processing speed.

The patient is asked to connect randomly arranged numbers from 1 to 25 which are scattered over a page by drawing a pencil line.

- *Reitan's trail making test B*

Numbers and letters are to be connected alternately. It tests set shifting (mental flexibility), sequencing, and planning.

- *Motor Luria*

Tests sequencing.

This is better known as fist-edge-palm test. The patient is asked to hit the top of the table, first with the fist, then edge of the hand followed by the palm.

Examiner demonstrates and the patient performs three series with examiner and three series alone. A score of 6 and above is considered normal.

- *Graphic Luria*

It is tested by asking the patient to make a triangle and square alternately by continuing a partially drawn sequence. Patients may perseverate (draw squares continuously) or simplify (draw a straight line instead).

- *Verbal similarities test*

This tests abstract thinking. The subject has to conceptualize the links between two objects from the same category, for example, table and chair (furniture), banana and apple (fruits).

- *Verbal fluency (FAS test)*

It requires the patient to name as many words from letters F, A, and S in one minute as possible.

- *Conflicting instructions/sensitivity to interference*

The patient is asked to tap twice when examiner taps once and vice versa. Patients with a frontal lobe lesion fail to obey the verbal command and tend to imitate the examiner.

- *Go-no-go test of Luria*

It is a test of response inhibition. The patient asked to tap once when examiner taps once and stop when examiner tap twice.

A person with frontal lobe impairment will imitate the examiner.

- *Proverb interpretation*

Tests abstract thinking. Give five commonly used proverbs, keeping in mind the educational and social background of the patient. Ask them to explain what it means.

- *Environmental autonomy*

This is the tendency to hold onto objects placed close to the patient. It is tested by placing the examiner's hands close to the patient and observing if he holds them. If he does, instruct the patient not to hold and observe.

- *Judgement*

Ask the patient what he would do if the place caught fire.

Temporal Lobe

Language

- *Spontaneous speech*

Observe the speech of the patient during the interview. Look at vocabulary, effortful speech, whether he is able to make full sentences, neologisms, whether the content makes sense to the context, etc.

- *Fluency*

Verbal fluency is assessed by asking the patient to name as many animals or vegetables as possible in one minute. A score of <13 is significant.

- *Comprehension*

It is assessed by asking leading questions like "Is this a hotel?" "Is it raining today?" or complex commands, for example, the lion got killed by the tiger; so, who survived?

- *Repetition*

Person is asked to repeat sentences of increasing complexity (a normal person can repeat a sentence of up to 19 syllables).

- *Naming*

Ask the person to name body parts, colors, and objects/parts of objects.

- *Reading and writing*
- *Reading comprehension*

Ask the patient to read and explain the meaning of statement. A defect is known as third alexia.

Papez Circuit

Memory

Immediate memory: It is the ability to hold information temporarily. It is assessed by forward digit span. In this, ask the patient to repeat a series of numbers after the examiner, in increasing order, avoiding natural sequences like 2, 4, and 6. Present numbers at the rate of 1/second. The normal range is 5–7 numbers.

Working memory: It is the ability to hold information temporarily and manipulate. It is assessed by digit backward test. For backward digit span, ask the patient to repeat numbers in reverse order. The normal range is at least two numbers.

Recent memory: Ask the patient to recall objects 3–5 minutes after presentation and ask for details of last meal.

Remote memory: Ask questions related to details of schooling and year of passing examinations.

Semantic memory: Ask the patient about facts, concepts, and general knowledge, for example, color of an elephant and number of days in a week.

Parietal Lobe

Lesions of **right parietal lobe** result in the following syndromes:

- *Neglect*: Patients ignoring one-half of their body or external space is called hemineglect. Neglect is almost always in the left hemifield. This is explained by left hemisphere monitoring only right hemispace, while right hemisphere monitors both hemispaces. Anosognosia is the inability to recognize the presence of somatic dysfunction. Visual extinction is a mild form of hemineglect, wherein the person can perceive either hemispace when stimulated individually, but only one hemisphere when both fields are stimulated simultaneously. It is best tested with line bisection.
- *Line bisection*: Draw a straight horizontal line and ask the patient to divide it into two equal parts. A person with left hemineglect will bisect the line to the right of the center as he cannot see left half of the line.
- *Constructional apraxia*: This is the inability to copy drawings accurately or make three-dimensional constructions. The right hemisphere lesions are associated with it. Necker's tube, overlapping pentagons, and clock drawing are bedside tests.
- *Dressing apraxia*: In this, spontaneous dressing ability is lost. It is tested by asking the patient to put on a jacket, which is given to him upside down with its sleeves deliberately turned inside out.
- *Cortical sensory loss*: It is tested under the following headings.

a. *Stereognosis*: It means perception of objects by touch. Give objects like key chain or pen to the patient and ask them to identify them.
b. *Graphesthesia*: Ability to identify numbers and letters written on palms/soles with blunt object.
c. *Two-point discrimination*[6]: This is the ability to detect that a stimulus consists of two blunt points when they are simultaneously applied. It is tested with pulp of finger or dorsum of the foot being touched by two blunt objects placed far apart and approximating them till the patient starts making errors. The normal ability to distinguish two points is 500 in the fingers and 5 cm on dorsum of the foot. In the presence of intact light touch and no signs of posterior column disease, impairment of two-point discrimination indicates a parietal lobe lesion.
d. *Tactile localization*[6]: The patient closes his eyes and then is touched on some point of the body with the examiner's finger or a pin. He is asked to indicate the point touched with his own forefinger. The significance is the same as for two-point discrimination.

Left (Dominant) Parietal Lobe

- *Apraxia*

Apraxia is a disorder of motor cognition wherein there is an inability to perform a motor task; this cannot be adequately explained by motor weakness, sensory loss, or a lack of understanding.

Conceptual apraxia: This denotes loss of tool action knowledge. For example, when given a paste and a toothbrush, the subject may not know what to do with the paste or he may hold the brush upside down.

Ideational apraxia: This refers to failure of sequencing of actions in the correct order to achieve an intended purpose. Ask the patient to pantomime a task (without object): for example, give a toothpaste and toothbrush to the patient and ask him to brush his teeth. A person with ideational apraxia may squeeze the toothpaste without opening the tube or brush teeth without applying paste to it.

Ideomotor apraxia: It is a disorder of action production system. Patients with ideomotor apraxia perform poorly when asked to pantomime an action. This is more evident in providing the object for the action which the patient was asked to pantomime. It is tested with four steps.

1. Transitive movements (movements where a tool or object is used): pantomime (enact) the use of a hammer (in the absence of the object)
2. Intransitive movements: wave goodbye.
3. Imitate the examiner: for example, blow out the cheeks.
4. Actual tool use: provide a pen to the patient and ask him to demonstrate its use. Person with ideomotor apraxia may write without opening the lid.

- *Calculation*

Commands range from simple subtraction to complex addition, subtraction, multiplication, and division.

- *Right-left orientation*

This is examined by identification of body parts and cross-command on self and examiner.

- *Finger agnosia*

Identify fingers on the subject touched by the examiner with the hand visible and hand hidden.

Occipital Lobe

- *Prosopagnosia*

Inability to identify familiar faces. It is tested by presenting photographs of famous personalities.

- *Visual agnosia*

It is the inability to consciously perceive objects (apperceptive agnosia) or inability to attribute meaning to what is perceived (associative agnosia) in individuals with intact primary sensation.

Apperceptive visual agnosia is tested by asking the subject to match similar items placed in two groups/copy a diagram. A person with this defect will be unable to do so.

Associative visual agnosia is tested with pyramids and palm trees test. In this test, a picture of pyramids in the desert is given and top and a palm tree, which is seen in the desert, and another tree, which is not seen in the desert, are given at the bottom. Patient is supposed to match pyramids with palm trees which is not possible if he has visual agnosia.

- *Color vision defects*

This can be tested with Ishihara charts.

- *Dorsal simultanagnosia*

This is due to restriction of visual attention which results from an inability to integrate visual information in the center of gaze with more peripheral information. It is due to defect in dorsal stream which lies in parieto-occipital region. It is tested with modified letter cancellation test. Ask the patient to circle all as in the figure with large and small as scattered among other letters. Person with simultanagnosia will circle all as except for the largest A in the center of the figure.

- *Ventral simultanagnosia*

This is due to slow visual processing speed and is due to a lesion in left temporooccipital region. In this, a person can perceive multiple objects simultaneously, but recognition is limited to one object at a time. It is tested by asking the patient to describe the cookie theft picture. They will be unable to describe the picture completely.

- *Optic ataxia*

It is the inability to reach a target under visual guidance. It is best tested with the finger-nose test. The patient will have no difficulty touching his own nose but will reach the hand of the examiner and gradually climb up to the finger. It is seen in Balint syndrome.

- *Clock drawing*is perhaps the single most comprehensive testing assessing constructional apraxia, visuospatial orientation, hemineglect, right-left orientation, planning, and sequencing.

Table 2 summarizes lobar function tests described.

For confirmation of subtype of dementia, formal neuropsychologist referral

Table 2: Summary of lobar function tests

Area of the brain	*Cognitive domain*	*Bedside neuropsychological test*
Frontal lobe	Attention	Random letter cancellation test
	Attention and processing speed	Reitan's trail making test A
	Set shifting, planning	Reitan's trail making test B
	Sequencing	Motor Luria and graphic Luria test
	Abstract thinking	Verbal similarities test, proverb interpretation
	Verbal fluency	FAS test
	Response inhibition	Go-no-go test
Temporal lobe	Language	Fluency, naming, reading, writing, repetition, comprehension
	Recent memory	Recall of 3–5 abstract words presented recently to the patient to memorize
Right parietal lobe	Neglect	Line bisection
	Constructional apraxia	Necker's tube, overlapping pentagons, clock drawing
	Cortical sensory loss: stereognosis	Ask the patient to identify objects with eyes closed
	Graphesthesia	Identify numbers or letters written on the palm or sole with a blunt object
Left parietal lobe	Apraxia	(Transitive and intransitive movements) pantomime, imitate, actual tool use
	Calculation	Simple and complex calculations
	Right-left orientation	Body parts identification on self and cross examination on self
	Finger agnosia	Identification and cross-examination on self with eyes closed
Occipital lobe	Prosopagnosia	Photographs of famous personalities
	Apperceptive visual agnosia	Match/copy similar objects
	Associative visual agnosia	Pyramids and palm trees test
	Color vision defects	Ishihara charts
	Dorsal simultanagnosia	Modified letter cancellation test
	Ventral simultanagnosia	Cookie theft picture
	Optic ataxia	Finger–nose–finger test

is needed to administer standardized testing batteries.

To conclude, history pertaining to the six cognitive domains and bedside lobar function tests help identify the possible type of dementia. Knowledge of the same is a tool every medicine/neurology resident can use for better patient care.

Suggested reading for graphics of lobar function tests: James Jose. Cognitive neurological examination.

Key Learning Points

- Differentiate delirium from true dementia in a patient presenting with forgetfulness.
- Leading questions in history pertaining to specific cognitive domains is the first step in assessment of a patient with cognitive impairment.
- Tests for attention should be performed at the outset to assess if a patient can sustain focus during detailed lobar function testing.
- Reitan's Trail Making Test, motor Luria, graphic Luria, FAS test, and go-no-go test are some of the tests for frontal lobe assessment.
- Forward digit span for immediate memory, backward digit span for working memory, recall for recent memory and autobiographical questions for remote memory, and language testing are some of the temporal lobe tests.
- Neglect, constructional apraxia, dressing apraxia, and cortical sensory loss are tested for assessment of right parietal lobe.
- Conceptual, ideomotor and ideational apraxia, calculation, finger agnosia, and right-left orientation were tested for left parietal lobe function assessment.
- Dorsal and ventral simultanagnosia, optic ataxia, prosopagnosia, visual agnosia, and color vision testing are done for assessment of occipital lobe.

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REVIEW ARTICLE

Topiroxostat—A Safer Uricostatic Drug with Enhanced Renal Protection: A Narrative Review

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Abstract

Background: Topiroxostat, a selective xanthine oxidase inhibitor, effectively reduces serum urate levels in hyperuricemia patients with or without gout. The present narrative review aims to evaluate the existing evidence regarding the effectiveness of topiroxostat on renal function in patients with and without kidney disease.

Materials and methods: A systematic search was conducted to identify relevant studies on renal function and topiroxostat published between 2005 and 2023. Various electronic databases were searched using different combinations of medical subject headings (MeSH) terms, and cross-referencing was performed. A total of 3146 articles were retrieved, and 18 met the inclusion and exclusion criteria.

Results: The review included 18 studies investigating the effectiveness of topiroxostat on renal function in patients with and without kidney disease. Topiroxostat demonstrated maintenance of renal function, as evidenced by stable levels of estimated glomerular filtration rate (eGFR), serum creatinine, urinary albumin, and urinary protein. Furthermore, topiroxostat led to improvements in renal function, including increased eGFR and decreased levels of urinary albumin, uric acid, urinary protein, urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG), and liver-type fatty acid-binding protein (L-FABP) following treatment. The literature also supports the safety profile of topiroxostat.

Conclusion: Topiroxostat shows promise as an efficient and safe renoprotective agent in patients, irrespective of renal disease status. However, further large-scale, long-term, and multicenter clinical studies are needed to generate high-quality evidence in different populations and settings.

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Introduction

Several large epidemiologic studies and clinical trials have corroborated the link between hyperuricemia and the advancement and progression of hypertension and chronic kidney disease (CKD). The prevalence of hyperuricemia increases with a reduction in kidney function, ranging from 11% in individuals with normal kidney function to 80% in those with stage 4 CKD. Similarly, 70% of individuals with gout and 50% of those with hyperuricemia have CKD stage 2 or higher.[1]

The American College of Rheumatology guidelines recommend initiating urate-lowering therapy with the first incidence of gout flare in patients with CKD stage ≥2.[2,3] Furthermore, xanthine oxidoreductase (XOR) inhibitors such as febuxostat, allopurinol, and topiroxostat have demonstrated dose-proportional serum uric acid-lowering responses in CKD patients.[4] According to an animal model study of human hereditary renal hypouricemia type 1 (RHUC1) by Hosoya et al., XOR inhibitors appear to be a feasible therapeutic alternative for the treatment of exercise-induced acute kidney injury (EIAKI), as they effectively reduced renal damage and improved functional indicators of EIAKI.[5]

Topiroxostat, a nonpurine selective hybrid inhibitor, reduces XOR activity by covalently binding to molybdenum and interacting with amino acid residues in the substrate-binding pocket. The drug has good oral bioavailability with a biological half-life of 4.5–7.5 hours and has been approved for clinical use in Japan since 2013.[6] Multiple studies have shown the uric acid-lowering and renoprotective effects of topiroxostat and its superiority over other XOR inhibitors.[7–9] Another distinct feature of topiroxostat is its dual mechanism of action. A mice model study by Nakamura et al. concluded that topiroxostat confers renoprotective effects by repressing oxidative stress and inflammation and facilitating the salvage pathway via XOR inhibition.[8] Topiroxostat is safe in reducing serum uric acid levels in hyperuricemia subjects receiving hemodialysis as opposed to allopurinol.[10] Unlike other XOR inhibitors, dose reduction is not necessary for the drug, even in subjects with renal dysfunction due to its nondialyzability.[11]

Serious adverse effects have been observed due to excessive accumulation of drug metabolites and active forms, particularly in patients with end-stage renal failure. However, Oyama et al. demonstrated that plasma levels of topiroxostat and its metabolites remained sufficiently low in patients undergoing hemodialysis, allowing for the continuous administration of the drug for up to 52 weeks. This finding suggests that topiroxostat can be safely administered to patients undergoing hemodialysis without significant concerns about drug accumulation.[10]

Recently, topiroxostat has been approved in India in three different strengths: 20, 40, and 60 mg. While there are various studies highlighting the potential therapeutic effects of topiroxostat, there is currently no single study that comprehensively summarizes its clinical effects and safety for the management of different renal diseases associated with hyperuricemia. Therefore, the objective of the present study is to evaluate the role of topiroxostat in managing renal disease, renal failure, and hyperuricemia accompanied by renal disease and providing renal protection.

Materials and Methods

A systematic literature search was performed to select relevant observational studies examining renal outcomes in patients with topiroxostat between 2005 and 2023. The search encompassed multiple electronic databases including PubMed, Embase, Web of Science, Scopus, Google Scholar, Europe PubMed Central, Science Direct, and the Cochrane Library. Inclusion and exclusion criteria were applied, and various

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combinations of searchable terms, including important medical subject headings (MeSH) terms, were used. The MeSH terms used were topiroxostat, hyperuricemia, renal outcome, and XOR inhibitors (details provided as supplementary file). Studies were eligible for inclusion if they involved adult patients treated with topiroxostat and assessed the clinical evidence of its effect on renal outcomes. Abstracts, reviews, animal studies, editorials, case reports, duplicated or nonrelevant studies, and studies lacking data on renal outcomes were excluded from the analysis. The articles were also cross-referenced to ensure comprehensive coverage. The Prisma flow chart illustrating the screening procedure is shown in Figure 1.

Results

A total of 3,145 articles were initially identified from various databases, and an additional 1 article was found through cross-referencing. After removing 1,227 duplicate studies (1,734 studies that were not relevant to the field of interest, 101 studies focusing on other drugs, and 21 articles not in English), 63 studies were selected for a full-text review based on the details in the title and abstract. Among these, 45 studies were excluded due to their classification as review articles, editorial or commentary articles, meta-analyses, case reports, protocols, animal studies, studies not in English, and studies that did not meet the inclusion criteria. As a result, a total of 18 studies were included in the present study comprising 8 randomized controlled trials and 2 crossover trials.

Renoprotective Action of Topiroxostat in Kidney Disease Patients

The studies evaluating the renoprotective action of the drug in CKD patients corroborate its effectiveness in reducing serum uric acid levels, providing renoprotective effects, and potentially preserving renal function in hyperuricemia patients, CKD, and diabetic nephropathy. Horino et al. found that topiroxostat significantly reduced serum uric acid levels and improved renal prognosis in CKD patients. While serum creatinine and estimated glomerular filtration rate (eGFR) remained unchanged, indicating preserved renal function, the decrease in urinary protein levels suggested renoprotective properties.[9] A 22-week randomized trial by Hosoya et al. demonstrated that daily 160 mg topiroxostat effectively lowered serum urate levels in hyperuricemic CKD stage 3 patients with or without gout. Although eGFR change did not differ substantially between the topiroxostat and placebo groups, there was a significant reduction in the urinary albumin-to-creatinine ratio (UACR) in the topiroxostat group. Additionally, 90% of topiroxostat-treated patients achieved serum urate levels ≤356.88 µmol/L at the end of the trial.[7]

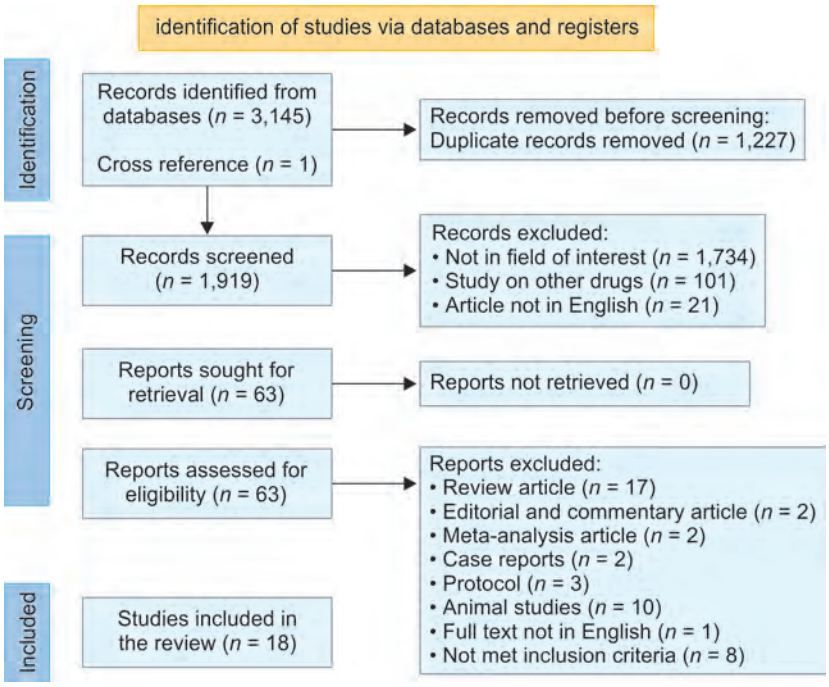

Fig. 1: Prisma flowchart outlining the screening procedure

Mizukoshi et al. found that topiroxostat reduced albuminuria in diabetic nephropathy patients, suggesting its potential to slow disease progression. High-dose topiroxostat led to a significant reduction in albuminuria (–122 mg/gCr, $p = 0.041$). Topiroxostat consistently lowered uric acid levels with a statistically significant difference observed from baseline to every time point ($p < 0.0001$).

