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Second and third trimesters of pregnancy. Biliary obstructive disorders. Severe hepatic impairment. The concomitant use of Telmisartan with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m2). **Warnings And Precautions - Fetal Toxicity** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. **Hypotension** In patients with an activated renin-angiotensin system, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. **Hyperkalemia** may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered particularly in patients at risk. **Impaired Hepatic Function** As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan should be initiated at low doses and titrated slowly in these patients. Impaired Renal Function as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function should be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System**: Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, combined use of drugs from different classes of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes in patients on Telmisartan and other agents that affect the RAS should be closely monitored. Aliskiren must not be co-administered with Telmisartan in patients with diabetes. Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m²) must be avoided. **Nonclinical Toxicology:** Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when Telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan. These same doses have been shown to provide average systemic exposures to Telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any Telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of Telmisartan. This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **Use In Specific Populations: Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. **Pediatric Use:** Safety and effectiveness of Telmisartan in pediatrics has not been established. Thus, the drug is not recommended in pediatrics. **Geriatric Use:** No dose adjustment is needed in elderly patients

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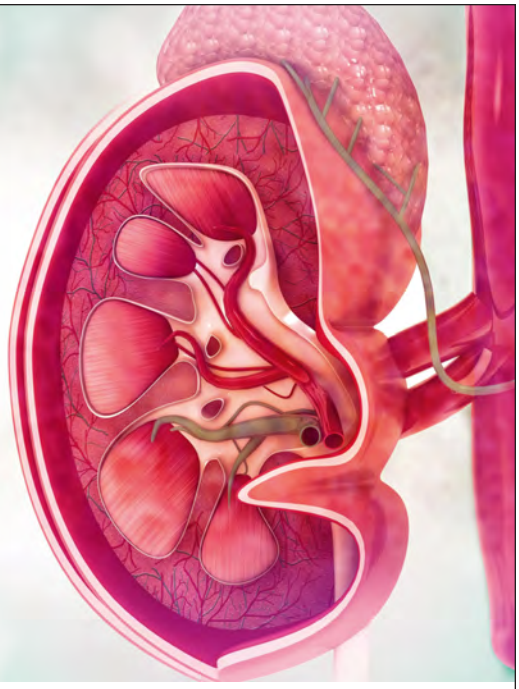

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This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **CILNIDIPINE Pregnancy:** Cilnidipine should not be administered to pregnant women as it has been reported that Cilnidipine prolongs the gestation period and delivery time in animal experiments (in rats). **Impaired Hepatic Function:** Close observation should be made and if any abnormality is observed appropriate measures, such as discontinuation of Cilnidipine, should be taken. **Elderly Patients:** Cilnidipine should be administered carefully under close observation of the patient's condition, start with low dose (5 mg) **Sudden Withdrawal:** It has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of Cilnidipine is necessary, appropriate measures, such as replacement with other antihypertensive agents, should be taken. **Effects on Ability to Drive and Operate Machine:** The symptoms, such as dizziness may occur because of the hypotensive action from this drug. It is hazardous to engage in activities which require alertness, such as working at a height, operating machinery or driving motor vehicles. **Others:** Precaution should also be exercised in patients with angina, chronic renal insufficiency, congestive heart failure, hypotension, liver dysfunction, or elevated liver enzymes, peripheral edema (confounding physical findings in congestive failure) and in patients with a history of serious adverse reactions to calcium antagonists. **USE IN SPECIFIC POPULATIONS Pregnancy:** Use of drugs that act on the renin-angiotensin system like Telmisartan, during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Cilnidipine has been reported to prolong the gestation period and delivery time in animal experiments (in rats). Therefore, the fixed dose combination of Telmisartan and Cilnidipine should be discontinued when pregnancy is detected, as soon as possible.**Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. Transfer of Cilnidipine to mother's milk has been reported in animal experiments (in rats). Therefore it is advisable to avoid the administration of the fixed dose combination of Telmisartan and Cilnidipine to nursing mothers. **Pediatric Use:** Safety and effectiveness of both Telmisartan and Cilnidipine in pediatrics has not been established. Thus, the fixed dose combination of Telmisartan and Cilnidipine is not recommended in pediatrics. **Geriatric Use:** The fixed dose combination of Telmisartan and Cilnidipine should be administered carefully under close observation of the patient's condition. No dose adjustment is needed in elderly patients

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Abbreviations: ARB, angiotensin II receptor blocker, ACE, angiotensin-converting enzyme, BP, blood pressure, MACE, major adverse cardiovascular events

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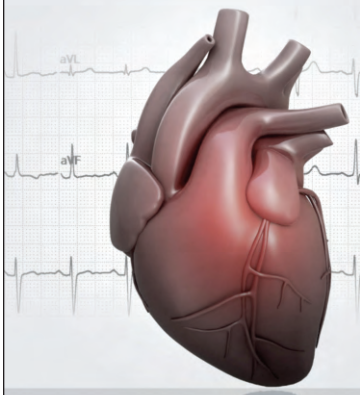

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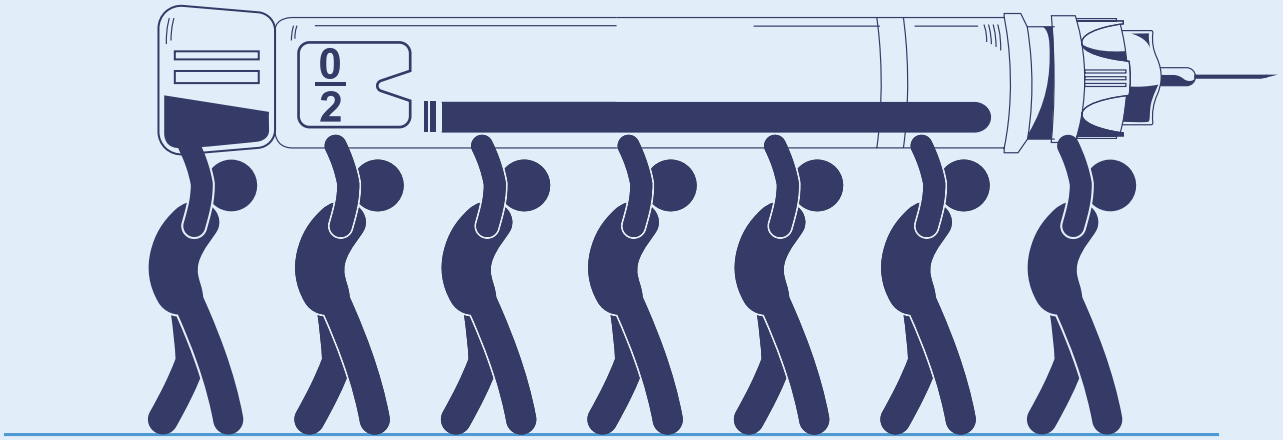