Regarding eGFR, patients treated with high-dose topiroxostat experienced a reduction of 2.4 ± 0.8 mL/minute/1.73 m^2 at 12 weeks, stabilizing at a decrease of 1.7 ± 0.9 mL/minute/1.73 m^2 at 24 weeks. Patients receiving low-dose topiroxostat had a reduction of 1.8 ± 0.6 mL/minute/1.73 m^2 at 8 weeks, reaching a minimum reduction of 1.7 ± 0.8 mL/minute/1.73 m^2 at 12 weeks, followed by recovery to a reduction of 1.1 ± 0.9 mL/minute/1.73 m^2 at 24 weeks. The high-dose group showed a significant difference in eGFR from baseline to 12 weeks ($p = 0.0041$), while the low-dose group demonstrated significant differences at 8 and 12 weeks ($p = 0.0078$ and $p = 0.034$, respectively). Additionally, the study found a significant decrease in urinary liver-type fatty acid-binding protein (L-FABP) levels at 12 weeks ($p = 0.0021$) and 24 weeks ($p < 0.0001$) in the high-dose topiroxostat group, and at 24 weeks ($p < 0.0001$) in the low-dose topiroxostat group.[12]

Wada et al. found that topiroxostat preserved renal function in hyperuricemia and diabetic nephropathy patients. The topiroxostat group showed stable eGFR, while the placebo group experienced a significant decline. UACR levels remained stable with topiroxostat but tended to increase in the placebo group. Topiroxostat significantly lowered serum uric acid levels compared to the control group (between-group difference: 2.74, 95% CI: 3.20–2.27, $p < 0.0001$).[13] Oyama et al. reported a significant reduction in serum uric acid levels in hemodialysis patients after topiroxostat treatment.[10] Katsuyama et al. found that topiroxostat had renoprotective effects in CKD patients. Serum uric acid levels significantly reduced after 3 and 6 months of treatment. eGFR showed a positive trend after 6 months. Patients with initial urinary protein positivity experienced a significant reduction in urinary protein levels at 3 and 6 months. The study also observed a correlation between the decrease in serum uric acid levels and the improvement in eGFR after 3 and 6 months of treatment.[14] Characteristics of studies involving kidney disease patients are summarized in Table 1.

Table 1: Characteristics of studies that included patients with kidney diseases

Study	*Intervention (mg/day)*	*No. of patients*	*Change in eGFR (mL/minute/1.73 m²) from baseline*	*Change in SUA (mg/dL) from baseline*	*Change in uProt (mg/gCr) from baseline*	*Change in UACR/ urinary albumin (mg/gCr) from baseline*	*Duration*
Horino et al.[9]	Tpx (40)	30	−0.8 (NS)	−1.53 (S)	795.5	NR	12 months
Hosoya et al.[7]	Tpx (160)	62	0.64 (95% CI: 0.55–1.84) (NS)	−45.38 ± 21.80	NR	−33.0 (95% CI: −45.0 to −20.0)	22 weeks
	Placebo	60	−0.46 (95% CI: 1.68–0.75) (NS)	0.08 ± 9.92		−6 (95% CI: −22.0 to 14.0)	
Kaiga et al.[19]	Tpx (40, 80, 160)	35	0.1		NR		3–6 months
	Alp (50, 100, 200)		1.9				
Matsuo et al.[21]	Tpx (40)	46	− 0.04 ± 4.59 (NS)	−2.6 ± 1.0	NR	NR	24 weeks
	FXT (10)	48	0.31 ± 4.70 (NS)	−2.7 ± 1.1			
Mizukoshi et al.[12]	Tpx high dose (160)	40	1.7 ± 0.9 (NS)	3.3 ± 0.26		−122 (95% CI: −5.1 to −240.1)	24 weeks
	Tpx low dose (40)		1.1 ± 0.9 (NS)	1.50 ± 0.26 (S)		−201.4 (95% CI: 14.5 to −417.3) (NS)	24 weeks
Wada et al.[13]	TPX (160 mg)	43	−0.2 (95% CI: −2.2 to 1.7)	2.94 (95% CI: −3.21 to −2.66)	NR	−2% (95% CI: −20, 19%)	28 weeks
	Placebo	22	−4.0 (95% CI: −6.7 to −1.2)	−0.20 (95% CI: −0.58 to 0.18)		28% (95% CI: −2, 69%)	
Oyama et al.[10]	TPX (40)	19	NR	231 (S)	NR	NR	52 weeks
Katsuyama et al.[14]	Tpx	41	−2.3	2	21.7		6 months
Nagaoka et al.[25]	Tpx (group A)	13	NR	5.9 6 ± 0.2	NR	NR	3 months
	Alp (group A)			6.9 6 ± 0.2			3 months
	Tpx (group B)	14		6.4 6 ± 0.2			3 months
	Alp (group B)			6.8 6 ± 0.2			3 months
Mitsuboshi et al.[26]	Tpx*	10	NR	−0.1(NS)	NR	NR	16 months

Data are presented as mean, mean ± standard deviation, median (interquartile range), mean (95% CI); Alp, allopurinol; eGFR, estimated glomerular filtration rate; FXT, febuxostat; NR, not reported; NS, nonsignificant; SUA, serum uric acid; Tpx, topiroxostat; UACR, urinary albumin-to-creatinine ratio; *Patients receiving febuxostat 10 mg/day were switched to topiroxostat therapy

Renoprotective Action of Topiroxostat in Patients without Kidney Diseases

A total of eight studies were considered for evaluating the renoprotective effects of topiroxostat in patients without kidney disease (Table 2). Tamiya et al. found that topiroxostat maintained renal function and lowered serum uric acid levels in elderly patients with hyperuricemia. Before topiroxostat administration, eGFR showed a significant reduction of 3.45 ± 0.72 mL/minute/1.73 m² ($p < 0.001$) over 6 months. However, after topiroxostat administration, the difference in eGFR was a nonsignificant reduction of 0.18 ± 0.94 mL/minute/1.73 m², indicating a suppression of eGFR decline. Topiroxostat effectively reduced serum uric acid levels, which remained lowered even after 36 months. Importantly, topiroxostat therapy did not lead to a significant increase in serum creatinine levels. These findings indicate that topiroxostat can slow down progressive kidney function decline over time.[15] Hosoya et al. found that topiroxostat significantly improved the UACR ratio. At the final visit, there was a significant reduction in serum urate levels compared to baseline ($p < 0.0001$, $n = 121$) with a decrease of −3.39 ± 1.36 mg/dL. Topiroxostat helped in achieving target serum uric acid levels in 57.9% (70/121) of patients receiving ≤120 mg, 67.8% (82/121) of patients receiving ≤160 mg, and 71.9% (87/121) of patients receiving all dosages.[16] In another double-blind, placebo-controlled study, Hosoya et al. reported a significant reduction in serum urate levels with topiroxostat compared to placebo.[17] A nonrandomized single-arm trial conducted by Wakita et al. Topiroxostat was administered to heart failure with preserved ejection fraction and hyperuricemia patients. The study reported a significant decrease in serum uric acid levels, plasma XOR activity, and urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) to creatinine levels. All the aforementioned studies have reported no significant change in eGFR levels compared to baseline.[18]

Comparison of Topiroxostat with Allopurinol and Febuxostat

In a study comparing topiroxostat and allopurinol in CKD and hyperuricemia patients by Kaiga et al., topiroxostat demonstrated superior efficacy in halting the progression of renal dysfunction with a more pronounced hypouricemic effect compared to allopurinol. The topiroxostat group showed higher eGFR compared to the allopurinol group (40.8 ± 19.8 vs 39.0 ± 21.5, $p = 0.034$) and significantly reduced serum uric acid, creatinine, and metabolites of free radical-providing molecules (d-ROM) in the former group than latter.[19]

Kario et al. observed a significant reduction in UACR from baseline to 12 (–20.3%; $p = 0.025$) and 24 weeks (–20.8%; $p = 0.021$) with topiroxostat in hypertensive patients with hyperuricemia. However, no significant differences were detected in the febuxostat group at 12 weeks (–10.1%; $p = 0.293$) and 24 weeks (–8.8%; $p = 0.362$). After 24 weeks of topiroxostat treatment, there was a significant reduction in eGFR from baseline [–2.2 mL/minute/1.73 m² (95% CI: –4.0, –0.3); $p = 0.02$]. However, no significant differences in eGFR from baseline were observed between the topiroxostat and febuxostat groups at 12 and 24 weeks. Plasma XOR activity was significantly decreased with

Table 2: Characteristics of studies that included patients without kidney diseases

Study	*Intervention*	*No. of patients*	*Change in eGFR (mL/minute/1.73 m²) from baseline*	*Change in sCr (mg/dL) from baseline*	*Change in SUA (mg/dL) from baseline*	*Change in UACR/urinary albumin (mg/gCr) from baseline*	*Duration*
Tamiya et al.[15]	Topiroxostat (m: 105.5 mg)	51	−0.5	−0.07	2.21(S)	NR	36 months
Hosoya et al.[16]	Total dose	121	0.47 ± 7.27 (NS)**	NR	−3.39 ± 1.36	0.794 95%CI (0.705, 0.894)**	58 weeks
	Topiroxostat 120 mg	84	NR		−3.23 ± 1.18	0.776 95% CI (0.675, 0.893)**	
	Topiroxostat 160 mg	18			−4.14 ± 1.55	0.792 95% CI (0.556, 1.127) (NS)**	
	Topiroxostat ≥200 mg	13			−4.22 ± 1.27	0.672 95% CI (0.534,0.844)**	
Kario et al.[20]	Topiroxostat	67	−2.2 95% CI (−4.0, −0.3)		−2.5 (−2.9, −2.2)	−20.8 95% CI (0.705, 0.894)	24 weeks
	Febuxostat	68	NR	NR	−2.9 (−2.9, −2.2)	−8.8 95% CI (−25.3, 11.3) (NS)	24 weeks
Hosoya et al.[17]	Placebo	36	−3.00 ± 7.29	NR	1.6 ± 10.8	NR	8 weeks
	TPX (40)	38	−0.67 ± 5.54		−23.5 ±9.5		
	TPX (60)	37	−0.68 ± 5.42		−22.4 ±10.7		
	TPX (80)	38	1.10 ± 6.60		−30.0 ± 12.0		
	TPX (120)	37	2.83 ± 6.48		−30.8 ± 12.2		
Sakuma et al.[22]	Topiroxostat 40–160	70	NR	NR	−2.7 ± 1.5	−0.13 ± 0.85 (NS)	24 weeks
	Allopurinol 100–200 mg	70			−2.2 ± 1.2	0.04 ± 1.03 (NS)	
Tezuka et al.[23]	Tpx	47	−3.4	NR	2.5	0.5	12 weeks
	FXT	47	0.3		2	0.3	
Sezai et al.[23]	Tpx	55	0.8	−0.11		NR	6 months
	FXT		0.3	0.08			
Wakita et al.[18]	Tpx	33	1.7 (NS)	−0.1	2.8	99 (NS)	24 months

Data are presented as mean, mean ± standard deviation, median (interquartile range), mean (95% CI); eGFR, estimated glomerular filtration rate; FXT, febuxostat; NR, not reported; NS, nonsignificant; sCr, serum creatinine; SUA, serum uric acid; Tpx, topiroxostat; UACR, urinary albumin-to-creatinine ratio; *Number of patients for SUA; **Full analysis set (*n*): total (118), 120 mg (82), 160 mg (18), ≥200 mg (13)

topiroxostat, but not with febuxostat when compared to baseline. (–2.9 and –2.5 mg/dL; both $p < 0.001$).[20]

Matsuo et al. noted that both topiroxostat and febuxostat significantly decreased serum uric acid levels (–2.6 and –2.7 mg/dL) at 24 weeks. However, no significant changes were observed in the urinary protein-creatinine ratio (uPCR) and eGFR in either treatment group.[21] Sakuma et al. reported the benefits of topiroxostat over allopurinol for renal oxidative stress and renal tubular damage in patients with chronic heart failure complicated by hyperuricemia. The allopurinol group showed a significant increase in oxidative stress marker 8-OHdG and the renal proximal tubular oxidative stress marker L-FABP. In contrast, no significant increase in these markers was observed in the topiroxostat group. The significant difference between the two groups suggests that allopurinol, but not topiroxostat, accelerated renal oxidative stress, leading to renal tubular damage. Additionally, when comparing topiroxostat and allopurinol, a greater reduction in uric acid levels was observed with topiroxostat compared to allopurinol.[22]

Tezuka et al. noted that topiroxostat, not febuxostat, improved eGFR in hypertensive patients with hyperuricemia, showing a significant increase in eGFR. Both topiroxostat and febuxostat significantly lowered uric acid levels. However, there was no significant change in UACR in either treatment group.[23] Sezai et al. reported on the comparable efficacy of topiroxostat and febuxostat in reducing uric acid and conferring renal protective and anti-inflammatory properties after 6 months of treatment in hyperuricemia patients with cardiovascular disease.[24] Nagaoka et al. found that patients undergoing hemodialysis were able to maintain their serum uric acid levels <7.0 mg/dL with a low dose of topiroxostat. The topiroxostat-treated group showed significantly lower mean serum uric acid levels compared to the allopurinol-treated group over time.[25] Furthermore, Mitsuboshi et al. in hemodialysis patients reported that serum uric acid levels tended to rise following treatment with febuxostat at a dosage of 10 mg/day. However, after switching to topiroxostat at a dose of 40 mg/day, serum uric acid levels tended to decrease. Serum uric acid levels were stabilized below the desired threshold of ≤6 mg/dL after decreasing the topiroxostat dose from 40 to 20 mg/day.[26]

Topiroxostat Safety in Patients with or without Renal Disease

Horino et al. reported that topiroxostat is safe and effective in treating CKD patients without causing side effects, even with long-term use.[9] A randomized controlled study by Hosoya et al. in hyperuricemic CKD stage 3 patients with or without gout found that the adverse events reported were mild to moderate in severity.[7] Comparison of topiroxostat and allopurinol in CKD patients with hyperuricemia by Kaiga et al. reported no side effects throughout the study duration.[19] Mizukoshi et al. observed no serious adverse events related to topiroxostat in diabetic nephropathy patients.[12] The UPWARD study by Wada et al. reported good tolerability and safety of the drug in hyperuricemic patients

with early diabetic nephropathy.[13] A study in CKD patients with hyperuricemia by Matsuo et al. reported no severe adverse events from topiroxostat or febuxostat.[21] Oyama et al. in patients receiving hemodialysis noted that topiroxostat and its metabolites were sufficiently cleared during hemodialysis, allowing for its continued administration for 52 weeks.[10]

Mitsuboshi et al. observed in hemodialysis patients receiving febuxostat who were switched to topiroxostat therapy that no patient had any laboratory values during the observation period that indicated hepatotoxicity, and the tolerability index did not statistically vary between baseline and 16 months after the patient's switch to topiroxostat therapy.[26] Tamiya et al. found no major side effects following topiroxostat treatment in patients with hyperuricemia. Apart from serum uric acid levels, none of the laboratory parameters showed noticeable alterations after the administration of topiroxostat.[15] Kario et al. reported that topiroxostat was well tolerated in hypertensive patients with hyperuricemia.[20] Hosoya et al. verified the safety of topiroxostat in hyperuricemic patients, regardless of gout status.[17] Sakuma et al. suggested that topiroxostat is safe for use in chronic heart failure patients.[22] Adverse events and adverse drug reactions reported in patients receiving topiroxostat in included studies are listed in Table 3.

Discussion

This comprehensive review has examined the current clinical evidence regarding the utilization of topiroxostat in treating hyperuricemia patients with or without any renal disease. The results from various studies support the safety, effectiveness, and kidney-protective benefits of topiroxostat, thus confirming its suitability for clinical application in lowering serum uric acid levels in CKD patients. Studies have reported that the usage of urate-lowering therapy may improve renal function and slow the advancement of CKD. This improvement is attributed to the preservation of eGFR and reduced excretion of protein and albumin.[27–29]

XOR inhibitors, such as topiroxostat, aid in reducing reactive oxygen species produced by XOR, thereby protecting endothelial cells and organs like the kidneys, liver, heart, and arteries.[21] Studies have suggested that XOR inhibitors may delay the progression of renal dysfunction in patients with kidney disease.[30,31]

The present review assessed the impact of topiroxostat therapy on kidney biomarkers. The results demonstrated the maintenance of renal function, as evidenced by stable levels of eGFR, serum creatinine, urinary albumin, and urinary protein following treatment with topiroxostat. Among the seven included studies, none of them reported a significant change in eGFR levels.[7,9,13,16–18,21]

Kaiga et al., Tezuka et al., and Katsuyama et al. reported elevated eGFR level posttreatment with topiroxostat.[14,19,23] In contrast, Tamiya et al. reported a suppression in the eGFR reduction, suggesting that topiroxostat therapy may have a beneficial effect on eGFR preservation.[15] Horino and Tamiya et al. showed no significant change in serum creatinine levels, indicating that topiroxostat treatment did not significantly affect kidney function in terms of creatinine clearance.[9,15] Additionally, Tezuka et al. and Wada et al. observed a nonsignificant change in urinary albumin levels, suggesting that topiroxostat therapy did not have a significant impact on albumin excretion.[13,23] Matsuo et al. reported no change in urinary protein levels, indicating that topiroxostat did not significantly alter urinary protein excretion.[21]

Increase in eGFR levels and decrease in urinary albumin, uric acid, urinary protein, urinary 8-OHdG, and L-FABP levels are indicative of improved renal function. Mizukoshi et al., Hosoya et al., and Kario et al. reported a reduction in urinary albumin levels, suggesting a decrease in albumin excretion associated with topiroxostat therapy.[7,12,16,20] A systematic review and network meta-analysis by Tsukamoto et al. reported that topiroxostat significantly increased eGFR and decreased the UACR compared to placebo, indicating improved kidney function and reduced albuminuria.[32] In a db/db mice model of diabetic nephropathy, Zhang et al. demonstrated that topiroxostat reduced albuminuria by preventing podocyte damage, further supporting its beneficial effects on renoprotection.[33] Additionally, two of the included studies showed a decrease in urinary protein levels, indicating a decrease in proteinuria associated with topiroxostat therapy.[9,14] Mizukoshi et al. reported decrease in urinary L-FABP level in diabetic nephropathy patients, and Wakita et al. observed a decrease in urinary 8-OHdG levels, indicating a decrease in oxidative stress.[12,18] Whereas Sakuma et al. found no change in the levels of both biomarkers.[22]

Recent research has revealed a significant inverse correlation between high uric acid levels and kidney function, highlighting uric acid as a risk factor for renal disease. Hyperuricemia has been recognized as a consequence of CKD and appears to accelerate the development of renal disorders.[27,34,35] In the present study, 16 included studies reported a significant decrease in uric acid levels following topiroxostat treatment.[7–10,12–18,20–22,24–26] A study using a puromycin aminonucleoside nephrosis rat model by Kawamorita et al. reported that topiroxostat reduced kidney damage and proteinuria. The renoprotective effect of topiroxostat was attributed to its antioxidant activities, which led to a decrease in the levels of 8-OHdG. Additionally, treatment with topiroxostat significantly decreased uric acid levels in the kidney cortex of panic attack network (PAN) rats.[36] A db/db mice study by Nakamura et al. reported that topiroxostat suppresses the uric acid (UA) and urinary albumin excretion. Topiroxostat may have a different mechanism of action from XOR inhibitors because it may ameliorate hypoxia and activate local renin-angiotensin system (RAS). As a result, topiroxostat has the ability to significantly diminish excess uric acid levels, particularly in microvascular complications associated with diabetic nephropathy, atherosclerosis, and hypertension.[8] A mice model study by Ohata et al. showed that topiroxostat medication resulted in a decrease in or attenuation of renal XOR, renal dysfunction, urinary L-FABP, tubulointerstitial damage, hypoxia, and

Table 3: List of adverse events and adverse drug reactions reported in patients receiving topiroxostat in included studies

List of AR/ADR
Increased: ALT, AST, urinary b2 microglobulin, urinary NAG, blood bilirubin, blood CPK, blood TG, γ-GTP, platelet count, urine albumin, beta-2-microglobulin, beta-*N*-acetyl-d-glucosaminidase, blood triglycerides, gamma-glutamyltransferase, urinary alpha-1-microglobulin, urinary albumin, and alpha-1-microglobulin urine
Nasopharyngitis, hematuria, leucopenia, gouty arthritis, headache, diabetic retinopathy, seasonal allergy, Stomatitis, leucopenia, arthralgia, allergic conjunctivitis, allergic rhinitis, diarrhea, colon cancer, musculoskeletal and connective tissue disorders, nausea, eruption, death, malignant neoplasm, gastric cancer, gout, cholelithiasis and malaise, hepatic function abnormality, and serious cardiovascular adverse events

AE and ADR, adverse events and adverse drug reactions; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; NAG, *N*-acetyl-beta-d-glucosaminidase; TG, triglycerides; WBC, white blood cell; γ-GTP, gamma-glutamyl transpeptidase

oxidative stress levels.[37] A case report by Tanaka et al. reported that topiroxostat was successful in lowering blood UA, urinary albumin excretion, and urinary L-FABP levels in a patient with CKD and hyperuricemic-associated arteriolopathy.[38] Topiroxostat may have an advantage over febuxostat and allopurinol in terms of its renoprotective effects. While the number of trials is limited, a few studies have shown the superiority of topiroxostat over the other two drugs. Kaiga et al. reported that topiroxostat, when compared to allopurinol, is potentially more effective in slowing the progression of renal failure and has a stronger hypouricemic impact.[19] Sakuma et al. found a benefit of topiroxostat over allopurinol for renal oxidative stress, renal tubular injury and reduction in UA.[22] Serum uric acid levels were significantly lower in the topiroxostat-treated arm compared to the allopurinol-treated arm throughout time, according to a study by Nagaoka et al.[25] Topiroxostat, in contrast to allopurinol, possesses a nonpurine structure, undergoes primarily hepatic metabolism, and is eliminated through both urine and feces. Unlike allopurinol, its impact on the kidney is limited, which means that dose adjustment based on renal function is not necessary.[24] Kario et al. indicated that topiroxostat but not febuxostat exhibited a significant decrease in urinary albumin levels and XOR activity.[20] In line with this, Tezuka et al. demonstrated that topiroxostat, rather than febuxostat, increased eGFR in hypertensive patients with hyperuricemia.[23] Mitsuboshi et al. observed that hemodialysis patients who were administered febuxostat at a daily dosage of 10 mg experienced a tendency for their serum uric acid levels to increase. However, upon switching to a daily dosage of 40 mg of topiroxostat, there was a noticeable tendency for the serum UA levels to decrease.[26] A study by Kamijo-Ikemori et al. used an adenine-induced renal injury mice model and found that topiroxostat reduced tubulointerstitial damage and renal dysfunction in adenine-induced nephropathy. Mice administered topiroxostat had lower levels of serum creatinine and urinary L-FABP compared to mice treated with febuxostat.[39] An increase in urinary albumin excretion can be attributed to elevated plasma and renal XOR activity. In a study using a type 2 diabetic mice model conducted by Nakamura et al., groups treated with topiroxostat exhibited significant suppression of plasma XOR activity compared to the group treated with febuxostat. Additionally, plasma uric acid levels decreased in the topiroxostat treatment group in comparison to the febuxostat treatment groups.[40] In the present study, a comprehensive review of eight included studies has consistently shown that topiroxostat exhibits excellent tolerability and safety in patients with renal disease without causing any serious adverse events.[7,9,10,12,13,19,21,26] An additional four studies have specifically reported the tolerability and safety of topiroxostat in patients with renal disease, with no incidence of serious adverse events.[15–17,20] Furthermore, one study evaluated the safety of topiroxostat in patients without any renal disease and deemed it to be a safe treatment option.[22] The present study holds significant relevance, as to the best of our knowledge, there is no review assessing nephroprotective effect of topiroxostat, which included both patients with and without any renal disease. Additionally, using a more precise and objective approach for the data extraction, compilation, and analysis helped in the critical evaluation of the study methodologies and the exclusion of papers with ambiguous study designs and protocols as well as those outside the study's field of interest. It is crucial to highlight that all the studies included in the review focused exclusively on the Japanese population, indicating the need for Indian evidential studies to confirm if renal protection is ethnically different for the Indian population.

However, the present study has certain limitations. The variability among the included studies prevented conducting a meta-analysis of the available literature. Consequently, the findings of the study cannot be widely generalized due to the absence of a meta-analysis. Additionally, the exclusive focus on the Japanese population in all the included papers reduces the generalizability of the results. Moreover, only full-text papers published in English were considered for the analysis, potentially overlooking studies conducted in other languages that may contain significant findings.

Conclusion

The available evidence corroborates the potential of topiroxostat as an effective and safe renoprotective agent for both patients with and without renal disease. However, it is important to note that the majority of the studies included in this review focused solely on the Japanese population, which limits the generalizability of the findings to other ethnicities. Therefore, further large-scale, long-term, and multicenter clinical studies conducted globally are necessary to provide high-quality evidence and validate the renoprotective effects of topiroxostat across diverse populations. These studies would contribute to a more comprehensive understanding of the efficacy and safety of topiroxostat in managing hyperuricemia and its potential renal benefits.

Author Contributions

Both authors have contributed equally to the conceptualization, data capturing, and developing the content.

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REVIEW ARTICLE

Management of Acute Pulmonary Embolism: A Review

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Abstract

Pulmonary embolism (PE) is an important cause of morbidity and mortalityespecially among hospitalized patients. Although the exact epidemiology of PE is not known in India, several studies have shown that it is missed and mismanaged not infrequently, leading to significant cardiovascular morbidity and mortality. Indian consensus for the diagnosis and treatment of acute PE has been previously published. Recent findings from studies including data available from Indian studies have expanded our knowledge with respect to the optimal diagnosis, assessment, and treatment of patients with PE and have been integrated into this review article. Acute PE patients should be stratified according to early mortality risk. Clinical measures, right ventricular (RV) dysfunction markers, and myocardial injury should be used to determine risk stratification. The clinical prediction criteria [pulmonary embolism severity index (PESI) and Hestia criteria] should be routinely used in emergency departments. Investigations, such as D-dimer, electrocardiogram (ECG), chest X-ray, routine labs, N-terminal pro B-type natriuretic peptide/brain natriuretic peptide (NT-ProBNP/BNP), troponin I or troponin T, heart-type fatty acid binding protein (H-FABP), echocardiography, lower limb compression ultrasonography (CUS), computed tomographic-pulmonary angiography (CTPA), ventilation-perfusion scintigraphy (V/Q scan), and pulmonary angiography should be appropriately selected in suspected cases of PE as per risk stratification. The main treatment in medical management of acute PE comprises anticoagulants and thrombolytics. According to current guidelines, oral anticoagulants such as warfarin are recommended to be started at the time of diagnosis together with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux (all grade IA). Owing to their predictable bioavailability and pharmacokinetics, novel oral anticoagulants (NOACs) can be given at fixed doses without routine laboratory monitoring. Recurrence is not uncommon on cessation of therapy, and hence long-term anticoagulation may be required in selected cases. Strong positive evidence is available for the use of thrombolytics in the management of acute PE.

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Introduction

Pulmonary embolism (PE) can be a fatal complication of venous thromboembolism (VTE). It is among the three leading causes of cardiovascular mortality and one of the common causes of sudden unexplained deaths in hospitalized patients.[1,2] Surgery increases the risk of PE by fivefold. Despite the widespread adoption of thromboembolic prophylactic measures, PE accounts for a 30-day major surgery-specific case fatality rate ranging between 16 and 31%, and a 1-year case fatality rate of 37%.[3]

Recent hospitalization, recent surgery, cancer, and immobilization are the major risk factors for VTE. Conditions such as inflammatory bowel disease, systemic lupus erythematosus, and disseminated intravascular coagulation are also risk factors for VTE.[4] Medications, such as those containing estrogen and progesterone, tamoxifen, and raloxifene also increase the risk of a venous thromboembolic event.[4] Approximately, 50–60% of the disease burden from VTE is associated with recent hospitalization, either for surgery or for acute medical illness. Cancer-associated VTE accounts for ≈20% of the total VTE burden. The remaining 20–30% of the burden consists mainly of unprovoked VTE, which occurs in the absence of identifiable risk factors or in association with only minor risk factors. Patients with unprovoked VTE are predominantly younger (<50 years of age) than those with hospital-associated VTE. This is consistent with the estimates of a higher attributable risk for genetic factors in patients of younger age.[1]

Venous thromboembolism is outcome of an interaction of the individual patient's risk factors and the setting or circumstances where it occurs. Patient-associated risk factors are usually permanent, whereas circumstances tend to be transient in nature.[5] Early diagnosis and intervention are paramount as most deaths from acute PE occur within the first several hours to days, with over 70% of deaths occurring within the first hour.[5] The diagnosed and treated PE is responsible for 3–8% of the mortality rate but increases to about 30% in untreated PE.[6] The presentation of acute PE can vary from asymptomatic to sudden death. Approximately, 81% of patients present with dyspnea, 70% with tachycardia, and 50% with hypoxia.[5] Nearly, one-third of patients with symptomatic VTE manifest PE, and two-thirds manifest deep vein thrombosis (DVT) only. Indian consensus statement for the diagnosis and treatment of acute PE has been previously published. However, recent findings from studies including evidence from Indian studies have expanded our knowledge with respect to the optimal diagnosis, assessment, and treatment of patients with PE. These new aspects have been integrated into this review article, based on an in-depth literature review, with an objective to provide an update in the diagnosis and management of patients with suspected or confirmed diagnosis of acute PE in India. The clinician should make use of evidence-based recommendations while treating an individual patient.

Classification of Pulmonary Embolism

Acute RV failure, defined as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output, is an important determinant of outcome in acute PE.[7,8] Tachycardia, low systolic blood pressure (BP), respiratory insufficiency (tachypnea and/or low SaO_2), and syncope, alone or in combination, have been associated with an unfavorable short-term prognosis in acute PE. Risk stratification of patients with acute PE is of paramount importance and one of the primary steps for determining the appropriate therapeutic management approach.

Initial risk stratification is based on clinical symptoms and signs of hemodynamic instability, which indicate a high risk of early death. In PE patients without hemodynamic instability, two prognostic criteria are required to be assessed for advanced risk stratification: (1) clinical, imaging, and laboratory indicators

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of PE severity—RV dysfunction; and (2) presence of comorbidities and any other aggravating conditions that may adversely affect early prognosis.[7] Based on this, the European Society of Cardiology (ESC) has classified PE into three categories[7]:

- High-risk PE: Patients need to present with one of the following clinical presentations: cardiac arrest, persistent hypotension (systolic BP <90 mm Hg or a systolic BP drop >40 mm Hg for >15 minutes) not caused by new-onset arrhythmia, hypovolemia, or sepsis.
- Intermediate risk PE: Includes acute PE without systemic hypotension (systolic blood pressure >90 mm Hg) but with either RV dysfunction or elevated cardiac troponin levels [pulmonary embolism severity index (PESI) class III-V or sPESI ≥1].
- Low risk PE: Includes no RV dysfunction/no elevated cardiac troponins/normal PESI.

In another way of initial classification, based on the clinical parameters, acute PE is classified into "high risk" and "nonhigh risk" categories. The latter can further be subdivided into "intermediate risk" and "low risk" cases.[7] The terminologies "high risk" for acute massive PE and "intermediate risk" for submassive PE are now being suggested and commonly used.[9,10] It might be appropriate to use this classification in India to simplify risk stratification. Recent guidelines suggest risk stratification based on PE-related early mortality risk rather than the anatomical position and burden of thrombus which describe massive and submassive PE (Table 1).[11–13] Patients with suspected PE need to be stratified into specific risk categories to provide appropriate investigation and treatment plan, as diagnostic workup and management differ depending on the risk categories.

Various clinical prediction systems are available for stratifying PE risk according to signs, symptoms, and comorbidities. We recommend routine use of these clinical prediction systems in emergency departments.[14]

Pulmonary Embolism Severity Index Criteria

Among the clinical scores that combine severity of PE and comorbidity, PESI has been extensively validated.[7] PESI and its simplified form, simplified PESI (sPESI), integrate clinical parameters of PE severity and comorbidity to permit assessment of overall 30-day mortality. One of the important features of PESI is to identify patients at low risk for 30-day mortality. PESI is more commonly used as compared to Hestia criteria, but it contains a limited list of aggravating conditions. sPESI excludes all patients with age >80 years, cancer, chronic heart failure/pulmonary disease, and patients who are tachycardic (>110/minutes), hypotensive (SBP <100 mm Hg), and hypoxemic (SpO_2 <90%) from the low-risk category. It is used in combination with other additional feasibility criteria and can be utilized to determine if the patient is a possible candidate for outpatient management. Overall, PESI and sPESI are extensively validated and most used clinical scores. They combine baseline indicators of PE severity with aggravating conditions and the comorbidity of the patient. A PESI of class I-II or an sPESI of 0 is a reliable predictor of low-risk PE (Table 2).

Hestia Criteria

The Hestia exclusion criteria do not gauge severity but is a checklist of questions or clinical parameters that can be obtained/answered at the bedside.[7] The parameters take into account aspects of feasibility, PE severity, and comorbidities for early discharge and home treatment. If answer to one or more of the questions in the criteria is "yes," then early discharge of the patient is not possible (Table 3).

Diagnosis of Pulmonary Embolism and Investigations

The most important barrier in management of PE is the early recognition and diagnosis of the event. PE remains largely undiagnosed in number of patients. In an autopsy study, PE was suspected antemortem in only 9.4% cases.[15–19] Clinical signs and symptoms of PE are neither sensitive nor specific but can only help in suspecting the diagnosis. The symptoms of PE include dyspnea, chest pain, cough, hemoptysis, and syncope while the common signs include tachycardia or bradycardia, tachypnoea, cyanosis, hypotension, and signs of DVT.[20] The battery of investigations for risk stratification and diagnosis in suspected acute PE include electrocardiogram (ECG), chest X-ray, routine labs, D-dimer, N-terminal pro B-type natriuretic peptide/brain natriuretic peptide (NT-proBNP/BNP), troponin I or troponin T,

Table 1: Risk stratification of PE based on early mortality risk[7]

Early mortality risk		*Indicators of risk*			
		Hemodynamic instability[a]	*Clinical parameters of PE severity and/or comorbidity: PESI class III-V or sPESI ≥I*	*RV dysfunction on TTE or CTPA*[b]	*Elevated cardiac troponin levels*[c]
High		+	(+)d	+	(+)
Intermediate	High	–	+e	+	+
	Low	–	+e	One (or none) positive	
Low		–	–	–	Assessment optional; if assessed, negative

BP, blood pressure; CTPA, computed tomography pulmonary angiography; H-FABP, heart-type fatty acid-binding protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricular; sPESI, simplified pulmonary embolism severity index; TTE, transthoracic echocardiogram; [a]Cardiac arrest, obstructive shock (systolic BP 90 mm Hg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP 40 mm Hg for >15 minutes, not caused by new-onset arrhythmia, hypovolemia, or sepsis); [b]Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE and the corresponding cutoff levels; [c]Elevation of further laboratory biomarkers, such as NT-proBNP >600 ng/L, H-FABP >6 ng/mL, or copeptin >24 pmol/L, may provide additional prognostic information. These markers have been validated in cohort studies but have not yet been used to guide treatment decisions in randomized controlled trials; [d]Hemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary; [e]Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of III or an sPESI of 0.234 until the implications of such discrepancies for the management of PE are fully understood. These patients should be classified into the intermediate-risk category

Table 2: PESI and sPESI[7]

Parameter	*Original version*	*Simplified version*
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 bpm	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 bpm	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhemoglobin saturation <90%	+20 points	1 point
	Risk strata	
	Class I: ≤65 points Very low 30-day mortality risk (0–1.6% risk)	0 points = 30-day mortality risk 1.0% (95% CI: 0.0–2.1%)
	Class II: 66–85 points Low mortality risk (1.7–3.5%)	≥1 point(s) = 30-day mortality risk 10.9% (95% CI: 8.5–13.2%)
	Class III: 86–105 points Moderate mortality risk (3.2–7.1%)	
	Class IV: 106–125 points High mortality risk (4.0–11.4%)	
	Class V: >125 points Very high mortality risk (10–24.5%)	

BP, blood pressure; bpm, beats per minute; CI, confidence interval; [a]Based on the sum of points

Table 3: Hestia criteria[7]

If any of the below are answered "yes" the patient should not be treated as outpatient
1. Hemodynamically unstable?
2. Is thrombolysis or embolectomy necessary?
3. Active bleeding or high risk of bleeding?
4. Oxygen supply to maintain oxygen >90% >24 hours?
5. PE diagnosed during anticoagulant treatment?
6. In severe pain, needing IV medication >24 hours or multiple doses in ED?
7. Medical or social reason for treatment in hospital >24 hours
8. Creatinine clearance <30 mL/minute?
9. Severe liver impairment or disease?
10. Pregnant?
11. Documented history of heparin-induced thrombocytopenia?

echocardiography, lower limb compression ultrasonography (CUS), and computed tomographic-pulmonary angiography (CTPA). Ventilation-perfusion scintigraphy (V/Q scan) is performed when CTPA cannot be performed, and conventional pulmonary angiography is rarely used nowadays.

D-dimer testing: The quantitative enzyme-linked immunosorbent assay (ELISA) and D-dimer assay can be used to exclude PE in patients with either low or intermediate but not high pretest probability risk. Specificity of D-dimer in suspected PE decreases steadily with age to 10% in patients >80 years of age. Use of age-adjusted cutoffs may improve the performance of D-dimer testing in the elderly (age × 10 µg/L above 50 years).[7]

ECG: The positive findings in ECG are sinus tachycardia, right axis deviation (RAD), new complete or incomplete right bundle branch block, P pulmonale, T wave inversion in right precordial leads and/or inferior leads, S1Q3T3 pattern, nonspecific St-T changes, and atrial tachyarrhythmias.[13]

Echo: Echocardiographic assessment of the function of the RV is widely recognized as a valuable tool for the prognostic assessment of normotensive patients with acute PE in clinical practice. Findings of RV dysfunction on echocardiography are associated with an increased risk of short-term mortality in patients who seem to be hemodynamically stable at presentation, as per reports from systematic reviews and meta-analyses. One of the weaknesses of echocardiography is that its overall positive predictive value for PE-related death has been reported low by <10% in a meta-analysis. This weakness can be attributed to the fact that echocardiographic parameters are difficult to standardize. In addition to RV dysfunction, echocardiography can identify right ventricle (RV) dilation (an RV/LV diameter ratio ≥1.0), pulmonary hypertension (PH) (estimated RVSP >40 mm Hg), interventricular septal shift or bowing, McConnell's sign (hypokinesia or akinesia of the mid-RV free wall), distended inferior vena cava (IVC) with diminished inspiratory collapsibility, and right heart mobile thrombus detected in right heart cavities. New echocardiographic parameters of RV dysfunction: tricuspid annular plane systolic excursion (TAPSE <16 mm) and right ventricle myocardial performance index (RV-MPI) correlate well with morbidity and mortality in acute PE. The sensitivity of echo in diagnosing acute PE is >90% while specificity ranges between 87 and 96%.[7,13]

Biomarkers: Elevated plasma troponin concentrations on admission are a marker of myocardial injury and may be associated with a worse prognosis in the acute phase of PE, not only in unstable but also in those who are hemodynamically stable at presentation. Similarly, elevated concentrations of heart-type fatty acid-binding protein (H-FABP) levels >6 ng/mL, another marker of myocardial injury, are associated with adverse short-term outcomes and mortality. RV pressure overload due to acute PE is associated with increased myocardial stretch which leads to release of N-proBNP (>500 pg/mL) and BNP (>90 pg/mL). Thus, the plasma levels of natriuretic peptides reflect the severity of RV dysfunction and hemodynamic compromise in acute PE.[7,13]

CUS: In most cases, PE usually originates from lower limb DVT, and a CUS can be done at bedside using simple four-point examinations, that is, two groin and two popliteal fossae. The sensitivity of CUS for the presence of PE was 39% while specificity was 99%.[7,13]

CT-PA: It is used to locate and estimate the size of thrombi. Mild RV dilation (RV/LV slightly above 0.9) on CT is a frequent finding (>50% of hemodynamically stable PE patients), but it probably has minor prognostic

significance. Increasing RV/LV diameter ratios are associated with rising prognostic specificity, even in patients considered to be at "low" risk based on clinical criteria. A meta-analysis of 49 studies investigating >13,000 patients with PE confirmed that an increased RV/LV ratio of >1.0 on CT was associated with a 2.5-fold increased risk for all-cause mortality and PE-related mortality risk was increased fivefold. Thus, RV/LV ratios >1.0 (instead of 0.9) on CT angiography may be more appropriate to indicate poor prognosis.[7,13]

Pulmonary angiography: PA is the gold standard test with 100% sensitivity and 90% specificity. However, it is rarely employed due to availability of CT and the invasive nature of the test.