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EDITORIAL

Updates in the Management of Type 1 Diabetes

Ritwika Mallik[1*], Partha Kar[2]

Introduction

Type 1 diabetes (T1D) is a complex and challenging chronic condition with a rising incidence. India has the highest incidence of T1D cases in the world, with the number projected to progressively increase. In India, T1D is growing at 6.7% annually compared to 4.4% for type 2 diabetes (T2D).[1] Pathogenesis involves an autoimmune process resulting in the destruction of pancreatic β cells. It is associated with short-term and long-term complications, decreased quality of life, and reduced life expectancy. Currently, there are 860,423 people living with T1D in India, and it is estimated that 45 healthy years of life are lost per person due to T1D.[1] It has been 102 years since the discovery of insulin, and there have been unprecedented advances in the field of T1D. Expedited by the pandemic, there has been increased focus and development in the fundamental but often overlooked principles underlying chronic disease management, including self-management, peer support, and access to trained healthcare professionals. In this editorial, we discuss the updates in the management of T1D.

Self-management

An essential part of any chronic disease is self-management. Digital tools to facilitate self-management in chronic disease have been seen to have a positive impact, and the development in this area has been expedited by the coronavirus disease 2019 (COVID-19) pandemic. T1D-related digital innovation in education has occurred due to the availability and acceptance of mobile apps, telehealth, electronic platforms, and structured education. While digital health technologies have an important role worldwide, there is immense potential in providing T1D care in India. Despite advancements, several challenges remain at various levels in India, which need to be addressed in order to provide more patient-centric and personalized management to people with T1D (pwT1D). In the meantime, we need to continue to guide patients and empower them with appropriate resources to encourage self-management.

Peer Support

When people use their own experience to help and support each other, it is referred to as peer support. Lack of social support can have a negative impact on pwT1D, which is a challenging condition that can result in pwT1D feeling lonely. Patient's perspective revealed that peer support has a unique role in creating social networks to help understand mutual situations. In India, there are in excess of 40 peer support groups for T1D available at state and national levels, which offer to meet the various needs of people with diabetes.[2] Integrating these support programs and increasing awareness of best practices will result in improved quality of life and help bridge the gap between healthcare professionals and pwT1D. There are various benefits of joining support groups, and pwT1D should be encouraged and signposted to appropriate groups. Increased education and psychosocial support are important not only for the patients but also for the caregivers, and interventions targeting these aspects have shown promising results in India. Incorporating counseling by peer educators in the management can be beneficial.

Trained Healthcare Professionals

There is a dearth of trained professionals who can manage T1D. It is known that patients admitted to the hospital still develop diabetic emergencies, with an increase in diabetic ketoacidosis (DKA) seen during the pandemic, and increased awareness is required. Newer technology such as virtual reality-based education is being used to train healthcare professionals to help reduce these complications.[3] Training and upskilling are required, and digital technology can help deliver education virtually and can be completed on their own time. One such successful educational platform targeted at diabetes technology is the Academy. In India, there is the emergence of diabetes education programs to help upgrade the skills of primary care physicians, including fellowships, diplomas, and certificate programs, with the view of providing customized training. D1abesties is a foundation in India that is an example of a local movement now becoming global. It caters to the fundamental principles, including awareness, advocacy, education, and support, which are often overlooked while managing pwT1D. Udaan, led by Dr Archana Sarda, is another organization looking at supporting those living with T1D.

Glucose Monitoring and Insulin Delivery

Traditionally, capillary blood glucose has been detected using fingerstick glucose monitoring. Access to test strips, insulin, and good self-management for all pwT1D in India would restore many healthy lives per person. Noninvasive techniques such as real-time or intermittently scanned continuous glucose monitoring (CGM) have been game-changing in T1D. However, global recommendations do not always cover other populations; hence, consensus recommendations for time in range (TIR) tailored to the Indian population are available.[4] Apart from changes in glucose monitoring, there have been significant changes in insulin delivery, which have reduced the work of managing T1D. However, ensuring a continuous supply of insulin and affordability remain an issue. Government subsidies do help, but the challenges of resale and delivery remain and need to be addressed. While the majority are still on multiple daily injections of insulin, rapid-acting insulin has evolved into ultrarapid-acting insulin, and basal daily/twice daily insulin has evolved into even longer-acting once-weekly formulations and concentrated formulations. Insulin pens have evolved to become more accurate, discrete, and user-friendly with connected insulin pens, which help connect to apps and record glucose readings and insulin doses.

In addition, there have been revolutionary advances in automated and semiautomated insulin delivery systems, including in pregnant women, with reduced maternal and fetal complications.[5] Sensor-augmented pump therapy (SAP) combines continuous

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subcutaneous insulin infusion (CSII) and CGM. Hybrid closed loop (HCL) insulin therapy is a form of automated insulin delivery (AID) that combines insulin pump therapy with CGM using an algorithm to maintain blood glucose levels. Clinical trials using HCL have shown impressive results, and even real-world data have shown translation of these results demonstrating improvement in glycemic control, reduction in complications, and improvements in quality of life. Hence, the National Institute of Health and Care Excellence (NICE) has guidance in the development, which can be life-changing.