V/Q scan: Unavailability of the test and expertise for interpretation particularly during odd hours, and high proportion of inconclusive results limit the use of V/Q scan. In the Indian context, out of many available investigations, based on available resources, CT and echocardiography appear to be the most appropriate investigations for definitive diagnosis of PE along with blood tests. The most common clinical indication for a V/Q lung scan is to assess the likelihood of PE when contrast or radiation exposure is contraindicated (pregnancy, renal insufficiency, chronic kidney disease stage 4 or more, or severe contrast allergy).[7,11,21–23]

Diagnostic and Treatment Algorithm

The algorithms for diagnosis of suspected PE are presented in Figures 1 and 2, respectively.[7]

Management of Acute Pulmonary Embolism

PE management goals include prevention of death from the current embolic event, reducing chances of recurrent embolic events and minimizing long-term morbidity. Prompt diagnosis and appropriate treatment are critical to avoid fatal complications of acute PE.[14]

Anticoagulants and Thrombolytics in the Management of Acute Pulmonary Embolism

The main treatment in medical management of acute PE comprises anticoagulants and thrombolytics. While heparin slows or prevents the progression of DVT and reduces the size and frequency of PE, thrombolytics

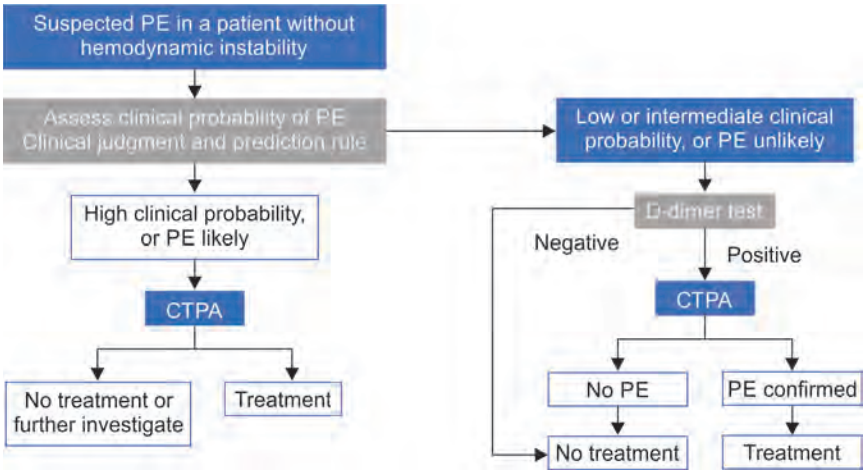

Fig. 1: Diagnostic algorithm for suspected PE without hemodynamic instability[7]; Diagnostic algorithm for patients with suspected PE without hemodynamic instability. CTPA, computed tomography pulmonary angiography/angiogram; PE, pulmonary embolism

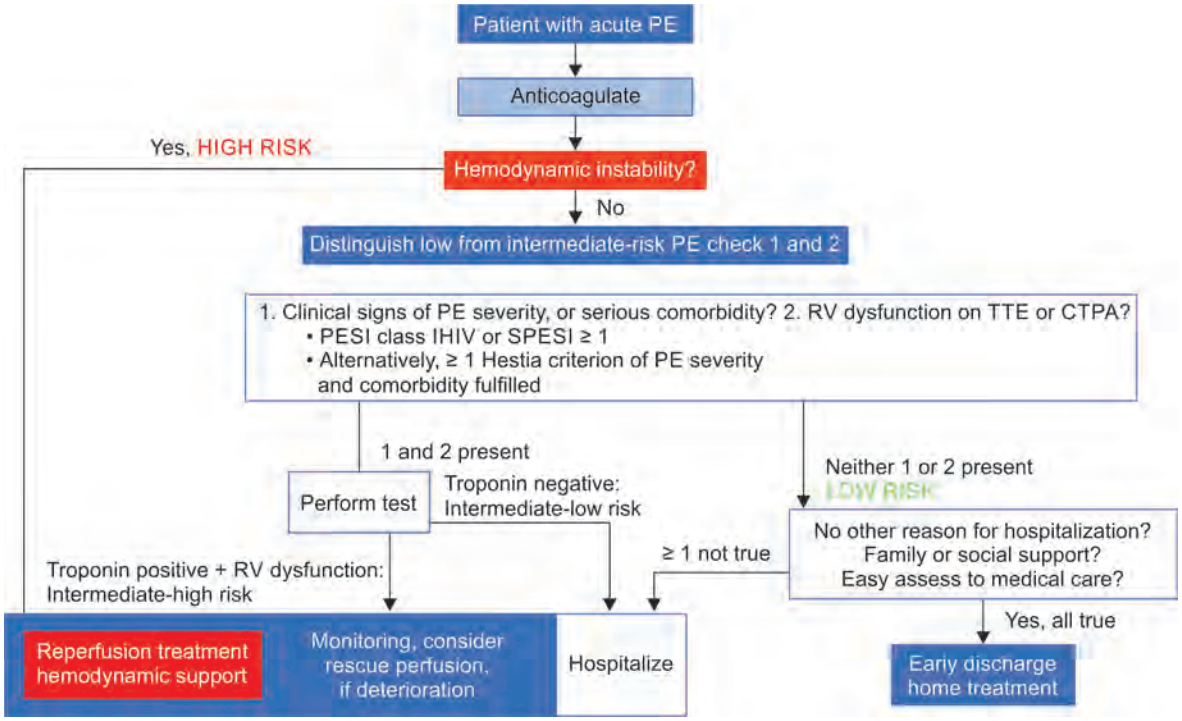

Fig. 2: Risk-adjusted management strategy for acute PE[7]; CTPA, computed tomography pulmonary angiography/angiogram; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricular; sPESI, simplified pulmonary embolism severity index; TTE, transthoracic echocardiogram

like alteplase and streptokinase break fibrin molecules and dissolve the clot.[24]

Initial Anticoagulation

We recommend that during diagnostic workup, anticoagulation should be started at the earliest for patients with an intermediate or high clinical probability of PE and had no contraindications to anticoagulation. Immediate full anticoagulation should be given to all patients with suspected PE.[14]

Unfractionated Heparin, Low-molecular-weight Heparin Therapy, and Fondaparinux

Current guidelines recommend starting UFH, LMWH, or fondaparinux (all grade IA) in addition to an oral anticoagulant (warfarin) at the time of diagnosis and discontinuing UFH, LMWH, or fondaparinux only after the international normalized ratio (INR) is 2.0–3.0 for 2 consecutive days but no sooner than 5 days after warfarin therapy has been started (grade IC recommendation). Evidence suggests that relatively long half-life of factor II, along with the short half-lives of protein C and protein S, may provoke a paradoxical hypercoagulable state if these agents are discontinued prematurely. The recommended duration of UFH, LMWH, and fondaparinux is based on this evidence. For patients with acute nonmassive PE, recommendation is to prefer LMWH over UFH (grade IA). However, in patients with acute PE and severe renal failure and morbid obesity, UFH is preferred over LMWH (grade IIC). The dosing of UFH is adjusted based on the activated partial thromboplastin time. Evidence suggests that increasing the dosage of LMWH in obese patients is more appropriate.[24]

Except in patients presenting with massive PE, LMWH or fondaparinux is recommended over IV UFH[25] due to its advantage of better predictable bioavailability, fast onset of full anticoagulant effect, and no need for monitoring anticoagulant effect. If needed, factor Xa levels can be monitored in case of ambiguity regarding dosing accuracy. UFH infusion has the advantage of quick adjustment of anticoagulation, especially when thrombolytic therapy is started.[14]

Thrombolytic Therapy for Pulmonary Embolism

In patients with acute PE, thrombolytic therapy induces faster clot dissolution than anticoagulation but is associated with an increased risk of hemorrhage. In randomized controlled studies comparing systemic thrombolytic therapy plus anticoagulation against anticoagulation alone, thrombolytic therapy was associated with a significant reduction of overall mortality as compared to heparin therapy. However, after the exclusion of studies including high-risk PE, this reduction was not statistically significant.[26] This implied that thrombolytic therapy showed significant results in hemodynamically unstable or high-risk patients with acute PE.

Examples of thrombolytic agents include streptokinase, urokinase, and recombinant tissue-type plasminogen activator. Bleeding is the major complication of this treatment. Among thrombolytics, the odds ratio (OR) for all-cause mortality was in the order of streptokinase (OR = 0.5) < alteplase (OR = 0.61) < tenecteplase (OR = 0.72) < urokinase (OR = 0.8), and for major hemorrhagic events, the order was: alteplase (OR = 0.71) < urokinase (OR = 2.23) < tenecteplase (OR = 4.95) (increasing odds ratio with reference to Heparin). This shows that alteplase had the lowest hemorrhagic risk and second lowest all-cause mortality among the thrombolytic options.[27]

Various available thrombolytics with their dosage are mentioned in Table 4. Approved thrombolytic agents for PE are streptokinase, urokinase, and alteplase. Reteplase and tenecteplase, though likely to be as effective, are not currently approved for acute PE and are not recommended as the first choice.

Evidence for Thrombolytics in Acute Pulmonary Embolism

Strong and positive evidence is available for the use of thrombolytics in the management of acute PE.[28] In a meta-analysis performed in 11 randomized studies in patients with acute PE, thrombolytic therapy was associated with a significant reduction in recurrent PE or death in high-risk hemodynamically unstable patients.[29] Other studies like ICOPER,[30] RIETE,[31] and EMPEROR[32] have also shown benefits with thrombolytics in significantly reducing the mortality rate in acute massive PE.[21] Alteplase should be preferred over streptokinase and urokinase based on the current evidence on efficacy, safety, and clinical experience.[21] Alteplase rapidly improves RV function and pulmonary perfusion in patients with PE and may lead to a lower rate of adverse clinical outcomes.[33]

Recently published results of moderate pulmonary embolism treated with thrombolysis (MOPETT) trial showed that <50% of the standard dose of tPA is safer and yet effective in the treatment of moderate PE. A presentation of 100 cases at the ACC 2014 recommended that when the clinician is undecided about thrombolysis or complete evaluation cannot be done due to nonavailability of tests or cost constraints, half-dose tPA (10 mg bolus and 40 mg infusion over 2 hours) can be administered along with UFH or subcutaneous enoxaparin. This is effective and decreases the risk of bleeding as pulmonary thrombi respond differently from arterial thrombi. However, this half-dose therapy is currently not an approved dose for thrombolysis.[34] Contraindications for the use of thrombolytic treatment are given in Table 5.

Table 4: Thrombolytic agents in acute PE[13]

	Thrombolytic dose
Alteplase	10 mg bolus, 90 mg IV infusion over 2 hours (100 mg over 2 hours)
Urokinase	4400 IU/kg bolus, followed by 4400 IU/kg/hour for 12–24 hours
Streptokinase	250000 IU IV bolus followed by 100000 IU/hour infusion for 12–24 hours
Reteplase	Two bolus doses of 10 U, 30 minutes apart
Tenecteplase	Weight-adjusted IV bolus over 5 seconds (30–50 mg with a 5 mg step up every 10 kg from <60 to >90 kg)

Please refer to the current locally approved prescribing information of each product for dosage, indication, contraindications, precautions, and other safety information

Table 5: Contraindications for thrombolytic treatment[13]

Absolute contraindications
Hemorrhagic stroke or stroke of unknown origin (any time) or ischemic stroke in last 6 months
Trauma or tumor of central nervous system
History of major trauma/surgery or head injury in last 3 weeks
Gastrointestinal bleeding in last month or known bleeding
Relative contraindications
Transient ischemic attack in last 6 months
Oral anticoagulant therapy
Pregnancy or within 1-week postpartum
Noncompressible punctures
Traumatic resuscitation
Refractory hypertension
Active peptic ulcer
Advanced hepatic disease
Infective endocarditis

Pulmonary Embolism with Intermediate Risk: Evidence to Thrombolyse or Not to Thrombolyse

It is known that isolated RV dysfunction is a marker for poor outcomes in patients with PE especially those with hemodynamic instability. RV dysfunction in hemodynamically stable patients is also a predictor of worse outcomes and appears to be related to the presence of recurrent PEs. Ten percent of hemodynamically stable patients with RV dysfunction will deteriorate into shock with a 50% mortality rate attributed to those with recurrent PEs.[35] The evidence for the use of thrombolytics in intermediate-risk PE is summarized below.

A randomized study involving 256 patients compared heparin plus alteplase with heparin alone in submassive PE showed a significantly higher incidence of inhospital death or clinical deterioration requiring an escalation of treatment in the heparin/placebo group compared to the heparin/alteplase group. Heparin-plus-alteplase group had higher probability of 30-day event-free survival. Fatal or cerebral bleeding was not observed in patients receiving heparin plus alteplase. Alteplase can improve the clinical course of stable patients with submassive PE.[36]

In another study that compared alteplase plus heparin vs anticoagulants alone, the total median hospital stay was significantly shorter in the alteplase group, and there was no difference in the intensive care unit (ICU) stay. For a prolonged hospital stay, patients with age >65 years and comorbidity were independent predictors. In multivariate analysis, thrombolysis independently predicted a shorter total stay. Thrombolysis may lead to a reduction of hospital stay for patients with intermediate-risk PE, possibly indicating that it is more effective than anticoagulant therapy alone in this group of patients.[35]

Tenecteplase, a mutant form of rt-PA that differs biologically from alteplase, is not yet approved for acute management of PE. In pulmonary embolism thrombolysis (PEITHO), a double-blind, randomized, comparative trial, tenecteplase prevented hemodynamic decompensation; however, major bleeding was seen in a higher number of patients receiving tenecteplase compared to placebo.[37]

Tenecteplase or placebo: cardiopulmonary outcomes at 3 months (TOPCOAT), a randomized trial in intermediate-risk PE patients, comparing tenecteplase with LMWH vs LMWH alone was terminated early. The results showed a greater survival rate in the first 5 days, shorter hospital stay, and greater quality of life at 90 days compared to LMWH alone.[38]

Various options to reduce bleeding while maintaining efficacy are being evaluated. In patients with intermediate-risk PE, ultrasound-accelerated thrombolysis (USAT) is superior to anticoagulation with only heparin in reversing right ventricular (RV) dilatation at 24 hours without increased bleeding risk.[39] The results of the ultrasound-accelerated thrombolysis of pulmonary embolism (ULTIMA) trial show that in patients with PE at intermediate risk of death, RV dilatation and dysfunction reversal at 24 hours is better with low-dose, catheter-directed ultrasound-accelerated thrombolysis with small doses of tPA than heparin alone. There is no risk of additional bleeding complications.[39] The results of a prospective, single-arm, multicenter trial of EkoSonic endovascular system and activase for treatment of acute PE (SEATTLE) II study, will provide additional information about the safety of USAT.[40]

The results justify the concept of risk stratification of normotensive patients with acute PE. Early "advanced recanalization" treatment prevents clinical deterioration in patients with evidence of RV dysfunction with cardiac necrosis. The patient's age should be taken into account when weighing the expected benefits vs risks of systemic thrombolysis in clinical practice.[14] For efficacy and safety data refer to Tables 6 and 7.[26]

Catheter-based Therapy or Surgical Treatment

Catheter-based therapy aims to rapidly reduce pulmonary artery pressure, RV strain, pulmonary vascular resistance, and increase systemic perfusion. Three types of percutaneous intervention include aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy.[21] All these have now been replaced by ultrasound-assisted low-dose tPA catheter-based therapy. This is a high-cost therapy and demands expertise which may not always be available. Surgical therapy is considered in high-risk patients when thrombolysis is contraindicated.[14]

Differences in Outcome between Systemic Thrombolysis and Catheter-directed Thrombolysis

A study was conducted to assess the utilization of catheter-directed thrombolysis (CDT) and its comparative effectiveness

Table 6: Efficacy of systemic thrombolysis[26]

	All studies		*Studies including*[a] *high-risk PE*	*Intermediate-risk PE*	*Low- and intermediate-risk PE*	*Group difference*
	OR (95% CI)	*p-value*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*p-value*
Mortality	0.59 (0.36–0.96)	0.034	0.48 (0.20–1.15)	0.42 (0.17–1.03)	0.96 (0.41–2.24)	0.36
PE mortality	0.29 (0.14–0.60)	<0.001	0.15 (0.03–0.78)	0.17 (0.05–0.67)	0.63 (0.20–1.97)	0.23
Death or treatment escalation	0.34 (0.22–0.52)	<0.001	0.18 (0.04–0.79)	0.37 (0.20–0.69)	0.35 (0.18–0.66)	0.67
PE recurrence	0.50 (0.27–0.94)	0.031	0.97 (0.31–2.98)	0.25 (0.06–1.03)	0.46 (0.17–1.21)	0.33

[a]Not exclusively

Table 7: Safety of systemic thrombolysis[26]

	All studies		*Alteplase*	*Alteplase*	*Alteplase*	*Group difference*
	OR (95% CI)	*p-value*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*p-value*
Major bleeding	2.91 (1.95–4.36)	<0.001	1.07 (0.43–2.62)	5.02 (2.72–9.26)	2.16 (1.03–4.54)	0.02
Fatal/intracranial hemorrhage	3.18 (1.25–8.11)	0.008	1.09 (0.27–4.40)	7.32 (1.64–32.63)	NA	0.07

against systemic thrombolysis in acute PE. The primary outcome of the study was inhospital mortality, and the secondary outcome was combined inhospital mortality and intracerebral hemorrhage (ICH). This study also compared acute blood loss requiring transfusion, acute renal failure, and disposition status between CDT and systemic thrombolysis groups. After the propensity scores were matched between the groups, the primary and secondary outcomes were found to be significantly lower in the CDT group as compared to systemic thrombolysis group. Refer to Table 8 for Study Outcomes in Systemic vs Catheter-Directed Thrombolytic Groups in Unmatched and Propensity Score-Matched Group.[41]

Inferior Vena Cava Filters

An IVC filter should not be used routinely as an adjuvant to anticoagulation and thrombolysis in acute PE treatment.[7] IVC use is relatively common but debatable in patients who had severe trauma with no recent history of VTE. Society of Interventional Radiology (SIR) recommends use of IVC filters in three clinical scenarios: (1) in patients with VTE and classic indications; (2) in patients with VTE and extended indications; and (3) in patients without VTE for primary prophylaxis against PE.[42] Refer to Table 9 for classic, extended, and prophylactic indications for IVC filter placement. After resolving contraindications to anticoagulation or active bleeding complications, anticoagulation should be restarted in patients with an IVC filter. Retrievable IVC filters should be used, and patients should be regularly evaluated for filter retrieval within the specific filter's retrieval window.[7] There is limited evidence, but observational studies have reported a lower risk of PE and PE-related death in trauma patients with IVC filters. IVC filters may pose an increased risk of VTE and mortality according to some conflicting reports.[42]

Based on the currently available data, guidelines for IVC filter placement from the American College of Radiology (ACR) in conjunction with SIR, American Heart Association (AHA), American College of Chest Physicians (ACCP), British Committee for Standards in Hematology (BCSH), and ESC support IVC filter placement in patients with VTE and a contraindication to anticoagulation. While there is consensus with respect to classic indications, guidelines on extended and prophylactic indications remain disparate given the lack of prospective data.

Warfarin and Nonvitamin K Antagonist Oral Anticoagulants

Warfarin Therapy

In venous thromboembolism, an INR should be maintained in the therapeutic range of 2–3.[44] The limitations of warfarin use include difficulty in dose titration, timing of drug intake with food and food restrictions, frequent INR monitoring and adjustment of dose accordingly, and its peak effect is not seen till 36–72 hours after dose administration.[45]

Nonvitamin K Antagonist Oral Anticoagulants

Nonvitamin K antagonist oral anticoagulants have multiple advantages including fast onset of action, predictable anticoagulation, targeting specific enzymes, and low interaction potential. In addition, they can be given in fixed doses and do not need regular coagulation monitoring.[46–52]

In the EINSTEIN-PE[53] study, rivaroxaban 15 mg bid for the first 3 weeks, followed by 20 mg once daily thereafter was compared with standard therapy (enoxaparin plus vitamin K antagonist). Rivaroxaban was found to be noninferior to standard therapy for the primary efficacy outcome of symptomatic recurrent venous thromboembolism. The first major or clinically relevant nonmajor bleeding episode occurred in 10.3% of rivaroxaban patients compared with 11.4% of standard therapy patients, while major bleeding was observed in only 1.1% of patients taking rivaroxaban compared to 2.2% in patients on standard therapy. The results support the use of rivaroxaban as monotherapy in the management of acute PE.

In RE-COVER[54] trial, dabigatran 150 mg bid was noninferior to warfarin for the prevention of recurrent VTE in patients presenting with acute venous thromboembolism. Dabigatran was initiated when the parenteral anticoagulant was stopped (once the parenteral anticoagulant had been given for

Table 9: Classic, extended, and prophylactic indications for IVC filter placement[43]

Patients with documented VTE and classic indications	*Patients with documented VTE and expanded indications*	*Patients without VTE*
Contraindication to anticoagulation	Iliocaval or large free-floating proximal DVT	Trauma patient with high risk of VTE
Complication of anticoagulation necessitating cessation	Inability to achieve/maintain adequate anticoagulation	Surgical procedure in a patient at high risk for VTE
Failure of anticoagulation	Massive PE with residual DVT in a patient at risk for further PE	Medical condition with high risk of VTE
Propagation/progression of DVT during therapeutic anticoagulation	Chronic VTE treated with thromboendarterectomy	
	Thrombolysis of iliocaval DVT	
	VTE with limited cardiopulmonary reserve	
	Recurrent PE with IVC filter in place (filter failure)	
	Poor compliance with anticoagulation	
	High risk of complication of anticoagulation (e.g., high fall risk)	

Table 8: Study Outcomes in Systemic vs Catheter-Directed Thrombolytic Groups[41]

Study Outcomes in Systemic vs Catheter-Directed Thrombolytic Groups				
Unmatched and propensity score-matched groups				
Outcomes	*Systemic thrombolysis (%)*	*Catheter-directed thrombolysis (%)*	*Odds ratio (95% CI)*	*p-value*
Inhospital mortality	20.02	10.23	0.45 (0.31–0.66)	<0.001
ICH	1.37	0.28	0.21 (0.03–1.55)	0.09
Propensity score-matched cohort (1:3 matching)				
Inhospital mortality	21.81	13.36	0.55 (0.36–0.85)	0.007
ICH	1.38	0	NA	0.08

at least 5 days). Warfarin was initiated on the day of randomization. First major or clinically relevant nonmajor bleeding episode occurred in 1.6% of dabigatran patients compared with 1.9% on standard therapy (warfarin) patients. Recurrent VTE or fatal PE was 2.4% on dabigatran and 2.1% on standard therapy (warfarin) patients.[55]

The AMPLIFY[56] trial compared apixaban (10 mg bid for 7 days, followed by 5 mg bid for 6 months) vs standard therapy (enoxaparin plus warfarin). Apixaban was noninferior to standard therapy in acute venous thromboembolism. Major clinically relevant nonmajor bleeding occurred in 0.6% of patients on apixaban compared to 1.8% on standard therapy. This results back use of apixaban monotherapy in the management of acute PE.

The Hokusai-VTE[57] trial compared edoxaban (Enoxaparin or UFH for 5 days followed by edoxaban 60 mg/day for 3–12 months). Major or clinically relevant nonmajor bleeding episodes occurred in 8.5% of edoxaban patients compared with 10.3% of standard therapy (warfarin) patients.

Recurrence Risk and Appropriate Duration of Anticoagulation

To complete the treatment of the acute episode and prevent recurrence of VTE over the long-term period is the main goal of anticoagulation after acute PE. The risk for recurrent VTE after discontinuation of treatment is related to the features of the index PE (or, in the broader sense, VTE) event. A study, which followed patients after an initial episode of acute PE, reported that when PE is associated with transient risk factors, the recurrence rate was ~2.5% per year after discontinuation of treatment, whereas the recurrence rate was 4.5% per year when PE occurred in absence of known cancer, known thrombophilia, or any transient risk factor.[8,58]

Based on the data collected from randomized control trials focusing on the risk of VTE recurrence following withdrawal of anticoagulation in the last 15 years, patients have been classified into several distinct groups. These groups are:

- Patients with a strong (major) transient or reversible risk factor, most frequently major surgery or trauma, can be identified as being responsible for the acute (index) episode.
- Patients in whom index episode might be partly explained by the presence of a weak (minor) transient or reversible risk factor, or if a nonmalignant risk factor for thrombosis persists.
- Patients with index episode occurring in the absence of any identifiable risk factor (the present Guidelines avoid terms such as "unprovoked" or "idiopathic" VTE).
- Patients having one or more previous episodes of VTE, and those with a major persistent prothrombotic condition such as antiphospholipid antibody syndrome.
- Patients having active cancer.

Recurrence is common; hence, long-term anticoagulation may be required in selected cases.[8,59–64]

Table 10 shows examples of transient/reversible and persistent risk factors for VTE, classified by the risk of long-term recurrence.

Role of Aspirin in Preventing Recurrence

Aspirin in the dose of 100 mg/day for 2 years reduced the recurrence risk without significant increase in major bleeding risk, in a double-blind, placebo-controlled study. This study involved patients who completed 6–18 months of oral anticoagulation after an initial episode of unprovoked venous thromboembolism. The protective benefits of aspirin against recurrent PE are inferior to warfarin and NOAC's; however, low-dose aspirin (75–100 mg) might find a place for long-term secondary prophylaxis in selected patients with high bleeding risk.[65]

Pulmonary Embolism and Pregnancy

One of the major causes of pregnancy-related maternal death in developed countries is PE. After a cesarean section, the risk of PE is higher in the postpartum period. When investigating suspected PE during pregnancy, exposure of the fetus to ionizing radiation is a concern. Modern imaging techniques lead to low

Table 10: Categorization of risk factors for VTE based on the risk of recurrence over the long term[7]

Estimated risk for long-term recurrence[a]	*Risk factor category for index PE*[b]	*Examples*[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with anesthesia for >30 minutes • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anesthesia for <30 minutes) • Admission to hospital for <3 days with an acute illness • Estrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Nonmalignant persistent risk factor	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episode of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

PE, pulmonary embolism; VTE, venous thromboembolism; [a]If anticoagulation is discontinued after the first 3 months; [b]The categorization of risk factors for the index VTE event is in line with that proposed by the International Society on Thrombosis and Hemostasis. The present Guidelines avoid terms such as "provoked," "unprovoked," or "idiopathic" VTE

radiation exposure in mother and fetus. For V/Q scans and CTPA, fetal radiation doses are below the threshold values that are associated with fetal radiation complications (which is 50–100 mSv). Due to evolution in technology, problems like high radiation exposure to the breast due to CTPA are resolved. Several techniques can now decrease the radiation exposure and not compromise image quality. These include reducing the kilovoltage, using iterative reconstructive techniques, reducing the contrast-monitoring component of the CTPA, and reducing the anatomical coverage of the scan. Heparin does not cross the placenta and is not found in breast milk in significant amounts.[66–75] Therefore, treatment of PE in pregnancy is based on heparin anticoagulation (Fig. 3).

Rising experience suggests that LMWHs are safe in pregnancy, and their use is recommended in several reports. Treatment should comprise a weight-adjusted dose of LMWH. Although routine monitoring is generally not justified, in women with extremes of body weight or renal failure, dosing based on anti-Xa monitoring may be considered.[7]

Recent Evidence from Indian Studies

A retrospective study done from 2012 to 2018 in Karnataka aimed to determine the clinical profile, management, and outcomes of patients with acute PE. Patients with proven diagnosis of PE (n = 304) and treated at a tertiary care center were included. The average age of the patients diagnosed with PE was 38.0 ± 26.8 years. Majority of these patients (n = 195; 64.14%) were male. 92 (30.66%) patients were smokers, and 81 (26.6%) were obese. Dyspnea (98.03%) was the most observed symptom. Of patients who underwent bilateral lower limb venous Doppler and 2D echocardiography, DVT was noted in 172 (56.57%) and RV dysfunction was detected in 241 (79.28%) patients. 158 (51.97%) patients received thrombolytic therapy. Low-molecular-weight heparin and UFH were used in 46.71 and 45.39% of patients, respectively. Inhospital mortality was 39 (12.8%). At discharge, 45 (14.80%) patients had inferior vena cava filters. After discharged from the hospital, 154 (50.65%) patients used oral anticoagulation with warfarin, and 84 (27.63%) patients used new oral anticoagulants. Chronic thromboembolic pulmonary hypertension (CTEPH) was seen in 17 (5.59%) patients at 12-month follow-up, and 11 patients of them underwent pulmonary endarterectomy. Although this study was nonrandomized and retrospective with small number of patients, the outcomes underscore the importance of early diagnosis and intervention in patients with acute PE.[76]

Another observational study was conducted in Karnataka to understand the clinical profile of patients with acute PE and its response to standard guideline-based treatment. It included 31 patients with confirmed diagnosis of acute PE by CT scan. The study reported that 71% (n = 22) of the patients belonged to the age range 20–50 years and 39% in the age-group 31–40 years. Patients over 65 years of age comprised only 19% (n = 6) of the total number. Dyslipidemia, prolonged immobilization, DVT, postoperative state, malignancy, and postpartum period were the commonly reported risk factors. Dyspnea was the most common symptom reported at presentation in all 31 patients. A total of 18 (58%) patients were thrombolysed, who had massive or submassive PE. Overall reported mortality rate was 6% (n = 2). The study reported higher incidence of acute PE in the middle age-group population and high prevalence of dyslipidemia, although the exact association of dyslipidemia in acute PE could not be determined. Further, the study reported that thrombolytic therapy can be considered for massive and submassive pulmonary thromboembolism.[77]

Another study from Chennai analyzed 140 patients who presented with acute pulmonary thromboembolism at a large center in India from 2015 to 2018. The mean age of the study population was 50 years with 59% being male. DVT, diabetes mellitus, hypertension, and chronic obstructive pulmonary disease were the comorbidities

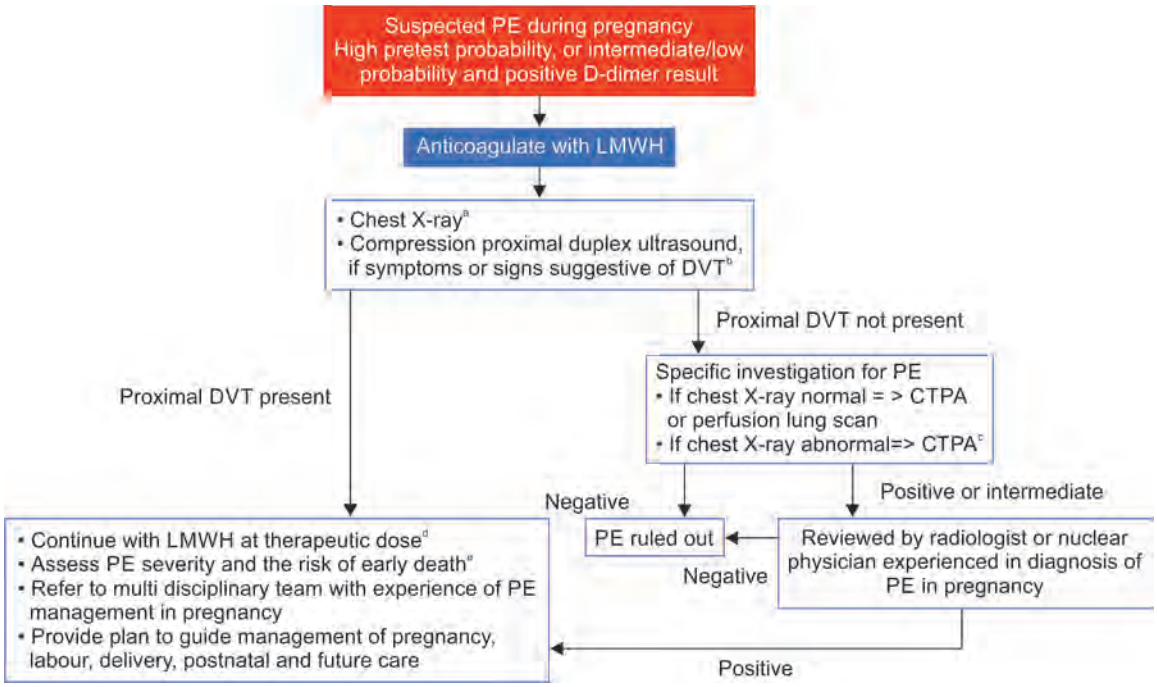

Fig. 3: Suspected PE in pregnancy[7]; [a]If chest X-ray abnormal, consider also alternative causes of chest symptoms; [b]DVT in pelvic veins may not be ruled out by CUS. If the entire leg is swollen, or there is buttock pain or other symptoms suggestive of pelvic thrombosis, consider magnetic resonance venography to rule out DVT; [c]CTPA technique must ensure very low fetal radiation exposure; [d]Perform full blood count (to measure hemoglobin and platelet count) and calculate creatinine clearance before administration. Assess bleeding risk and ensure absence of contraindications

in 52.9, 40, 35.7, and 7.14% of patients, respectively. Of the 140 patients in the study, 40 (28.6%) had massive pulmonary thromboembolism, 36 (25.7%) had submassive pulmonary thromboembolism, and 64 (45.7%) had low-risk pulmonary thromboembolism. Death was reported in 25.7% of patients with PE and 72.5% of patients with massive PE. Thrombolysis was administered in 62.5% of patients with massive pulmonary thromboembolism and 63.9% of patients with submassive pulmonary thromboembolism. The inhospital mortality for the patients with massive PE who received thrombolytic therapy was 60%, while for those who did not receive thrombolytic therapy was 93.3%, with an absolute risk reduction of 33.3%, thereby highlighting the importance of initiating therapy promptly. This difference was not seen in the submassive pulmonary thromboembolism group. The study concluded that patients with acute pulmonary thromboembolism in India presented more than a decade earlier than our western counterparts, and it was associated with poor clinical outcomes. Inhospital mortality rate reduced significantly in patients with massive pulmonary thromboembolism who were thrombolysed. Measures like public education of the illness, effective and quickly recognizing acute pulmonary thromboembolism and the concept of the Pulmonary Embolism Response Team (PERT) serving such patients will be beneficial in achieving improved patient outcomes.[78]

Another study from Kashmir included patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with no obvious cause of exacerbation on initial evaluation. A total of 100 patients of AECOPD with unknown etiology were included, out of which PE as a possible cause of AE-COPD was observed in 14% of patients. Among patients with PE, 63% (n = 9) had concomitant lower extremity deep venous thrombosis. In AECOPD patients with PE, the rate of hemoptysis and chest pain was significantly higher [(35.7 vs 7%, p = 0.002) and (92.9 vs 38.4%, p = 0.001)]. Likelihood of PE was significantly higher in patients with tachycardia, dyspnea, respiratory alkalosis ($PaCO_2$ <45 mm Hg and pH >7.45) and hypotension at presentation. The study highlighted that patients who present with chest pain, hemoptysis, tachypnea, tachycardia, and respiratory alkalosis should be particularly screened for PE.[79]

Strategies for Patient Follow-up after Pulmonary Embolism

Patients should be assessed for persistence, new-onset dyspnea or functional limitation. To check for possible signs of VTE recurrence, cancer, or bleeding complications of anticoagulation, evaluation of the patients 3–6 months after the acute episode of PE is recommended.[7,76] TTE should be considered as the next step to assess the probability of (chronic) PH and thus possible CTEPH in patients complaining of persisting dyspnea and poor physical performance. Patients with a high echocardiographic probability of PH, or those with intermediate probability combined with elevated NT-proBNP levels or risk factors/predisposing conditions for CTEPH, should be considered for a V/Q scan. Referral to a PH or CTEPH expert center for further diagnostic workup is indicated if mismatched perfusion defects are found on the V/Q scan. If, on the other hand, the V/Q scan is normal and the patient's symptoms remain unexplained, Cardio Pulmonary Exercise Test (CPET) may be performed. By reducing maximal aerobic capacity, CPET supports the necessity for additional follow-up visits and aids in the identification of candidates for pulmonary rehabilitation, exercise, or weight-reduction programs. CPET may also be helpful in patients with suspected CTEPH and coexisting left heart and/or respiratory disease by establishing the main limiting factor. This can help to set priorities for the treatment strategy (Fig. 4).[7,80]

Around 1–5% of PE survivors are affected by CTEPH. In order to prevent acute VTE

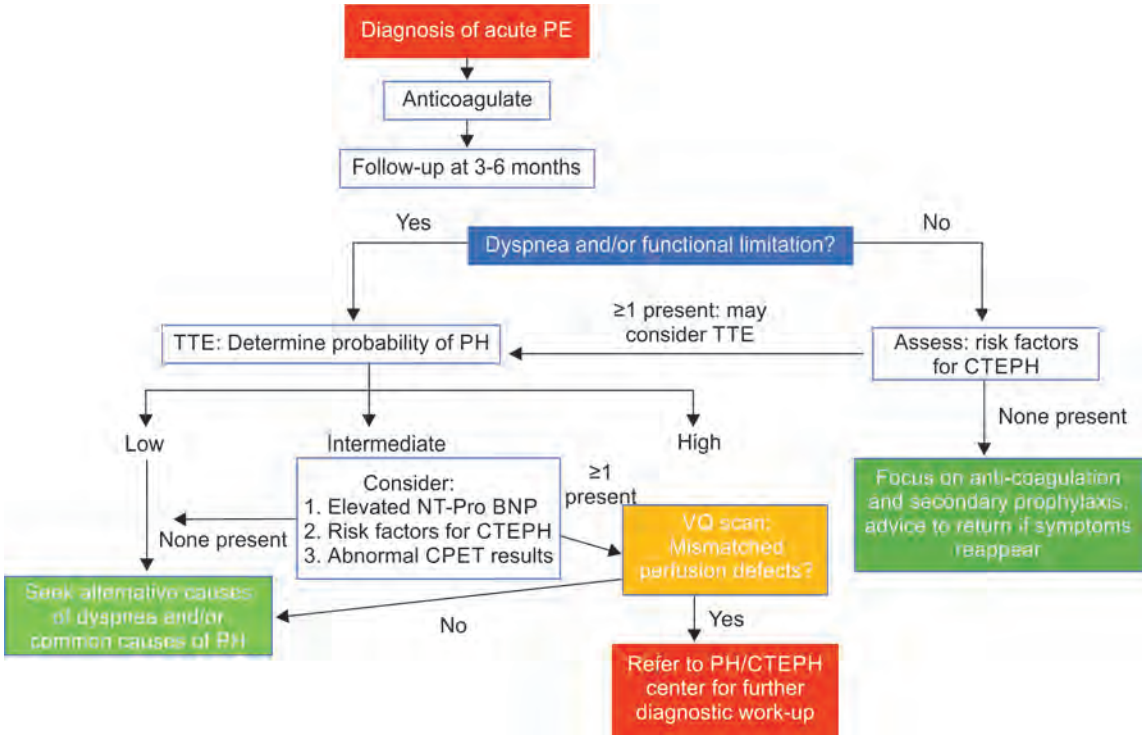

Fig. 4: Strategies for patient follow-up after PE[7]; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; NT-proBNP, N-terminal pro B-type natriuretic peptide; PE, pulmonary embolism; PH, pulmonary hypertension; TTE, transthoracic echocardiography/echocardiogram; V/Q, ventilation/perfusion (lung scintigraphy)

recurrence, lifelong anticoagulation is required for CTEPH treatment. The optimal intensity is not clear. However, most are maintained on therapeutic doses if bleeding risk is low. There are also three other treatment options used to address the problem of chronic vascular occlusions and PH: (1) surgical pulmonary thromboendarterectomy, (2) interventional balloon pulmonary angioplasty (BPA), and (3) pulmonary vasodilator medications. Treatment strategy can be selected based on an individual patient and hemodynamic characteristics. Long-term management of CTEPH involves anticoagulation and monitoring for recurrent symptoms.[81]

Future Directions: Use of Multidisciplinary Approach

Recently, a new concept of a pulmonary embolism response team (PERT) comprising of specialists from various fields has been suggested. PERT team consists of specialists from cardiology, emergency medicine, vascular medicine, cardiac surgery, and pulmonary/critical care. This can help to streamline management of severe PE. On activation, an on-call PERT colleague immediately calls a meeting of PERT, which enables to provide rapid consultation with multidisciplinary approach.[7] This approach can be utilized in India for improving PE diagnosis and outcomes.

Summary and Conclusion

- Acute PE requires prompt diagnosis and treatment as it is a highly morbid condition.
- Patients with acute PE should be immediately stratified according to early mortality risk.
- For risk stratification, parameters used are clinical measures, markers of RV dysfunction, and myocardial injury. To make it simple, terms "high risk," "intermediate risk," and "low risk" should be used.
- Emergency departments should regularly use the clinical prediction criteria (simplified Geneva score and PE rule-out criteria).
- ECG, chest X-ray, routine labs, D-dimer, NT-ProBNP/BNP, troponin I or troponin T, heart-type fatty acid binding protein (H-FABP), echocardiography, lower limb CUS, CT-pulmonary angiography, V/Q scan, and pulmonary angiography should be selected in suspected cases of PE as per risk stratification.
- Treatment modalities include medical and surgical. Treatments vary from systemic anticoagulation in patients who have no signs of right heart dysfunction to systemic thrombolysis, catheter-directed therapy, and surgical embolectomy in patients with submassive and massive PE.
- Surgical outcomes have improved over the years and now offer a safe and appropriate treatment option in a select group of patients with massive/high-risk PE that can reduce the mortality and morbidity.
- Anticoagulation should be immediately started in high or intermediate clinical probability of PE during ongoing diagnostic workup. In high-risk PE, anticoagulation with UFH should be started immediately. For nonhigh-risk PE, initial treatment with LMWH or fondaparinux is recommended.
- Patients having high risk of bleeding and severe renal dysfunction should be initially treated with UFH, with an aPTT target of 1.5–2.5 times normal. Initial treatment with anticoagulants like unfractionated heparin, LMWH or fondaparinux should be administered for at least 5 days. Only after target INR levels are achieved for >2 consecutive days it may be replaced by vitamin K antagonists. When oral anticoagulation is initiated in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, or rivaroxaban), a NOAC is preferred over warfarin. NOAC's can be started immediately on diagnosis or after 5–7 days of parenteral anticoagulants.
- Routine use of thrombolytics in nonhigh-risk PE is not recommended but may be considered in selected cases with intermediate-risk PE. Thrombolytics are not recommended in patients with low-risk PE.
- Recurrence is common on withdrawal of therapy; hence, long-term anticoagulation may be required in selected cases.
- The PERT is unique team-based program for acute PE patients to provide better and more coordinated care by facilitating rapid consultation and expert consensus with a multitude of experienced specialists.