These systems labeled as hybrid still require patients to enter some information such as carbohydrate intake for bolus dosing and is a step toward the artificial pancreas. In contrast, the bionic pancreas, which automates the calculation and delivery of insulin doses, and results showed a greater reduction in glycated hemoglobin (HbA1c) compared to standard care at 13 weeks.[6] While in this study, insulin was used, bihormonal systems using insulin and glucagon are available, too. Without devices, the average person spends 18 years annually managing T1D, and if everyone in India had access to devices, another 6.5 years of healthy years would be restored.[1]

Immunotherapy

The only treatment for T1D is insulin, which is lifesaving but does not address the autoimmune process resulting in β-cell dysfunction. Hence, the role of disease-modifying therapies in T1D has been explored with the aim of reducing or, ideally, completely eradicating the need for insulin.

A major milestone in T1D is the approval of the drug teplizumab by the United States Food and Drug Administration (FDA). It is a human anti-CD3 monoclonal antibody for use in individuals ≥8 years or older with stage 2 T1D (two or more diabetes-related antibodies and elevated blood glucose but no symptoms), with the aim to delay the onset of clinical T1D (stage 3). Approval was based on the impressive results demonstrated in the phase 2 randomized control trial (RCT) in at-risk individuals without clinical diabetes. Teplizumab was able to delay the development of clinical T1D by a median 2 years compared to placebo.[7] The mechanism of action of teplizumab is to reduce the β-cell loss by modifying the $CD8^+$ T lymphocytes in β-cell death. While this therapy is indeed promising and may change how we deal with autoimmune diseases, detecting patients with stage 2 diabetes will require resources, and it has still not been approved for clinically evident T1D.

Various other immunotherapies investigated include anti-CD3 monoclonal antibodies (otelixizumab), anti-CD20 monoclonal antibodies (rituximab) a cytotoxic T lymphocyte associated antigen (CTLA)—4 immunoglobulin fusion protein (abatacept), recombinant fusion protein that binds to CD2 (alefacept), inhibitor of IL-8 receptor CXCR1/2 (ladarixin) and antithymocyte globulin (ATG) of which low dose appear to be promising.

Reduction in glucagon may be beneficial in T1D. Volagidemab, antiglucagon receptor antibody, as an adjunct to insulin therapy, appeared to be safe and well tolerated in a phase 2 study.[8]

Other Emerging Therapies for β-cell Protection

Glutamate decarboxylase (GAD) is the enzyme that catalyzes the conversion to γ-aminobutyric acid (GABA) in β cells. In preclinical studies, GABA has been found to promote insulin secretion, inhibit glucagon, and reduce inflammation, while GAD may preserve β cells.[9] A study to evaluate the role in the preservation of residual insulin secretion, oral low-dose GABA, or combined with GAD in addition to insulin, has confirmed the safety and tolerability of GABA for the first time in children with recent-onset T1D.[9] Although it did not reveal preservation of β-cell function, it did demonstrate a reduction in fasting and nutrient-stimulated glucagon, and it is proposed that an increased dose or longer-acting GABA may preserve islet cells.

Verapamil, a nondihydropyridine calcium channel blocker (CCB), is licensed for use in cardiac arrhythmia and hypertension. It has shown promise in T1D by reducing thioredoxin-interacting protein expression and β-cell apoptosis. Verapamil in children and adolescents with newly diagnosed T1D partially preserved stimulated C-peptide secretion at 52 weeks.[10] There are other trials underway to see if verapamil can increase β-cell mass.

Resveratrol, a food-derived compound, has shown antihyperglycemic and antioxidant properties. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) have demonstrated overwhelming benefit in patients with T2D, and although not licensed for use in T1D, real-world data showed overall benefit of off-label use, increased cardiorenal with increased risk of DKA, more so with SGLT2i than GLP-1 RA.[11]

Transplantation

For patients with severe complications, pancreatic transplantation is an option but is challenging and not without complications. With cadaveric islet cell transplantation, the issue has been the availability of islets and immunosuppression related. Hence, stem cell therapy is emerging as a treatment option. In a recent announcement, stem cell-derived fully differentiated islet cell therapy has continued to show promise in T1D, and it was reported that two participants were able to come off insulin for a year, with few others heading in that direction.[12] With advances in tissue engineering, the function of three-dimensional bionic printed pancreatic scaffolds with pancreatic islets in preclinical studies is also being explored.

For the first time, cell therapy (donislecel) has been approved by the FDA for brittle T1D.[13] The results did demonstrate insulin independence in a small number of patients. Although referred to as biological treatment, the allogeneic pancreatic islet cells from a deceased donor are used to synthesize the therapy. However, this may open avenues for how we combat autoimmune conditions.

Routine Care and Patient Empowerment

With novel treatments, the importance of routine care in T1D must not be undermined. Due to disruption in routine care during the COVID-19 pandemic, there was an increase in non-COVID-19-related mortality. Another lesson from the pandemic was the potential of social media in providing patient education in a safe and flexible manner. While online platforms are a great way to educate, tackling misinformation is imperative, too. There is also an increased awareness of the use of psychological and behavioral interventions, which have demonstrated not only significant improvements in the quality of life but also in the care of patients with T1D.

While there are remarkable advances in this field of T1D, there are various challenges still present in India for pwT1D, including supply and cost of insulin, availability of other consumables, availability of healthcare professionals, and structured education and support. While there is no national structured education available for T1D, a chronic care model is being piloted in West Bengal with the aim to provide comprehensive care.[14] With the affordability and availability of newer technology in India, the T1D community has started to close the loop itself with the aim to automate the delivery of insulin, referred to as do-it-yourself artificial pancreas (DIYAP), and has the potential to transform patient care.[15] Patient empowerment is of paramount importance, and language used by healthcare professionals can have a significant effect; hence, guidance regarding this is available.

Steps need to be taken to eradicate the stigma faced by pwT1D, and it remains the role of healthcare professionals to speak up and support pwT1D.