Disclosure

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REVIEW ARTICLE

Stable Angina Pectoris: A Review of Pathophysiology, Diagnosis, and Its Management

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Abstract

India is at the cusp of an impending epidemic of cardiovascular diseases (CVD). It has been triggered by rapid urbanization, industrialization, and globalization. Coronary artery disease (CAD) and ischemic heart disease (IHD) clinically present as angina pectoris (chest pain and discomfort). Despite advances in treatment options for CAD, a lack of awareness of risk factors and disease, access to healthcare, and affordability are the primary concerns in low- and middle-income countries. In India, CAD results in >7 million deaths annually. There is a need for active collaboration between patients, physicians, and healthcare providers to identify the early and adequate use of lifestyle, pharmacological, and primary and secondary preventive measures. Antianginal treatment options are categorized as first line (calcium channel blockers (CCBs), β-blockers, and short-acting nitrates) and second line (ivabradine, nicorandil, ranolazine, and trimetazidine) drugs. This review discusses different CCBs (dihydropyridines (DHPs) or nondihydropyridines) for the management of angina pectoris.

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Introduction

Angina pectoris is characterized by chest pain or discomfort in patients with coronary artery disease (CAD).[1] The underlying etiology is an imbalance in the supply and demand of oxygen due to atherosclerosis or vasospasm.[2] Exercise, stress, and excessive emotions often precipitate these episodes. If not managed well, it results in myocardial ischemia or hypoxia (Fig. 1). CAD is a spectrum of conditions ranging from asymptomatic atherosclerosis and stable angina, including stable coronary artery disease (SCAD), to acute coronary syndrome (ACS), which includes unstable angina, non-ST-elevation myocardial infarction (N-STEMI), and ST-elevation myocardial infarction (STEMI).[3]

Unlike the West, where CHD is declining, there has been an increase in CHD cases (adults >20 years) across India.[4] Urbanization, industrialization, and globalization are the main factors that lead to cardiovascular disease (CVD).[5] This increase has been observed over the past 60 years in both urban (from 1% to 9–10%) and rural (from <1% to 4–6%) areas.[4] The impact of this meteoric rise is compounded, as it affects a higher proportion of young adults and has a higher mortality rate. The high prevalence of smoking/tobacco chewing and diabetes (risk factors for CVDs) further adds to this challenge.[6]

Managing angina pectoris in stable CAD in India is hindered by various challenges such as lack of awareness, limited healthcare access, and affordability issues. Symptom recognition and knowledge of preventive measures are often lacking, leading to delayed diagnosis. Rural areas face healthcare disparities and scarcity of diagnostic facilities, exacerbating delays.[7] Affordability concerns extend to medication costs and interventional procedures, thereby restricting access to a significant population. Posthospitalization, inadequate follow-up care, and absence of widespread cardiac rehabilitation programs pose additional hurdles. Low health literacy and cultural stigma surrounding heart-related illnesses contribute to suboptimal disease management.[8,9]

Addressing these concerns requires a comprehensive approach involving public health campaigns, improvements in healthcare infrastructure, affordable solutions, and educational programs aimed at both healthcare providers and the general population. Initiatives should focus on increasing awareness, early detection, and ensuring that effective treatments are accessible to all segments of the population.[8,9]

Pathophysiology

Ischemic heart disease (IHD) and associated angina occur due to an imbalance in the supply and demand of oxygen in the cardiac tissues. The supply is determined by the appropriate coronary blood flow and oxygen-carrying capacity, while the factors influencing demand are heart rate, myocardial contractility, and tension or stress in the myocardial wall. Blood flow in coronary vessels is phasic, with the diastolic phase being the major contributor. The contributors (≈75%) to resistance are epicardial (resistance 1—R1), prearteriolar (R2), and arteriolar/intramyocardial vessels (R3). The key drivers are R2 and R3. Intramyocardial vessels have an intrinsic ability to vary R2 and R3

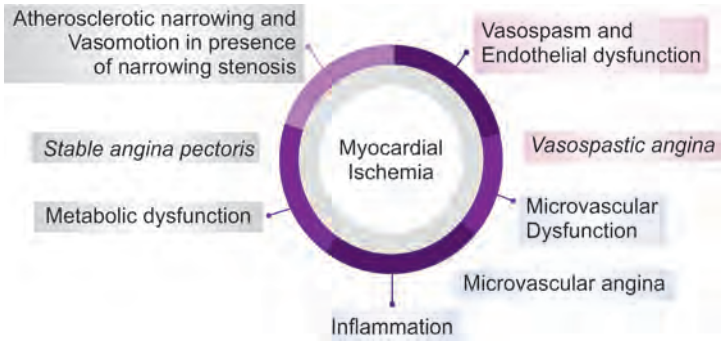

Fig. 1: Aetiology of myocardial ischemia

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with changing O_2 requirements (stressful conditions and exercise).[10]

The supply of O_2 to cardiac tissues is impaired in atherosclerosis or vasospastic conditions (narrowed coronary lumen). Depending on the extent and duration of the reduction, it can result in myocardial ischemia or infarction.

Current Diagnostic Techniques

In angina pectoris, chest pain or discomfort is retrosternal. It develops gradually over several minutes and is often precipitated by physical exertion, emotional stress, or occurs at rest (ACS).[11] Pain may radiate to the left arm, neck, or jaw and is often associated with breathlessness, nausea, and dizziness. Appropriate treatment helps to relieve symptoms quickly (in minutes).

Clinical examination (history and physical assessment) is the primary diagnostic approach to SCAD. The symptoms and signs, medical history, risk factors, and other etiologies related to CVD support this process. Resting heart rate, electrocardiogram (ECG), echocardiography, and laboratory investigations, such as hemoglobin, glycated hemoglobin (HbA1c), lipid profile, and liver, renal, and thyroid function tests, are recommended.[12,13] Different diagnostic techniques can be individualized for patients with suspected microvascular, vasospastic, or silent angina.[14] Exercise stress tests and Holter monitoring are recommended to identify silent ischemia in 15–65% of high-risk patients (based on symptoms, age, and sex).[15] An invasive coronary angiogram is performed in symptomatic patients with high-risk features on noninvasive testing. In patients with suspected angina due to coronary heart disease, computed tomography (CT) coronary angiography clarifies the diagnosis, enables targeting of interventions, and might reduce the future risk of myocardial infarction (MI).[16]

High-sensitivity cardiac troponin concentration is a reliable predictor of obstructive CAD in patients with suspected stable angina. In diagnosing MI, troponin measurement surpasses CK-MB, which was previously considered the "gold standard," by offering a significantly higher sensitivity for detecting myocardial injury. The release kinetics of troponins T and I are similar, with both released within 4–12 hours after myocardial necrosis and reaching their peak value 12–48 hours from symptom onset, depending on the duration of ischemia and reperfusion.[13]

The severity and extent of left ventricular function, presence of IHD or other comorbid conditions, and fasting blood glucose levels influence the prognosis.[17] In addition, elevated heart rate (resting heart rate >70 bpm) and low hemoglobin levels are associated with poor outcomes (vascular) and higher mortality.[12,13] The annual mortality rate ranges from 1 to 3% across low-to-high-risk patients.

Management of Angina

The treatment approaches for angina include non-pharmacological (lifestyle), preventive strategies for risk factors (primary and secondary), and pharmacology. Active or passive smoking, tobacco chewing (smokeless), and alcohol consumption are major risk factors for angina and should be avoided.[18,19] Lifestyle measures such as diet modulation and exercise are recommended.[20–22]

The use of statins to achieve an optimal LDL-C level of <70 mg/dL is recommended.[23,24] Similarly, a systolic/diastolic blood pressure goal of 140/90 mm Hg[25] and HbA1c of <7.0%[26] is advisable in patients with comorbid hypertension and diabetes. First-line antianginal drugs include calcium-channel blockers, β-blockers, and short-acting nitrates. In patients with efficacy and safety concerns, ivabradine, nicorandil, ranolazine, and trimetazidine are alternative options.[27] The efficacy of both these first- and second-line antianginal agents is comparable. Combination treatments (double or triple medications) are often used in severe conditions or nonresponders. Because of limited comparative data, guideline recommendations for SCAD are based on experience and expert opinion (Table 1).[28]

The goals of drug therapy are to resolve acute symptoms of SCAD and reduce subsequent episodes. In addition, they should help in the secondary prevention of cardiovascular events. Current treatment options either relieve symptoms or prevent progression and CVD outcomes.[29] The treatment options for acute symptoms are provided below.

Calcium Channel Blockers

Calcium channel blockers (CCBs) [dihydropyridine (DHP) or nondihydropyridines] are potent first-line antihypertensive drugs. They are part of the standard of care for patients with angina (variant, exertional, and unstable) and peripheral vascular diseases (PVD) across ages and genders.[30,31] Though they have a common mechanism of action (L-type voltage-gated calcium channels), DHPs show a predominant vasodilatory action, while nondihydropyridines have a negative inotropic effect.[32] Both these groups are equally effective in lowering BP. However, non-DHPs (diltiazem and verapamil) have an edge in patients with CKD and diabetic neuropathy.[33,34] Since these CCBs were first discovered in the 1960s, four generations of DHPs have been developed.[31] First-generation DHPs include nifedipine and nicardipine, which are short-acting and potent and are associated with side effects such as headaches and BP fluctuations. Benidipine and efonidipine are second-generation DHPs with features of slow release, shorter action, and fewer side effects.

Third-generation DHPs such as amlodipine and azenidipine exhibit stable pharmacokinetics, are less cardioselective, and are well tolerated. Lercanidipine,

Table 1: Antianginal drugs as per guideline recommendations of the European Society of Cardiology (ESC), American Heart Association/American College of Cardiology (AHA/ACC) and Indian Expert Consensus

Antianginal drugs	*ESC*	*AHA/ACC*	*India*
Nitrates			
Short acting nitrates Sublingual nitroglycerine	IB	IB	II
Long-acting nitrates	IIB	IB	Not available
Beta-blockers			
Uncomplicated patient	IA	IB	I
Previous MI	IB	IB	I
Reduced LVEF (40%)	IB	IB	I
Calcium channel blockers			
Dihydropyridine	IA	IB	I
Nondihydropyridine	IA	IIB	I
Others			
Ranolazine	IIa(B)	IIa(A), IIa(B)	II
Ivabradine	IIa(B)	Not available	II
Nicorandil	IIa(B)	Not available	II
Trimetazidine	IIb(B)	Not available	II

cilnidipine, and lacidipine are fourth-generation DHPs with features of higher lipophilicity.[35] They are associated with stable activity, reduced adverse effects, and a broad spectrum of action in MI and congestive heart failure (CHF).

In a retrospective study, 5,582 hypertensive patients were prescribed CCBs. Patients prescribed amlodipine showed lower blood pressure variability (BPV) than patients prescribed other CCBs (12.90 vs 13.76 mm Hg, $p < 0.05$ and 9.47 vs 10.06 mm Hg, $p < 0.05$). For hypertensive patients with comorbidity, those prescribed amlodipine also had lower BPV than patients prescribed other CCBs (13.24 vs 14.23 mm Hg, $p < 0.05$ and 9.66 vs 10.28 mm Hg, $p < 0.05$).[36] New CCBs like cilnidipine act through N-, T-, and L-type calcium channels, resulting in cardiovascular and renal benefits.[37] Additionally, as N-type calcium channels are found in nerves and the brain, cilnidipine produces an antihypertensive effect *via* modulation of sympathetic tone.[38] Despite all these benefits, cilnidipine appears weaker than amlodipine in lowering BP.[39]

Amlodipine is more potent than cilnidipine, benidipine, and azelnidipine. It results in superior BP control at lower doses, with comparable effects on renal parameters and tolerability. Thus, amlodipine is preferred despite the availability of newer CCBs.[40]

The common side effects include systemic hypotension, headache, dizziness, flushing, palpitations, and leg edema. Patients often report reduced left ventricular contractility and intestinal motility (constipation) on verapamil. Diltiazem and verapamil interact with ivabradine at cytochrome P450 3A4, resulting in severe bradycardia (Table 2).[41]

Table 2: Summary of clinical trials of CCBs

Sr. no.	*Study name, year*	*N*	*Angina—inclusion criteria*	*Intervention*	*Treatment duration*	*Results (efficacy and safety)*	*Reference*
1.	Felodipine and amlodipine instable angina pectoris: results of a randomized, double-blind crossover trial 1997	52	Exercise-induced angina pectoris and myocardial ischemia during 24-h electrocardiographic monitoring	Felodipine, extended-release 5–10 mg vs amlodipine, 5–10 mg once daily	8 weeks	Amlodipine = felodipine The mean number of ischemic episodes/24 hours was reduced from 19.9 at baseline to 2.3 during amlodipine and to 2.4 during felodipine; the total duration of ischemic episodes decreased from 69.8 minutes/24 hours to 15.2 minutes and 15.5 minutes during amlodipine and felodipine, respectively (for both variables, $p = 0.83$ and $p = 0.53$ between treatments, and both treatments, $p < 0.001$ compared with baseline) Safety—Well tolerated	Koenig and Höher[42]
2.	Bisoprolol alone and in combination with amlodipine or nifedipine in the treatment of chronic stable angina 2000	198	Stable angina	Bisoprolol 10 mg once daily, bisoprolol plus nifedipine 20 mg BD, and bisoprolol plus amlodipine 5 mg once daily	12 weeks	Bisoprolol = bisoprolol + amlodipine/nifedipine	Ferguson et al.[43]
3.	Effects of amlodipine and isosorbide dinitrate on exercise-induced and ambulatory ischemia in patients with chronic stable angina pectoris 1997	59	Stable angina	Once-daily administration of 5–10 mg amlodipine with two daily doses of 40 mg sustained-release isosorbide dinitrate	10 weeks	Amlodipine > isosorbide dinitrate Amlodipine significantly reduced anginal episodes ($p < 0.001$) compared to isosorbide dinitrate	Steffensen et al.[44]
4.	Effect of metoprolol and amlodipine on the myocardial total ischemic burden in patients with stable angina pectoris 1997	52	Patients with a history of stable exercise-induced angina pectoris and at least six episodes of significant ST-segment depression during 24-hour ambulatory electrocardiographic monitoring after 9 days of placebo were included in the study	Beta-1-blocker metoprolol (metoprolol CR/Zok) vs amlodipine; doses of 100 mg OD and 5 mg OD, respectively	8 weeks	Both drugs reduce the total ischemic burden by reducing ischemic episodes and antianginal attacks; metoprolol 100 mg OD > amlodipine 5 mg OD	Klein et al.[45]
5.	Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomized, double-blind, multicenter, noninferiority trial 2007	1195	Patients with a ≥3-month history of chronic, stable effort-induced angina	Ivabradine 7.5 mg ($n = 400$) or 10 mg ($n = 391$) twice daily or amlodipine 10 mg once daily ($n = 404$)	3-month, double-blind period	Ivabradine = amlodipine (in improving exercise tolerance) Ivabradine > amlodipine (on the reduction of rate-pressure product (a surrogate marker of myocardial oxygen consumption) and similar safety	Ruzyllo et al.[46]

Contd…

Contd…

Sr. no.	*Study name, year*	*N*	*Angina—inclusion criteria*	*Intervention*	*Treatment duration*	*Results (efficacy and safety)*	*Reference*
6.	Comparison of effects of nisoldipine-extended release and amlodipine in patients with systemic hypertension and chronic stable angina pectoris 2003	120	Patients with stage 1–2 systemic hypertension [90–109 mm Hg diastolic blood pressure (BP)] and chronic stable angina pectoris	Nisoldipine-ER (20–40 mg) or amlodipine (5–10 mg) once daily, titrated as necessary after 2 weeks to achieve diastolic BP <90 mm Hg	3-week placebo run-in period + 6 weeks treatment arm	Nisoldipine-ER = amlodipine Well tolerated	Pepine et al.[47]
7.	Amlodipine in patients with stable angina pectoris treated with nitrates and beta-blockers. The influence on exercise tolerance, systolic and diastolic functions of the left ventricle 1992	21	Stable angina pectoris and multivessel CAD	Placebo, amlodipine 5 mg and 10 mg	2 weeks	Amlodipine significantly improved the exercise tolerance and the function of the left ventricle in a dose-dependent way and was well tolerated	Meluzín et al.[48]
8.	Amlodipine in postinfarction angina 1992		Patients with postmyocardial infarction angina	Once-daily administration of amlodipine		↓The number of angina attacks and nitroglycerin consumption and improved ability to perform physical exercise	Taylor[49]
9.	Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial 2004	823	Symptomatic chronic angina	Twice-daily placebo or 750 mg or 1000 mg of ranolazine	12 weeks	Twice-daily doses of ranolazine increased exercise capacity and provided additional antianginal relief	Chaitman et al.[50]
10.	An 8-week double-blind study of amlodipine and diltiazem in patients with stable exertional angina pectoris	80	Stable exertional angina pectoris	Amlodipine (2.5–10 mg once daily) Diltiazem (60–120 mg three times daily)	2-week placebo run-in period, 8-week double-blind treatment phase	Amlodipine = diltiazem (antianginal efficacy and tolerability)	Bernink et al.[51]
11.	Effect of amlodipine and lacidipine on left ventricular diastolic and long axis functions in arterial hypertension and stable angina pectoris	59	Hypertensive patients with associated CAD (stable angina pectoris) and isolated diastolic dysfunction	Amlodipine and lacidipine	4 weeks	Amlodipine improves diastolic and long-axis functions of the left ventricle	Zaliunas et al.[52]
12.	Patient compliance and therapeutic coverage: amlodipine versus nifedipine SR in the treatment of hypertension and angina: interim results. Steering Committee and Cardiologists and General Practitioners involved in the Belgium Multicentre Study on Patient Compliance	234	Hypertension outpatients with or without angina	Amlodipine (5 mg daily) and 20 mg twice-daily nifedipine	Interim analysis	Amlodipine > nifedipine	Detry[53]

Role of Fourth Generation Calcium Channel Blockers in Cardiovascular Disease

The fourth-generation CCBs, e.g., cilnidipine (5–20 mg once a day), effectively manage 24-hour BP without adversely affecting pulse rate. In addition, the ACHIEVE-ONE trial (n = 2,319; 12-week study) has shown its effectiveness in decreasing morning BP levels.[53] Cilnidipine has improved left ventricular function, blood pressure, and renoprotective effects in the CANDLE and CARTER trials.[35] Antianginal effects have been observed in preclinical studies; however, these effects need to be confirmed in clinical settings.

Conclusion

Cardiovascular diseases pose a threat to impending epidemics across the nation. To rein in this meteoric rise, close collaboration

between patients, physicians, and healthcare providers is the need of the hour. Collective efforts for patient education, preventive measures, early identification, and timely diagnosis and treatment are vital to helping reverse this scenario. Individualization of treatment based on comorbidities and characteristics of antianginal drugs helps to optimize management and outcomes. The advantage of once-daily dosing and excellent control of angina make amlodipine a good choice for therapy.

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POINT OF VIEW

Research Methodology and Biostatistics in the Postgraduate Curriculum: The AIIMS-Bhubaneswar Experience

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Abstract

Inclusion of research methodology and biostatistics in the postgraduate curriculum by the National Medical Commission is a welcome step to improve the research milieu in medical colleges in India. This step will have a long-term impact on research outcomes and scientific publications. In 2019, AIIMS-Bhubaneswar implemented the revised postgraduate curriculum, which introduced a faculty-facilitated program on research methodology and biostatistics for all postgraduate students. The institute also made the examination in research methodology mandatory, which can be viewed as a complementary mechanism. As the revised curriculum has been in practice for the last 4 years and six sessions of examinations have been completed, the authors tried to look back to check whether the program is having the expected results and share the experience they gained.