Insulin is necessary for survival; however, signs of T1D are still missed or misdiagnosed. In India, 8.9% of children who develop T1D are never diagnosed.[1] Program pilots to increase diagnosis rates and timely referrals are key areas to be investigated. Even the ones diagnosed are losing decades of healthy life. Hence, access to timely diagnosis, strips, and insulin, newer technology such as pumps and CGMs, and ongoing research to help find the cure is the way forward.

Currently, there is a lot of work being undertaken in India to identify the root causes of the challenges faced by pwT1D with ongoing projects led by organizations such as the Research Society for The Study of Diabetes in India (RSSDI) to help provide solutions at the individual, local, district, state, and central levels. The aim remains to provide affordable and feasible management and support and utilize available novel technology and treatment to help improve the quality of life.

Self-management, peer support, and trained professionals remain the cornerstones of T1D management. While embracing change and digitalization is necessary, the pwT1D should remain the center of our focus, with our role being that of a facilitator.

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ORIGINAL ARTICLE

Mycophenolate Mofetil with Steroid, a Reasonable Alternative to Current First-line Therapy, for Idiopathic Membranous Nephropathy in Resource-constrained Settings: A Randomized, Open-label Study

Manjuri Sharma[1], Amit Roy[2*], Prodip Kumar Doley[3], Gayatri Pegu[4]

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Abstract

Background: The modified Ponticelli regimen (mPR) is a first-line therapy in patients with idiopathic membranous nephropathy (IMN); however, it has a less favorable safety profile. Though mycophenolate mofetil (MMF) + steroid (S) is not recommended by Kidney Disease Improving Global Outcomes guidelines, it can be used as an alternative to mPR due to higher tolerability and steroid-sparing effect. Thus, we compared the safety and effectiveness of MMF + S and mPR regimens in patients with IMN.

Methods: This randomized, open-label study enrolled patients with adult-onset nephrotic syndrome (NS) and biopsy-proven IMN. Forty-two patients were allocated to MMF + S group (MMF 1 gm twice daily + oral prednisolone 0.5 mg/kg/day; $n = 21$) and mPR group [methylprednisolone (1 gm intravenous) for 3 days followed by alternating monthly cycles of oral prednisolone (0.5 mg/kg/day) for the next 27 days and cyclophosphamide (2 mg/kg/day) for 6 months; $n = 21$]. The primary outcome measure was change in urinary protein creatinine ratio (UPCR).

Results: At 6 months, both groups demonstrated a significant increase in serum albumin levels and estimated glomerular filtration rate (eGFR) (both p-values <0.0001) as well as a decrease in 24-hour proteinuria (MMF + S group: p-value = 0.003, and mPR group: p-value <0.0001) and UPCR (both p-values <0.0001). However, the groups did not differ in any of these parameters at any of the monthly follow-up visits. Moreover, the groups did not differ significantly in terms of the composite remission rates (61.91% for MMF + S group and 71.43% for mPR group).

Conclusion: MMF + S and mPR had comparable tolerability and effectiveness, with MMF-associated advantage of reduced steroid exposure.

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Introduction

Membranous nephropathy (MN) is responsible for more than a quarter of adult patients with nephrotic syndrome (NS).[1] In this population, it has an overall incidence of 1.2 per 1,00,000 per year, with the peak occurring in the fourth and fifth decades of life.[2,3] Around three-quarters of these patients have idiopathic MN (IMN), characterized by a variable outcome, with a third of patients undergoing spontaneous remission, another third experiencing persistent proteinuria, while the remaining third progressing to advanced renal failure.[2,4]

In patients with IMN, proteinuria level and renal excretory function are markers of disease activity and prognosis. Thus, a key indicator of treatment effectiveness is control of proteinuria with or without immunosuppression.[5] The use of immunosuppression is further supported by the identification of antiphospholipase A2 receptor (anti-PLA2R) antibodies in around three-quarters of patients with MN.[6] The desired immunosuppression is usually achieved with a regimen involving the combined use of steroids (S) and alkylating agents, as studied by Ponticelli et al. The initial regimen included methylprednisolone and chlorambucil; however, the modified Ponticelli regimen (mPR), introduced later, includes methylprednisolone and cyclophosphamide (CYC).[7–10] The mPR is recommended by the Kidney Disease Improving Global Outcomes (KDIGO) for the management of IMN.[11] Though mPR has been shown to result in remission induction in significant proportion of patients, it is associated with considerable adverse events (AEs).[12–15]

Apart from mPR, KDIGO recommends rituximab (RTX) and tacrolimus (TAC) therapy for the management of IMN.[11] However, these therapies are costly and inaccessible in resource-constrained settings in the northeastern part of India. Though mycophenolate mofetil (MMF) is usually used for the management of glomerular diseases, it is not recommended by the KDIGO.[16] Earlier studies reported that MMF + S is equi-efficacious to mPR for the treatment of MN.[17,18] It is associated with steroid-sparing effect and less AEs relative to other commonly used cytotoxic drugs. Recently, an indirect comparison of MMF + S and CYC + S revealed favorable efficacy and safety profile of the former over the latter.[19]

In our setting, MMF + S and mPR are most commonly used. The northeastern population has a diverse genetic makeup relative to other parts of India, and the effectiveness of these regimens has not been evaluated among this population. Thus, we compared the safety and effectiveness of MMF + S and mPR regimens in induction of remission in patients with IMN over a period of 6 months.

Materials and Methods

This randomized, open-label study involved 42 patients with adult-onset NS, having a normal BMI and biopsy-proven IMN. The study was performed in the Department of Nephrology of a tertiary care institute located in northeast India over a period of 12 months (June 2021 to May 2022). Patients with systemic diseases, renal vein thrombosis, diabetes mellitus, malignancy, viral hepatitis, uncontrolled hypertension (≥160/100 mm Hg), pregnant or lactating women, life expectancy of <1 year, and those exposed to steroids or immunosuppressive drugs within the past 6 months were excluded. The study commenced after obtaining approval from the Institutional Ethics Committee and written informed consent from the patients.