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Introduction

Modern medicine continually updates treatments based on new research and evidence, evolving through basic and applied science.[1] Even though the vast population of India with ample clinical material is available for doctors to do research, the research output from India in medicine is meager.[2,3] A scientometric analysis done on the publication output from Indian medical institutions showed that around 60% of Indian institutions lack any form of scientific publication for a decade.[4] The inadequate resources, infrastructure, incentives, and difficulty in securing funding are major demotivators for Indian physicians and well-known reasons for the poor research outflow from India.[5] Postgraduate medical education is a crucial phase that lays the scientific, rational, and ethical foundation for the practice of medicine in the future. Hence, an opportunity to do research during this phase is likely to make the physician more rational, logical, and responsible, besides inculcating an interest in research. Such exposure will enable postgraduates to realize their potential and interest in taking up a career in research in the future.[6,7]

Though research is an integral component in postgraduate training, in most cases, research is undertaken due to administrative reasons rather than the advancement of medical knowledge. To tackle these problems and improve the contribution of Indian medical researchers, the National Medical Commission (NMC) has introduced measures such as integrating research methodology training into the academics of postgraduates and publishing/presenting a research paper as essential criteria for appearing in the final examinations. They have also made the online basic course in biomedical research (BCBR) for postgraduates and faculty, which is conducted by the Indian Council of Medical Research–National Institute of Epidemiology (ICMR–NIE), mandatory and encourage researchers to attend manuscript writing and biostatistics workshops, preferably annually.[8–10] The ICMR also provides financial support for postgraduate theses to promote good quality research and to improve the visibility and accessibility of their research work to a larger research audience. Apart from this, some institutions conduct faculty-facilitated programs on research methodology and biostatistics to augment and familiarize postgraduates with the principles of biomedical research, statistics, and scientific writing.

After the implementation of the NMC guidelines on research methodology in the postgraduate curriculum, few studies have been published on the perspectives of postgraduate students regarding postgraduate research activities and the need for such training. Mohan et al. reported that only 54.1% of students were satisfied with the guidance from the faculty for their thesis work, 66.9% of students affirmed that they were taught basic research methodology and biostatistics, and 68.6% of students were encouraged to participate in conferences, workshops, and training programs.[11] In another study by Paul et al., the workshop on scientific writing had a positive impact on boosting the competency of scientific writing skills of first-year postgraduate students.[12] However, faculty involvement in postgraduate research is less than desired, and consequently, most postgraduates do not take thesis work seriously. This is partly due to a lack of knowledge and interest for both mentors and mentees in research methodology and biostatistics.[6] Even though the step by NMC will improve the quality of the postgraduate thesis, training of the trainers is equally important to deliver adequate and appropriate guidance to postgraduates.

Experience of AIIMS-Bhubaneswar

Change in the Curriculum

At AIIMS-Bhubaneswar, postgraduate courses started in July 2016. For the initial 3 years, the curriculum of the mentoring institute, i.e., AIIMS-New Delhi, was followed; however, the faculty believed that it was time to relook at the curriculum to cover the gaps in the present postgraduate medical training. After a series of brainstorming sessions with faculty, the Medical Education Unit of AIIMS-Bhubaneswar came up with the revised curriculum, which was approved by the Boards of Studies and the academic committee and finally ratified by the governing body and the institute body. One of the most important highlights of the revised curriculum was the inclusion of training in research methodology and biostatistics and the compulsory written examination at the end of the second semester. Passing the examination was considered one of the eligibility criteria to appear for the final exit examination. The examination was made mandatory and linked to the final examination so that students would take it seriously.

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Implementation

The revised curriculum was implemented from January 2019 session for MD, MS, MDS, DM, and MCh courses. The Dean's office conducts a 25-hour basic course in research methodology and biostatistics twice a year for newly joined postgraduate students in the months of March and September. The resource persons are faculty members from different specialties of the institute. The written examination on research methodology and biostatistics is conducted in the first week of January and July every year. The students should appear for the examination at the end of their second semester, and if anyone fails the examination, they can reappear in the examination scheduled for the next session.

Facilitatory Research Environment

It is well understood that only conducting a course on research methodology and implementing a mandatory examination cannot improve the research milieu alone, and it should be facilitated through other means parallelly. The central library at AIIMS-Bhubaneswar provides access to a good number of online and subscribed journals, web resources for books, atlases, and also subscribed Clinical Key, Access Medicine, UpToDate, BMJ Best Practice, Grammarly, and iThenticate. The institute also provided access for faculty and postgraduates to online courses on literature search and reference management from the QMed Knowledge Foundation. The institutional ethics committee of AIIMS-Bhubaneswar efficiently conducts monthly meetings and provides a user-friendly online platform for the submission, revision, and final approval of research projects. As an incentivized approach, the faculty members also get an intramural grant of up to five lakh rupees toward the expenses of consumables and contingencies for research work. The Research Cell, which was established for the purpose of promoting research, observes an annual research day and conducts monthly research meets where all faculty and residents are encouraged to present their research work. The institute also organizes regular panel discussions and webinars involving eminent scholars from different domains.

Evaluation

After the course completion, qualitative feedback is taken through hard copy or Google Forms where every student has to rate every session on a scale of 1–5, where 1 = poor, 2 = average, 3 = good, 4 = very good, and 5 = excellent. Additionally, open suggestions are also sought for future improvements. The question paper for written examination in research methodology and biostatistics consists of 20 questions of five marks each and is conducted over 3 hours. Most of the questions are scenario-based to assess higher cognitive domains and evaluated with an objective marking scheme.

Feedback on the Course

For individual sessions, seven sessions were rated very good to excellent by 67–74% of students, whereas other three sessions were rated very good to excellent by 75–80% of students. For the overall quality and usefulness of the course, 25.6% of students rated it as excellent, and 45.1% rated it as very good. The common open suggestions were requests to provide study material, including the PowerPoint slides, requests to repeat biostatistics during thesis completion time to help in analysis, and requests for spacing between the sessions.

Performance of the Students

The first examination was conducted in January 2020, and till the end of 2022, a total of six examinations have been conducted. To evaluate the progress of the program, the performance of the students has been analyzed. It has been noticed that the mean score of the students has improved from 56 ± 11.6 in January 2020 to 64 ± 10.5 in July 2022 session (Table 1). Similarly, the percentage of passing also increased from 81% in January 2020 session to 93% in July 2022 session. In a comparative analysis, it was found that the score of MD/MS/MDS students in every examination was more than DM/MCh students, though the difference was not statistically significant (Table 2).

Table 1: Change in mean score in six examinations on research methodology and biostatistics (maximum score 100)

Examination session	*N*	*Score (mean ± SD)*
January 2020	69	56.02 ± 11.62
July 2020	52	58.23 ± 10.52
January 2021	64	55.01 ± 9.36
July 2021	50	55.04 ± 7.69
January 2022	79	61.97 ± 8.99
July 2022	44	64.02 ± 10.45

N: number of students appeared for the examination

What We Learnt?

Conducting an examination in research methodology and making it obligatory for postgraduate students to pass it has an upstream ripple effect. Faculty are motivated to refresh themselves and start asking better research questions. The confidence in their ability to write and defend proposals led to an increased number of proposals being submitted for extramural and intramural funding, increased funds received as extramural research grants, and the establishment of centers for research in specific areas of study. In 2017, only one postgraduate student from AIIMS-Bhubaneswar received the ICMR thesis grant of Rs. 50,000, whereas eleven students in December 2021 session and eight students in June 2022 session received the grant from the ICMR. Even though all these positive outcomes cannot be entirely attributed to the examination alone, this statistic exemplifies the enthusiasm, improved protocol writing skills, and better topics that were being done as the postgraduate thesis in various departments.

Implementing the examination may not be possible in medical colleges that are under the ambit of the NMC, as the strict regulations and pedagogy followed make it difficult to change unless mandated by the NMC. However, considering the impact we have seen at AIIMS-Bhubaneswar, we believe it should be strongly considered by the NMC for adoption. This would certainly not be without its teething troubles, and the probable logistical issues can be worked out with some innovative thinking.

We hope that the experience we have gained in the past 4 years will encourage many institutions to follow similar training and assessment methods, and the NMC will also consider instituting such changes in the postgraduate curriculum so that the research output and quality will improve in the medical colleges of our country.

Table 2: Comparative scores in research methodology and biostatistics (maximum score 100)

Examination session	*DM/MCh students*	*MD/MS/MDS students*	*p-value**
January 2020	54 (45–59)	57 (52.75–67)	0.21
July 2020	53 (37.25–59.25)	60 (52–65.75)	0.25
January 2021	54 (50–62.5)	56 (50–62)	0.86
July 2021	54.5 (41.75–62)	56 (53.5–58.5)	0.54
January 2022	63 (57–68)	64 (57–68)	0.85
July 2022	61 (57–65)	64 (60–71)	0.25

Data in median [interquartile range (IQR)]; *Mann–Whitney *U* test

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Announcement

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CASE REPORT

Hypersensitivity Pneumonitis: The Diagnosis Lies in History

Jyoti Chauhan[1], Tanvi Batra[2*], Atul Kakar[3], Rahul Kumar[4], Naveen Goud Bollapally[5], Anjana Jangid[6]

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Abstract

Hypersensitivity pneumonitis (HP)/extrinsic allergic alveolitis (EAA) is defined as a response of lungs to inhaled organic and inorganic substances. This disease is relatively rare, comprising 2% of cases in the category of interstitial lung diseases. Here, we discuss a case of 61-year-old female, who presented with sudden onset breathlessness, with bilateral coarse crackles on physical examination, initially thought to be due to heart failure or atypical pneumonia, but later diagnosed as HP. She was managed initially with antibiotics but due to poor response, steroids were introduced which led to significant improvement. This report emphasizes the importance of exposure history of substances that are toxic, lack of specificity of clinical manifestations, importance of invasive methods for diagnosis, and poor response to therapy in case of delayed diagnosis.

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Introduction

Hypersensitivity pneumonitis (HP) is an inflammatory lung disease, caused by inhalation of antigens repeatedly, such as microbes, animal proteins, and chemicals.[1] This disease can have a highly variable presentation, depending on exposure. With its prevalence, being low, mild, or subclinical HP can be misdiagnosed as asthma, as both may have nonspecific clinical findings.[2] Definite diagnosis of this disease is difficult due to lack of gold standard diagnostic tests. Presence of clinical features, significant exposure history to allergens, detection of precipitating antibodies, ruling out other possible interstitial lung diseases, bronchoalveolar lavage (BAL), radiology, and pathology are the trademarks for diagnosing HP.[3]

Case Description

Sixty-one-year-old female, known hypertensive, presented with complaints of breathlessness which was progressive in nature, from New York Heart Association (NYHA) grade I to IV over a period of 1 month. This was followed by an episode of desaturation with SpO_2 of 70% on room air after which she was brought to hospital. On examination, she was afebrile, normotensive, tachycardic (HR—100/minute), and tachypenic (RR—30/minute). On auscultation, she had coarsely crept into bilateral infrascapular region with no other systemic findings.

Laboratory investigations revealed leukocytosis [total leukocyte count (TLC) 26.77 thous/µL] and raised liver enzymes [serum glutamate oxaloacetate transaminase (SGOT) 99.5 IU/L, serum glutamate pyruvate transaminase (SGPT) 225.7 IU/L]. Rest of the routine investigations were normal. C-reactive protein was 110.3 mg/L and procalcitonin was 0.42 ng/mL. Blood cultures were sterile. Respiratory BioFire was also negative. Viral markers [human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B] were negative. Serum immunoglobulin E (IgE) level was 88.5 IU/L. Electrocardiogram (ECG) was normal. Chest X-ray revealed signs of fluid overload (Fig. 1).

The patient received intravenous (IV) antibiotics, diuretics, deep vein thrombosis (DVT) prophylaxis, oxygen supplementation, and intermittent noninvasive ventilation (NIV) support. Two-dimensional (2D) echo showed grade II left ventricular diastolic dysfunction, mild pulmonary artery hypertension (PAH) [pulmonary artery systolic pressure (PASP) = 37 mm Hg] with rest normal study. N-terminal pro-B-type natriuretic peptide (NT-pro BNP) was done which was 900 pg/mL. D-dimer was 0.36 (normal).

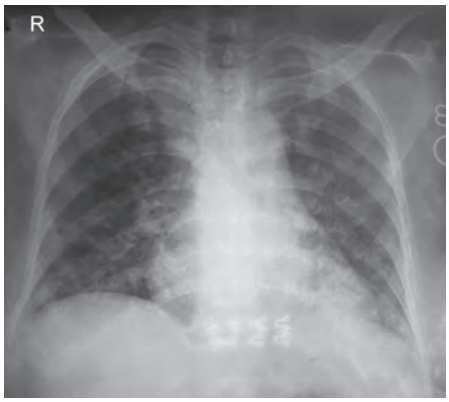

Fig. 1: Increased bronchovascular markings in both lung fields

In view of persistent breathlessness, high-resolution computed tomography (HRCT) chest showed large areas of mosaic attenuation in bilateral lungs with interstitial septal thickening, atelectatic bands in bilateral lower lobes with multiple subcentimetric lymph nodes, and suggestive of infective etiology (Fig. 2).

An ultrasound of the whole abdomen was suggestive of hepatomegaly with diffuse hepatic steatosis. The patient gave a history of recurrent nasal congestion following which noncontrast computed tomography (NCCT) paranasal sinuses was done and it showed minimal small polypoidal thickening in right sphenoid sinus. Direct nasal endoscopy was done which showed raw areas on both sides of nasal septum.

On reviewing her history, the patient mentioned recent exposure to pigeon droppings. She was treated with doxycycline and Chlamydia IgM which was negative. However, her symptoms did not improve and on revisiting history, it was found that she had started painting pots for 1 month which

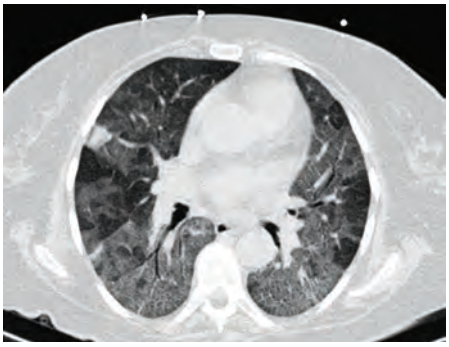

Fig. 2: Large areas of mosaic attenuation in bilateral lungs with interstitial septal thickening with atelectasis in bilateral lower lobes and multiple subcentimetric lymph nodes

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was the exact duration when her symptoms had begun.

The patient was managed with intermittent oxygen and steroids in view of suspected HP. Autoimmune markers were also sent which were found to be negative.

She gradually improved and was discharged on tapering doses of oral steroids with no oxygen support and strict instructions to avoid the allergen. She is on regular follow-up and is currently doing well.

Discussion

Hypersensitivity pneumonitis is a granulomatous interstitial lung disease, due to inhalation of specific antigens repeatedly *via* occupational or environmental exposure in individuals who are sensitized to the same.[4]

It occurs because of an immune response that is exaggerated, leading to symptoms resembling acute/progressive lung damage, that can be irreversible.[5]

Clinical features and severity of these symptoms depend on frequency as well as intensity of exposure. The interval between antigen exposure and clinical manifestations remains unknown, although symptoms may begin 4–12 hours after exposure. In more chronic and low-level exposures, however, the onset is insidious, which was more likely the case in our patient. Cough, fever, weight loss, fatigue, and dyspnea are common symptoms. Patients can have crackles, inspiratory squeaks, and digital clubbing associated with cases where the disease is advanced.

Hypersensitivity pneumonitis can be divided into fibrotic (FHP) and nonfibrotic (NFHP) forms as per the new ATS/JRS/ALAT clinical practice guidelines.[6] Obtaining a thorough history of antigen exposure is difficult, imaging remains an important assessment tool for the same. HRCT shows a pattern of diffuse infiltrative parenchymal abnormalities in NFHP, usually bilateral, symmetrical, and diffuse. FHP, on the contrary, shows changes in concomitant fibrosis and bronchiolar obstruction in HRCT, commonly involving mid/lower lung zones, with even distribution and basilar sparing in some cases. Bronchial obstruction can be seen in the form of ill-defined centrilobular nodules, ground-glass opacities (GGOs), mosaic attenuation, air trapping, and/or three-density pattern (highly specific for FHP).

As per the new guidelines, three domains, that is, exposure identification (history, antigen-specific serum IgG ± inhalational challenge), radiologic findings, and lymphocytosis in BAL are the keys to diagnosing HP. Lymphocytes >30% is considered reasonable as per ATS guidelines.[7]

Treatment mainly comprises identification and complete antigen avoidance as the mainstay, especially in nonfibrotic HP antigens. Empirical treatment comprises prednisone of 0.5 mg/kg/day for 1–2 weeks and is gradually tapered to achieve a maintenance dose of 10 mg/day.[3] Corticosteroids alone or in association with azathioprine/mycophenolate mofetil are the line of management in such cases, with fewer adverse effects where combination therapy is used.

As per the emerging evidence, rituximab is shown to stabilize or improve lung function in few patients having fibrotic HP, especially in cases without usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP) pattern.[8] Leflunomide has also shown beneficial effects as a steroid-sparing immunomodulatory drug with significant pulmonary function improvement.[9]

Conclusion

In order to identify HP, a thorough history of environmental exposure to antigens and the time of onset of symptoms is of utmost importance. These details, combined with HRCT and BAL findings as well as histopathological findings, helps in clinching the diagnosis.

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CASE REPORT

An Unusual Case of Pancytopenia

Sweety Singh[1*], Rishabh Jha[2], Nimisha Bajaj[3], Alok Ranjan[4], Arshad Ahmad[5]

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Abstract

Multiple myeloma is a rare hematological disorder that causes overproduction of plasma cells within the bone marrow, leading to suppressed hematopoiesis, renal insufficiency, bony lesions, and recurrent infections. Patients with multiple myeloma commonly present with anemia. Although rare, neutropenia and thrombocytopenia can also develop in these patients, leading to pancytopenia, as seen in our case. Therefore, multiple myeloma should be kept as one of the differentials in elderly patients who present with pancytopenia for early screening and diagnosis of the disease.

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Introduction

Multiple myeloma is a neoplastic disease of plasma cells accounting for 10–15% of all hematologic cancers.[1] It is characterized by abnormal multiplication of plasma cells resulting in the production of a monoclonal immunoglobulin. The clinical presentation varies from symptomless to severe disease owing to the accumulation of anomalous immunoglobulin chains in various tissues.[2] For diagnosis of multiple myeloma, evidence of damage to one or more end organs, such as anemia, hypercalcemia, renal insufficiency, or bony lesions, in conjunction with clonal plasmacytosis in bone marrow must be present. It commonly presents with anemia, but pancytopenia as an initial presentation is quite rare.[3] Here, we report a case of an elderly male patient who presented with pancytopenia and upper gastrointestinal (GI) bleeding and was subsequently diagnosed with multiple myeloma.

Case Description

A 60-year-old male visited our hospital with complaints of fatigue for 15 days and passage of black tarry stool for 10 days. He did not give any history of fever and had no previous comorbidities. On examination, he had pallor with bilateral pitting pedal edema. His systemic examination was unremarkable.

His laboratory investigations showed hemoglobin of 5.2 gm/dL, total leukocyte count of 3520/cmm, with differential count showing 50% neutrophils, 45.2% lymphocytes, 3.7% monocytes, and platelet count of 25000/cmm. Peripheral blood smear examination revealed normocytic normochromic red blood cells (RBCs) with moderate anisopoikilocytosis and mildly reduced platelets. However, rouleaux formation was not seen on smear. Erythrocyte sedimentation rate (ESR) was 99 mm/hour. His biochemistry showed total serum protein of 5.5 gm/dL and albumin levels of 2.8 gm/dL with normal bilirubin and liver enzymes. Kidney function tests were deranged with elevated blood urea (72 mg/dL), serum creatinine (1.5 mg/dL), and uric acid (9.8 mg/dL). His serum calcium, lipid profile, coagulation profile, and routine urine were normal. Serum folate, vitamin B12, and iron profile were also normal.

The patient was admitted to the general medicine ward and managed with pantoprazole infusion, packed RBCs, and platelet transfusions. Upper GI endoscopy of the patient was carried out, which revealed mild erosive gastritis; however, gastric biopsy was not done. A bone marrow examination was performed for evaluation of pancytopenia. Bone marrow aspiration smears were hemodiluted showing reactive changes and plasma cells constituting 12% of nucleated cells as shown in Figure 1, which was an incidental finding. Bone marrow biopsy disclosed trilineage hematopoiesis with plasmacytosis (14%). Skeletal survey done for myeloma showed no bony lesions. Serum protein electrophoresis revealed the existence of a protein band in the gamma globulin region suggestive of "M" spike with immunofixation electrophoresis identifying as immunoglobulin G (IgG) and kappa as shown in Figure 2. Free light chain (FLC) assay was also done, which showed monoclonality of plasma cells with markedly raised kappa light chain. Serum lambda chain measured 19.81 mg/L whereas kappa chain was significantly elevated measuring 59.80 mg/L. A fluorescence in situ hybridization (FISH) panel for multiple myeloma was planned but could not be done due to financial limitations of the patient. A final diagnosis of multiple myeloma was made in view of bone marrow findings, anemia, and renal dysfunction, and the patient was transferred to the medical oncology department for initiation of chemotherapy.