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A random number table was used and patients were randomly and equally allocated to the study groups: MMF + S group ($n = 21$) and mPR group ($n = 21$). All the patients received treatment for a duration of 6 months with monthly follow-up visits. The patients in the MMF + S group received MMF (1 gm twice daily) and oral prednisolone (0.5 mg/kg/day). While the patients in the mPR group received methylprednisolone (1 gm intravenous) for 3 days followed by oral prednisolone (0.5 mg/kg/day) for the next 27 days in the 1st, 3rd, and 5th months and oral CYC (2 mg/kg/day) in the 2nd, 4th, and 6th months.

All patients received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs) as well as low-salt and low-protein diet. When required, loop diuretics and supplementary antihypertensive drugs were used to control edema and blood pressure, respectively. Moreover, statins were used when indicated. The spot urine samples were used to measure urine protein creatinine ratio (UPCR). The presence of anti-PLA2R antibodies in the biopsy sample confirmed the idiopathic nature of the MN.

The effectiveness of the therapy was assessed with baseline and monthly UPCR, 24-hour proteinuria, and serum albumin. While safety was evaluated with an assessment of total leukocyte count, serum alanine aminotransferase, and patient-reported AE at each visit. Details of any AE, for example, leukopenia, infectious episodes, and gastrointestinal intolerability, were noted. At 6 months, remission rates [RRs, both complete remission (CR) and partial remission (PR)] were evaluated. Moreover, anti-PLA2R antibody titers were assessed at 6 months and compared with baseline levels.

Outcome Measures

The primary outcome measure was the change in the UPCR or 24-hour urine proteinuria. While the secondary outcome measure was the proportion of patients attaining CR or PR. CR was defined as proteinuria with protein <0.3 gm/24 hours or UPCR <0.3 mg/mg, with normalization of serum albumin (3.5 gm/dL or more). PR was defined as reduction of 24-hour urine protein (or UPCR) to <50% of baseline to <3.5 gm/day (or UPCR <3.5 mg/mg), but >0.3 gm/day (or UPCR >0.3 mg/mg).

Sample Size

Choi et al. evaluated MMF for primary glomerulopathies and reported 44% decrease in mean UPCR over 10 months (from 7.7 ± 4.8 to 3.4 ± 3.8 gm/gm).[20] Considering a 50% decline in mean UPCR between the groups with 5% α, 90% power, and 20% loss to follow-up, we estimated 21 patients per group to detect the estimated differences.

Statistical Analyses

The data was analyzed with SPSS (IBM, Armonk, NY, USA) version 23.0 for Windows. Intention-to-treat analysis was used for all the statistical analyses. If the patient was lost to follow-up for any reason, then the last observed values were carried forward for the analysis. The categorical and continuous variables are represented as frequency (percentage) and mean [standard deviation (SD)], respectively. Between-group comparison of categorical and continuous variables was performed with Fisher's exact and independent sample *t*-test, respectively. Moreover, within-group comparison of continuous variables was performed with repeated measures ANOVA followed by Bonferroni's multiple comparison test. A two-tailed probability value of <0.05 was considered as statistically significant.

Results

A total of 52 patients were screened and 42 were enrolled, with 21 in each group. In the MMF + S group, two patients were lost to follow-up, including discontinuation of the study in one patient due to persistent diarrhea and another succumbed to COVID-19-associated acute respiratory distress syndrome. In the mPR group, one patient developed leukopenia and was removed from the study. Thus, a total of 39 patients (19 in MMF + S group and 20 in mPR group) completed the study (Fig. 1). However, we have analyzed all 42 patients under the intention-to-treat analysis.

Table 1 depicts baseline characteristics of both the groups. On analyses, the groups did not differ significantly in any of the baseline characteristics. The majority of the patients were

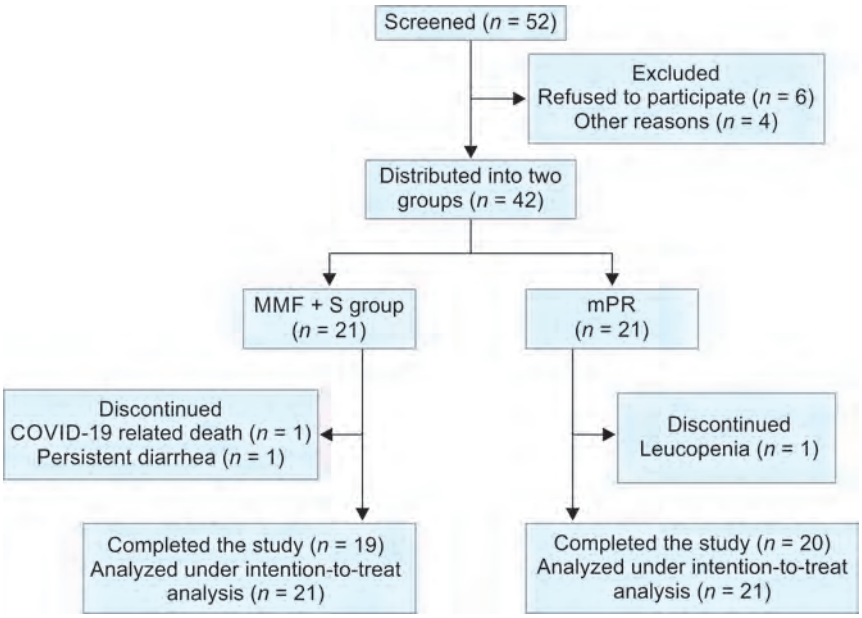

Fig. 1: Study flowchart

Table 1: Baseline characteristics

Parameters	*MMF + S group (n = 21)*	*mPR group (n = 21)*	*p-value*
Age, year	50.29 ± 7.87	51.24 ± 5.36	0.649
Sex, male	18	19	1.000
Serum creatinine, mg/dL	1.07 ± 0.29	1.02 ± 0.22	0.551
Serum urea, mg/dL	34.48 ± 8.66	36.09 ± 9.54	0.568
eGFR	84.68 ± 11.29	85.04 ± 12.56	0.842
Urine protein			1.000
4+	8	9	
3+	13	12	
Proteinuria, gm/day	7.99 ± 4.86	7.72 ± 3.49	0.834
Serum albumin, gm/dL	2.31 ± 0.45	2.35 ± 0.40	0.803
Hemoglobin, gm/dL	10.97 ± 0.92	11.28 ± 0.70	0.230
Total cholesterol, mg/dL	210.09 ± 31.32	214.90 ± 26.38	0.593
Triglyceride, mg/dL	180.14 ± 22.66	174.95 ± 28.24	0.515

male and had full-blown NS with decreased serum albumin level, proteinuria between 5 and 10 gm/day and raised serum lipid levels. At enrollment and throughout the study, all patients had normal renal function, as assessed with estimated glomerular filtration rate (eGFR).

Outcomes

Table 2 depicts laboratory parameters used to assess the efficacy of the treatment. At 6 months, both the groups demonstrated significant increase in serum albumin levels (both *p*-values <0.0001) and eGFR (both *p*-values <0.0001) as well as a decrease in 24-hour proteinuria (MMF + S group: *p*-value = 0.003, and mPR group: *p*-value <0.0001) and UPCR (both *p*-values <0.0001). Moreover, in both the groups, post-hoc analysis revealed significant improvement in all three laboratory parameters between various follow-up visits.

Table 2: Laboratory parameters at various intervals

Parameters	*MMF + S group (n = 21)*	*mPR group (n = 21)*
24-hour proteinuria, gm/day		
Baseline	7.99 ± 4.86	7.72 ± 3.49
1 month	6.92 ± 3.89$^{\#}$	6.46 ± 2.88$^{\#}$
2 months	5.67 ± 3.22$^{*,@}$	5.16 ± 2.21$^{*,\$}$
3 months	4.86 ± 2.55$^{*,\$,\%}$	4.46 ± 2.16$^{*,\$,\wedge}$
4 months	4.13 ± 2.09$^{*,\$,\%,£}$	3.69 ± 1.59$^{*,\$,\wedge,£}$
5 months	3.29 ± 1.56$^{*,\$,\%,£,\beta}$	2.99 ± 1.27$^{*,\$,\wedge,\alpha,\sigma}$
6 months	2.65 ± 1.22$^{*,\$,\%,£,\beta}$	2.39 ± 1.14$^{*,\$,\wedge,\alpha,\sigma,\mu}$
p-value	0.003	<0.0001
Serum albumin, gm/dL		
Baseline	2.31 ± 0.45	2.35 ± 0.40
1 month	2.55 ± 0.39^{a}	2.59 ± 0.38^{a}
2 months	2.82 ± 0.45^{a}	2.87 ± 0.37^{a}
3 months	3.02 ± 0.48^{a}	3.09 ± 0.43^{a}
4 months	3.19 ± 0.46^{a}	3.34 ± 0.39^{a}
5 months	3.38 ± 0.47^{a}	3.54 ± 0.43^{a}
6 months	3.55 ± 0.49^{a}	3.72 ± 0.46^{a}
p-value	<0.0001	<0.0001
UPCR		
Baseline	7.81 ± 5.31	7.93 ± 4.32
1 month	7.12 ± 4.39	6.71 ± 3.55$^{\#}$
2 months	5.92 ± 3.55$^{\#,@}$	5.42 ± 2.78$^{*,\$}$
3 months	5.07 ± 2.87$^{\#,@,\%}$	4.71 ± 2.64$^{*,\$,\wedge}$
4 months	4.27 ± 2.39$^{\#,\%,£}$	3.93 ± 1.97$^{*,\$,\wedge,£}$
5 months	3.43 ± 1.81$^{*,\$,\%,£,\beta}$	3.18 ± 1.59$^{*,\$,\wedge,\alpha,\sigma}$
6 months	2.75 ± 1.25$^{\#,\%,£,\beta}$	2.55 ± 1.41$^{*,\$,\wedge,\alpha,\sigma,\mu}$
p-value	<0.0001	<0.0001
eGFR, mL/min/1.73 m^2		
Baseline	84.68 ± 11.29	85.04 ± 12.56
1 month	85.73 ± 11.17*	86.33 ± 12.06*
2 months	86.80 ± 11.09$^{*,\$}$	87.49 ± 11.45*
3 months	87.66 ± 10.88$^{*,\$,\%}$	88.89 ± 10.93$^{*,\$,\wedge}$
4 months	88.53 ± 10.81$^{*,\$,\%,£}$	89.11 ± 11.35*
5 months	89.31 ± 10.74$^{*,\$,\%,£}$	90.49 ± 11.22$^{*,\$,\varepsilon,\sigma}$
6 months	90.68 ± 10.58$^{*,\$,\%,£,\beta}$	91.56 ± 10.92$^{*,\$,\varepsilon,£,\sigma,\mu}$
p-value	<0.0001	<0.0001

*Repeated measures ANOVA followed by post-hoc analysis by Bonferroni's test; *p*-value <0.05 was considered as statistically significant; Post-hoc analyses—Both groups: ^{a}*p*-value <0.0001 all follow-up visits compared to baseline and between each other, **p*-value <0.0001 compared to baseline, $^{\#}$*p*-value <0.05 compared to baseline; $^{\$}$*p*-value <0.0001 compared to 1 month, $^{£}$*p*-value <0.05 compared to 3 months; MMF + S group: $^{@}$*p*-value <0.05 compared to 1 month, $^{\%}$*p*-value <0.05 compared to 2 months, $^{\beta}$*p*-value <0.05 compared to 4 months; modified Ponticelli group: $^{\wedge}$*p*-value <0.0001 compared to 2 months, $^{\varepsilon}$*p*-value <0.05 compared to 2 months, $^{\alpha}$*p*-value <0.0001 compared to 3 months, $^{\sigma}$*p*-value <0.0001 compared to 4 months, $^{\mu}$*p*-value <0.0001 compared to 5 months

Table 3 depicts the comparison of the change in laboratory parameters between the groups. Compared to baseline, the mean decline in 24-hour proteinuria and UPCR as well as the mean rise in serum albumin and eGFR were slightly greater in the mPR group, but it did not a reach statistically significant level at any of the follow-up visits (all *p*-values >0.05).