Discussion

Multiple myeloma is a rare hematological disorder accounting for about 1% of all neoplasms and 10–15% of hematological cancers.[1] It is marked by increased production of malignant plasma cells within the bone marrow causing suppression of hematopoiesis, renal insufficiency, bony lesions, and recurrent infections.[2] Multiple myeloma predominantly affects the elderly population, with its incidence increasing with age. The usual age for diagnosis is 70 years with a slight male preponderance.[4] The initial symptoms are usually nonspecific such as weakness, fatigue, recurrent infections, and bony pain.[3] Although myeloma patients are commonly present with anemia, rarely

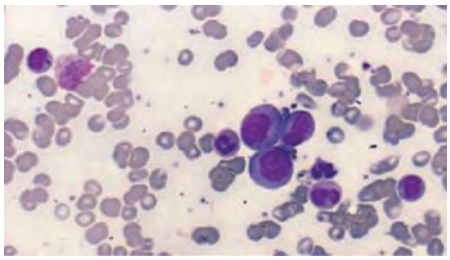

Fig. 1: Plasmablasts scattered in bone marrow aspirate with eccentric nucleus

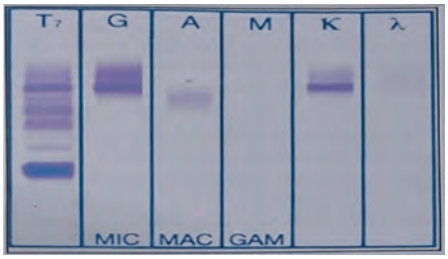

Fig. 2: Immunofixation electrophoresis identifies the "M" spike as IgG and kappa

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neutropenia and thrombocytopenia may also develop leading to pancytopenia as seen in our patient.

Development of pancytopenia in patients with multiple myeloma can occur due to various factors. Most commonly, it happens because of the proliferation of plasma cells, which replaces regular hematopoietic cells. It also causes cytokine-mediated suppression of bone marrow as well as erythropoietin deficiency secondary to renal failure.[5] Myeloma patients also have a propensity to bleed during the course of their disease, which varies from petechial rash to exsanguination.[2] However, its pathogenesis still remains obscure with the proposed causative factors suggested as the existence of unusual plasma proteins, which impair coagulation and cause defective clot retraction.[6]

Conclusion

Presentation of multiple myeloma with pancytopenia is quite uncommon and may be misleading, potentially causing delayed diagnosis and management. Therefore, a differential of multiple myeloma should be kept in mind in older patients presenting with pancytopenia, mild renal insufficiency, and raised ESR and should be subjected to serum protein electrophoresis as well as FLC assay for early detection of multiple myeloma.

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CASE REPORT

Chronicles from the Nest: A Case of Psittacosis in India

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Abstract

Psittacosis is a rare zoonotic disease caused by a gram-negative obligate intracellular bacterium *Chlamydia psittaci*, which is transmitted through contact with infected birds. It comprises approximately 1% of all community-acquired pneumonia cases. However, this can be just the tip of the iceberg pertaining to the lack of routine testing and awareness of this disease entity, thereby requiring a high index of suspicion for its diagnosis.

We report a case of a 37-year-old male presenting with high-grade fever with chills, acute onset of dyspnea, dry cough, arthralgia, and myalgia which was not responding to broad-spectrum empirical antibiotics and supportive care. We started evaluating the patient as a case of pyrexia of unknown origin (PUO), but the fever workup turned out to be inconclusive. This prompted us to revisit the history. It was found that the patient owned a parrot that was sick for the last 15 days. The temporal correlation of the illness with a history of exposure made us suspect psittacosis, which was confirmed by treatment with doxycycline resulting in a drastic improvement in the patient's condition. By this, we want to highlight that history remains the time-tested guide for diagnosing and treating PUO.

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Introduction

Psittacosis is a zoonotic infection caused by *Chlamydia psittaci*. It is estimated to cause 1% of cases of community-acquired pneumonia.[1] It is usually transmitted to humans through inhalation of contaminated droplets from bird excreta or respiratory secretions. The clinical presentation of the disease can vary from asymptomatic to severe respiratory illness requiring hospitalization.

We present a case of a 37-year-old male who presented with a history of fever, cough, and shortness of breath for 10 days which was not responding to empirical antibiotics. Despite extensive workup for pyrexia of unknown origin (PUO), the diagnosis eluded the medical team until a revisit to the patient's history revealed exposure to parrots. Based on this information, the patient was suspected to have psittacosis and doxycycline was started. Confirmatory diagnosis of psittacosis requires polymerase chain reaction (PCR)-based or serological confirmation testing.

Despite being a condition, that is easily treatable with appropriate antibiotics, physicians are likely to miss this condition pertaining to the lack of routine testing and awareness of this disease entity. In such disease conditions where diagnostic facilities are difficult to procure, a good history taking is a clinician's most powerful clue to diagnosis.

Case Description

We present a case of a 37-year-old male who presented with a sudden onset of continuous high-grade fever, accompanied by headache, generalized weakness, arthralgia, and myalgia that had persisted for 10 days. The patient subsequently developed a dry cough and breathlessness, which gradually worsened over time. No diurnal or positional variation was noted, and the patient denied experiencing orthopnea, expectoration, chest pain, or rash. Upon examination, the patient was conscious, tachypneic, and hemodynamically stable, with no abnormalities noted during systemic examination except for occasional wheeze in bilateral chest fields. His initial evaluation showed a hemoglobin level of 14.2 gm/dL, a total leukocyte count of 10.4 thous/µL, and a platelet count of 210 thous/µL. His liver function test showed mild transaminitis with aspartate aminotransferase (AST) 54 IU/L and alanine aminotransferase (ALT) 134 IU/L. His initial erythrocyte sedimentation rate (ESR) was 13 mm in 1 hour and C-reactive protein (CRP) was 6 mg/dL. Based on the history and examination findings, acute bronchitis was suspected, and the patient was started on broad-spectrum empirical antibiotics; cefoperazone + sulbactum.

Further investigation, including respiratory BioFire for bacterial, viral, atypical infections, urine routine, culture, and blood culture were negative. Workups for infections including typhoid, dengue, malaria, tuberculosis, and rickettsia infections were all negative. Chest X-ray was normal, while contrast-enhanced computed tomography (CECT) thorax revealed mild atelectasis changes in the right middle, left lingular, and bilateral lower lobes (Fig. 1). CECT of the abdomen and two-dimensional (2D) echocardiography were grossly normal. Despite 3–5 days of ongoing empirical antibiotics, the fever persisted. The patient's transaminitis was gradually worsening with rising levels of inflammatory markers like CRP and ESR, prompting a reassessment of the patient's history. Upon further inquiry, it was revealed that the patient had been caring for a sick parrot for the past 15 days, raising suspicion of psittacosis. Chlamydia and Chlamydophila serology was sent which showed positive antibody titers of 1:64 for *chlamydia pneumoniae* antibody. The patient was started on intravenous doxycycline 100 mg twice a day for 10 days. The patient improved significantly and became afebrile on day 2 of starting the treatment and finished a total of 10 days of course. On follow-up, the patient is healthy and doing fine with no history of fever after 2 weeks.

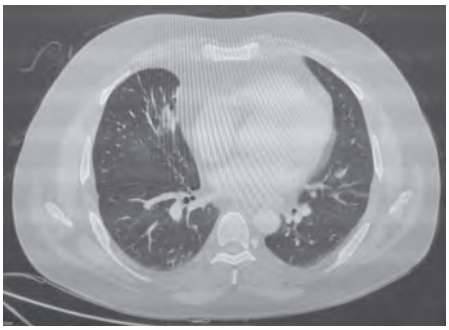

Fig. 1: Contrast-enhanced computed tomography thorax—atelectasis changes in the right middle, left lingular, and bilateral lower lobes

Discussion

Psittacosis, also referred to as parrot fever, is a rare but potentially life-threatening disease caused by the bacterium *C. psittaci*. The disease is primarily contracted by inhaling contaminated dust or bird droppings, typically from infected parrots, pigeons, and other birds.

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Psittacosis is relatively rare in India. To the best of our knowledge, this is the first reported case of psittacosis in India. The global incidence of psittacosis is challenging to estimate, as many cases remain undiagnosed or misdiagnosed, and the disease is not a notifiable disease in many countries.

In this case report, we discuss a patient who presented with influenza-like illness and was extensively evaluated before ultimately being diagnosed with psittacosis based on a careful review of exposure history.

Laboratory findings usually show raised inflammatory markers like ESR and CRP and mild elevation of liver enzymes as in our case.[2] Other lab abnormalities include hyponatremia, mildly raised serum creatinine, and blood urea nitrogen levels.[3] However, in our case there were no other significant laboratory abnormalities. Computed tomography (CT) may reveal nodular pulmonary infiltrates with surrounding ground glass opacities.

Furthermore, diagnostic testing for psittacosis can be challenging. Microimmunofluorescence (MIF) is considered the gold standard for chlamydial serology.[4] In our case, chlamydial serology by MIF showed 1:16 and 1:64 titers for *C. pneumoniae* antibodies immunoglobulin A (IgA) and IgG respectively. However, *C. psittaci* antibodies IgG, IgA, and IgM titers were <1:64, <1:16, and <1:10 respectively. Accurate serological diagnosis of chlamydial infections in the clinical laboratory is challenged by the cross-reactivity of antibodies among the clinically relevant species, *C. pneumoniae*, *C. psittaci*, and *C. trachomatis*, nonspecific antibody stimulation, or past exposure to more than one of these organisms. IgM titers of 1:10 or greater are indicative of recent infection, but IgM is highly cross-reactive, often demonstrating titers to multiple organisms. Any IgG titer indicates past exposure to that particular organism. Additionally, these serological tests necessitate testing of paired sera collected weeks apart, delaying or preventing confirmation of clinical diagnosis. While reverse transcription polymerase chain reaction (RT-PCR) assays are more sensitive and specific, they are not widely accessible and are only available at the Centers for Disease Control and Prevention (CDC) in the United States.[5] In such cases, the diagnosis of psittacosis relies on the exposure history and high clinical suspicion.

Although, the disease usually improves with adequate treatment, endocarditis, hepatitis, pneumonia, and inflammation of the nerves or brain, leading to neurological problems are some of the known complications of this disease.[6] With adequate treatment with antibiotics, psittacosis is rarely known to cause death (<1 in 100 cases).[6] Our patient recovered completely after 10 days of treatment with doxycycline.

It is essential to consider the possibility of psittacosis in patients with a history of bird exposure. A proper history-taking is an essential component of diagnosing PUO. A thorough evaluation of occupational, environmental, and travel history is necessary to exclude exposure to unusual pathogens. In the case of this patient, the initial evaluation did not reveal any obvious cause of his fever. However, revisiting the patient's history, specifically their exposure to parrots, was key to the final diagnosis.

Conclusion

Psittacosis should be considered as a potential differential diagnosis in a patient presenting with fever, with further detailing of any contact with birds, be it occupationally or for personal interest. This disease is often underdiagnosed, and a high index of suspicion is necessary to prompt appropriate testing and treatment. This case report highlights that history remains the time-tested guide for diagnosing and treating PUO. In addition, it highlights the challenge of serological testing for chlamydial infections, emphasizing the need for more sensitive and specific assays and their easy accessibility. As such, continued surveillance and reporting of cases are necessary to understand better the true burden of this disease and develop prevention and control measures.

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Green Urine

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A 42-year-old chronic alcoholic, nondrug addict male patient with a normal sexual and marital history was brought by relatives to the emergency department of Government Medical College, Kota. He had gradually increasing yellow discoloration of eyes and body for 7 days, progressively worsening altered sensorium for 4 days, up to the extent of not being able to recognize family members for the last 2 days. There was no history of any drug intake. On examination, vitals were in the normal range with blood pressure (BP) 130/80 mm Hg, pulse rate (PR) 80/min, peripheral oxygen saturation (SpO_2) 98% at room air, no pallor, and deep icterus was present. The patient was irritable, disoriented, semiconscious, and not responding to commands. Bilateral plantar reflex was extensor. P/A examination showed generalized distension and nontender 4 cm firm hepatomegaly.

The routine lab investigations revealed hemoglobin (Hb): 11.1 gm, platelet count: 13,000/mL, total leukocyte count (TLC): 26,000/mL (N: 87.3%, L: 8.1%, M: 4.3%, E: 0.3%), blood urea: 226 mg/dL, serum creatinine: 5.9 mg/dL, serum sodium: 136, total serum bilirubin: 21.0 mg/dL, direct serum bilirubin: 13.2 mg/dL, serum glutamic oxaloacetic transaminase (SGOT): 114 IU, serum glutamic pyruvic transaminase (SGPT): 41 IU, serum alkaline phosphatase (SALP): 40 IU, prothrombin time/international normalized ratio (INR): 17.6/INR 1.6, and positive hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV).

The treatment was initiated with the diagnosis of chronic liver disease (alcohol, HBsAg, and HCV associated), acute hepatic encephalopathy, and hepatorenal syndrome. Urinary bladder catheterization revealed that the drained urine in the tube as well as Urobag (refer to Figs 1 and 2) was green in color (amount 1200 mL). Ryle's tube aspiration was also green in color. Distension of abdomen, sensorium, and irritability showed gradual recovery over the next 4–5 days, but serum bilirubin remained elevated and urine drained was consistently dark green in color. The patient finally succumbed to the illness after 8 days.

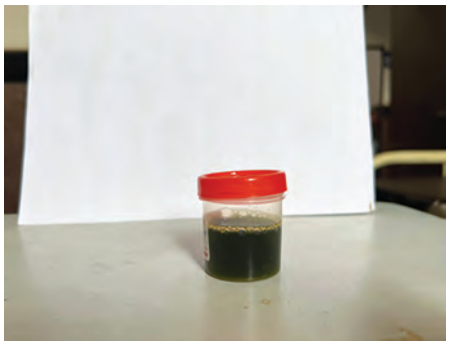

Fig. 1: Green urine in container

Fig. 2: Green urine in Urobag

Any deviation in normal urine color is an alarming sign to the clinician. Phenol group containing drugs such as promethazine, thymol, cimetidine, and propofol, after conjugation in the liver, get subsequently excreted by the kidneys as green urine. Nonphenol medications that can produce green urine are metoclopramide, amitriptyline, and indomethacin. Water-soluble artificial dyes can also cause green urine.[1] Biliverdin, the oxidation product of bilirubin in urine, can give a green hue. Biliverdin, a green tetrapyrrolic bile pigment, is converted to yellow bilirubin by biliverdin reductase in the reticuloendothelial system (liver, spleen, lymph node). In this case, excess biliverdin not adequately reduced to bilirubin by the failing liver led to an increased amount of biliverdin excreted in urine, giving rise to green urine.

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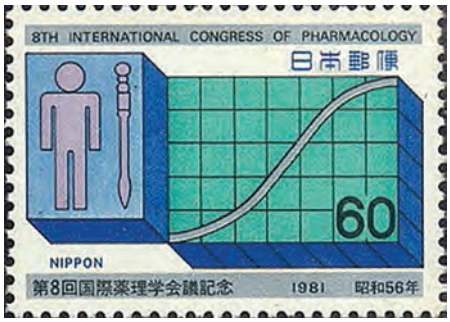
Corneille Heymans and Carotid Body

Jayant Pai-Dhungat

Corneille Heymans—Nobel Prize 1938 for Physiology or Medicine Stamp, Belgium, 1987

Corneille Heymans (1892–1968) was born in 1892 in Ghent, Belgium. Heymans received his doctor's degree in 1920 from the University of Ghent. He studied physiology in Paris, Lausanne, Vienna, and London under EH Starling and in the United States after graduation. He took up a lectureship in pharmacodynamics at the University of Ghent (1922) and was promoted to professor of pharmacology (1930).

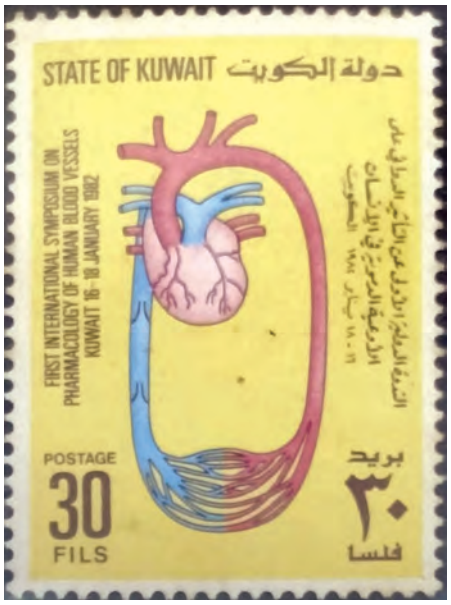
His research, which began in 1924, sought to determine the way in which changes in blood composition and pressure cause alterations in heart and respiratory function. Experimenting with dogs, Heymans and coworkers demonstrated the existence of sensory organs, known as pressoreceptors, in the wall of the carotid sinus, at the bifurcation of the common carotid artery as a slight enlargement of the artery. He showed that these receptors monitor blood pressure and help to regulate heart rate and respiration. Close to the carotid sinus (a dilatation of the internal carotid near its beginning)



8th International Congress of Pharmacology Stamp, Japan, 1981

exists a small gland-like structure called the carotid body, or glomus caroticum, rich in nerve supply. These are chemoreceptors responding to composition of the blood gases. Heymans and coworkers also found pressoreceptors near the base of the aorta along with a set of chemoreceptors, or glomera (glomus aorticum), that monitored the oxygen content of blood and help to regulate breathing through the respiratory center in the brainstem. The discovery of the reflexogenic role of cardio-aortic and carotid sinus areas in the regulation of respiration and blood pressure was worked out by Heymans with hard work over years with several coworkers.

The above work consisted of using two anesthetized dogs and a cross-perfusion technique. The head of one dog was separated from its body except for intact vago-aortic nerves connecting to the respiratory center; the isolated head of this dog was then linked to the body circulation of the other dog by anastomosis with common carotids and external jugular veins of the other dog. A method was now available to show whether high and low pressure affected the medullary center directly by circulating blood or by means of nervous reflex. Heymans noted that induced arterial hypotension, solely limited to the decapitated dog, stimulated the respiratory center in the perfused head and augmented arterial pressure in the trunk of the other dog. Upward and downward cardiovascular reflex arc traffic was carried by



First International symposium on Pharmacology of human blood vessels - Kuwait, 1982

its own vagus nerves; whereas a hypertensive dose of adrenaline introduced into the dog with the head intact did not cause any change in the decapitated head. He thus showed that effects once thought to be due to direct action of blood pressure on the respiratory center were really brought about by a nervous reflex.

In 1938, the Nobel Prize for Physiology or Medicine was awarded to Heymans "For his discovery of the role played by the sinus and aortic mechanisms in the regulation of respiration." Heymans died in Flanders, Belgium, due to a stroke in 1968.

Professor (Retired), Department of Medicine, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital; Honorable Physician, Bhatia Hospital, Mumbai, Maharashtra, India

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Samajdar SS, Mukherjee S, Gupta S, et al. Effect of α-blockers on Handgrip Test Response of Diastolic Blood Pressure in Hypertensive, Benign Hypertrophy of Prostate Patients in a Therapeutics Clinic, Kolkata: A Cross-sectional Study. J Assoc Physicians India 2024; 72(4):21–23

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Dear Sir,

We read with interest the article "Samajdar SS, Mukherjee S, Gupta S, et al. Effect of α-blockers on handgrip test response of diastolic blood pressure in hypertensive, benign hypertrophy of prostate patients in a therapeutics clinic, Kolkata: a cross-sectional study. J Assoc Physicians India 2024;72(4):21–23."[1]

We would like to congratulate the authors on such a wonderfully well-conducted study. However, we have some queries as mentioned below:

- In the methods section, the authors have mentioned: "The greatest tension reached during these trials was recorded as the maximal force at the end of the test; that is, after 3 minutes, the BP of all the subjects was recorded using an OmronHEM-7600T BP monitor. After completion of the test, the BP of all the subjects in both the prazosin and tamsulosin groups was measured." This seems to be a repetition. Is this a printing mistake that needs to be corrected?
- Basic demographics of all patients have been given as an average. It would have been better to display readings of both groups.
- In the results section, the text mentions: "Post-IHG, four subjects in the prazosin group showed an increment of DBP >16 mm Hg, whereas Figure 1 was 16 in the tamsulosin group." However, in Table 3, the corresponding figure is 33. Which one is correct? This sentence needs to be corrected or the figure needs correction.
- We suggest that an additional group not on any α-blockers should have been included to know their response in the handgrip test.
- We would also like to know which dynamometer was used in the study, as the results of this test are affected by many parameters such as instrument, gender, age, dominance, time of assessment, body position, sincerity of effort, anthropometric characteristics, and grip span etc.[2,3]

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