Table 4 depicts the comparison of the anti-PLA2R antibody titers between the groups. At baseline and 6 months, there was no significant difference between the groups (both *p*-values >0.05). Moreover, in both the groups, treatment led to significant reduction in anti-PLA2R antibody titers (both *p*-values <0.0001).

At 6 months, a greater proportion of patients in the mPR group than in the MMF + S group achieved remission [CR: 5 (23.81%) vs 4 (19.05%), and PR: 10 (47.62%) vs 9 (42.86%)]. However, there was no significant difference between the groups (both *p*-values = 1.0000). Moreover, 8 (38.09%) patients in MMF + S group and 6 (28.57%) in mPR group did not achieve remission (*p*-value = 0.744). At 6 months, one patient in each group relapsed (*p*-value = 1.000).

Safety

In the MMF + S group, one patient developed COVID-19-associated acute respiratory distress syndrome and died at 3 months, while another patient developed persistent diarrhea at 5 months and discontinued the study. In the mPR group, one patient developed leukopenia and dropped out of the study. AEs that did not lead to study discontinuation included nausea and vomiting (*n* = 2) and epigastric discomfort (*n* = 1) in the MMF + S group. While two patients in the mPR group developed lower respiratory tract infections. All AEs were managed conservatively.

Discussion

In recent times, this is the first Indian study to compare the safety and effectiveness of MMF + S with mPR in patients with IMN, as a first-line therapy. At the end of 6 months, both MMF + S and mPR resulted in significant improvement in serum albumin, 24-hour proteinuria and UPCR. Though treatment with mPR resulted in slightly greater mean change in serum albumin, 24-hour proteinuria and UPCR, both the treatment groups did not differ significantly at any of the follow-up visits. Moreover, both the treatment groups had identical RRs and safety profile. Thus, the findings of the study demonstrated comparable safety and effectiveness of MMF + S and mPR.

Table 3: Change in laboratory parameters

Parameters	*MMF + S group (n = 21)*	*mPR group (n = 21)*	*p-value*
24-hour proteinuria, gm/day			
Baseline to 1 month	−1.07 ± 1.15	−1.64 ± 1.38	0.153
Baseline to 2 months	−2.32 ± 1.82	−2.94 ± 2.01	0.302
Baseline to 3 months	−3.13 ± 2.52	−3.64 ± 2.05	0.477
Baseline to 4 months	−3.85 ± 3.08	−4.41 ± 2.63	0.532
Baseline to 5 months	−4.69 ± 3.70	−5.11 ± 2.99	0.685
Baseline to 6 months	−5.34 ± 4.46	−5.71 ± 3.23	0.759
Serum albumin, g/dL			
Baseline to 1 month	0.23 ± 0.14	0.25 ± 0.14	0.735
Baseline to 2 months	0.51 ± 0.21	0.52 ± 0.16	0.869
Baseline to 3 months	0.71 ± 0.24	0.74 ± 0.22	0.693
Baseline to 4 months	0.88 ± 0.25	0.99 ± 0.31	0.219
Baseline to 5 months	1.07 ± 0.24	1.19 ± 0.37	0.204
Baseline to 6 months	1.23 ± 0.23	1.37 ± 0.43	0.202
UPCR			
Baseline to 1 month	−0.69 ± 1.09	−1.21 ± 1.43	0.194
Baseline to 2 months	−1.89 ± 2.11	−2.51 ± 2.03	0.156
Baseline to 3 months	−2.74 ± 2.81	−3.22 ± 2.18	0.311
Baseline to 4 months	−3.54 ± 3.28	−4.00 ± 2.71	0.410
Baseline to 5 months	−4.38 ± 3.84	−4.75 ± 3.06	0.529
Baseline to 6 months	−5.06 ± 4.71	−5.38 ± 3.41	0.617
eGFR, mL/min/1.73 m^2			
Baseline to 1 month	1.04 ± 0.44	1.29 ± 0.83	0.254
Baseline to 2 months	2.12 ± 0.61	2.44 ± 1.58	0.389
Baseline to 3 months	2.98 ± 0.87	3.85 ± 2.24	0.107
Baseline to 4 months	3.85 ± 1.13	4.07 ± 2.98	0.760
Baseline to 5 months	4.63 ± 1.86	5.45 ± 3.37	0.339
Baseline to 6 months	6.00 ± 2.12	6.51 ± 4.32	0.627

Table 4: Anti-PLA2R antibody titers

Anti-PLA2R antibody titers (RU/mL)	*MMF + S group (n = 21)*	*mPR group (n = 21)*	*p-value*
Baseline	202.29 ± 76.35	198.00 ± 82.88	0.861
6 months	61.76 ± 76.67	62.14 ± 86.20	0.988
p-value	<0.0001	<0.0001	

Current KDIGO guidelines recommend biologics including RTX and TAC, as first-line alternatives to mPR in patients with IMN.[11] A meta-analysis reported comparable RRs among TAC + S and mPR.[21] Contrarily, a subsequent systematic review and meta-analysis concluded that TAC + S results in better therapeutic effect and less AEs relative to CYC + S. They further observed that CR was significantly greater with TAC + S mainly after 6 months of follow-up, while there was no significant difference between the treatments after 12 months of follow-up.[22] However, the recent findings of a long-term (6-years) randomized controlled trial clearly demonstrate the superiority of mPR over TAC + S.[13] Data related to RTX suggest superior safety profile than CYC + S.[23] A recent systematic review and meta-analysis observed no significant difference between RTX and control group (including CYC + S) in serum albumin, serum creatinine, urinary protein, e-GFR, and total RRs. However, RTX resulted in significantly higher CR rate relative to the control group.[24] A recently concluded RI-CYCLO trial demonstrated comparable RRs associated with RTX and CYC + S with identical short-term safety profile.[25] All the above findings suggest that mPR is at least comparable to RTX and TAC + S in terms of efficacy. Thus, mPR remains the only well-established first-line therapy for IMN in resource-constrained settings.

The steroid-related AEs of mPR led to the search for an equally efficacious agent with steroid-sparing effect. MMF was proposed as an alternative for patients with poor response to conventional therapy, including CYC and calcineurin inhibitors (CIs), and patients who cannot tolerate RTX. However, it has not been sufficiently evaluated, and there is lack of recent randomized controlled trials. A study reported that both MMF + S and original Ponticelli regimen (oPR) led to a significant decrease in proteinuria and increase in serum albumin, but they did not differ significantly. Moreover, at 15 months, the MMF + S and oPR groups had a comparable composite RRs of 63.7% (CR 27.3% and PR 36.4%) and 66.7% (CR 33.3% and PR 33.3%), respectively.[17] Another study reported similar findings in terms of improvement in proteinuria and serum albumin levels. At a maximum of 20 months follow-up, the composite RRs with the MMF + S and mPR were 63.63% (CR 45.5% and PR 18.2%) and 80% (CR 30% and PR 50%), respectively, with no significant difference between the treatment groups.[18] In the present study, we observed similar findings in both primary and secondary outcome measures. At 6 months, the composite RRs were 61.91% (CR 19.05% and PR 42.86%) for MMF + S groups and 71.43% (CR 23.81% and PR 47.62%) for mPR group. Moreover, a recent network meta-analysis evaluated all the available treatment options for the management of IMN and reported that MMF + S and CYC + S ranked second and fourth, respectively in induction of total remission among patients with pretreatment proteinuria >8 gm/day. Moreover, CYC + S was second only to RTX + TAC in terms of bone marrow suppression and gastrointestinal AEs.[19] These latest findings highlight the superiority of MMF + S over mPR and suggest the need for well-designed randomized controlled trials comparing both the treatments.

Though oPR led to decline in proteinuria and enhanced 10-year renal survival by 50%,[8,26] it was replaced by mPR due to less favorable safety profile. However, the latter was still capable of inducing leukopenia and malignancy.[9] Relative to cytotoxic agents and CIs, MMF is a promising alternative due to its potent immunosuppressive action, high tolerability, and absence of nephrotoxicity. Studies involving patients with lupus nephritis have reported fewer AEs with MMF than CYC.[27,28] In the present study, both treatment groups had statistically comparable safety profile. One patient in each group discontinued due to treatment related AEs (MMF + S group: persistent diarrhea, and mPR group: leukopenia). Other AEs were mild in nature and managed conservatively. Treatment with MMF + S led to nausea and vomiting (n = 2) and epigastric discomfort (n = 1), while mPR resulted in lower respiratory tract infection (n = 2). Other studies have reported similar safety profile.[17,18] However,

in the present study, absence of new-onset diabetes and disseminated tuberculosis could be attributed to the short duration of treatment exposure.

The KDIGO guidelines recommend steroid sparing agents including RTX, TAC, and CIs. However, only RTX can be used as monotherapy, while TAC and CIs are required to be administered with steroids. Also, the use CIs is reported to have an RRs of 70–75%, similar to mPR.[17,18] However, it is associated with concerns, including nephrotoxicity and high relapse rates (40–45%). Thus, TAC and CIs were not used in the present study.

Additionally, high cost of RTX and TAC are a concern in developing countries, including India. Currently, direct cost-effective comparisons of RTX and MMF + S are lacking. A recently published health economic model demonstrated cost-effectiveness of RTX over mPR; however, this was at the cost of reduced quality of life.[5] In our tertiary care institute, located in the northeastern part of India, unlike RTX, MMF + S is provided free of cost to the patients. As of today, the cost of MMF (500 mg per 10 tablets) ranges from INR 120 to INR 1,021,[29] while that of RTX (500 mg per vial) ranges from INR 6,500 to INR 42,350.[30] Thus, in resource-constrained settings, free availability of MMF + S could provide better compliance.

The present study had certain limitations. First, the study had small sample size and was not powered enough to demonstrate superiority of one treatment modality over the other. Second, patients were followed-up for 6 months, thus long-term outcomes and AEs could not be evaluated. Third, short follow-up period did not allow us to assess the relapse rate, thus further studies with longer duration of follow-up are required. Fourth, use of ACEIs/ARBs could have confounded the findings; however, the composite RRs were comparable.

Conclusion

The findings of the study demonstrate that 62% patients with IMN respond favorably to MMF + S as a first-line therapy. Use of MMF + S showed comparable tolerability and effectiveness relative to mPR, with advantage of reduced steroid exposure.

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Authors' Contribution

Conception and design of study; acquisition of data; data preparation and presentation: MS, AR, PKD. Literature review; revising and editing the manuscript critically for important intellectual contents: MS, AR, PKD, GP. Analysis and interpretation of data; research investigation and analysis: AR, PKD. Data collection: AR, GP. Drafting of manuscript: MS, AR, PKD, GP. Supervision of the research; research coordination and management, funding for the research: MS.

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ORIGINAL ARTICLE

A Study of Prevalence of Renal Function Abnormalities and Their Association with the Individual Components of Metabolic Syndrome

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Abstract

Introduction: Metabolic syndrome (MetS) is one of the most important emerging pandemics of the 21st century and is associated with renal dysfunction in a significant number of subjects, the association of which is shown to be of greater significance in the South Asian population.

Aims and objectives: The prevalence of renal dysfunction in patients with MetS is the primary outcome. The secondary outcome is to assess the strength and significance of the association between the individual components of MetS and the presence of renal dysfunction.

Materials and methods: This is a hospital-based cross-sectional observational study conducted for 2 years in a tertiary care hospital in India. A total of 100 diagnosed subjects of MetS were taken as cases and underwent relevant blood tests. Data were collected and analyzed in a Statistical Package for the Social Sciences (SPSS) v29 sheet.

Results: Over a period of 18 months, 100 subjects with MetS were documented, among which 66% had albuminuria, with microalbuminuria being 24% and the rest being macroalbuminuria. Among the same subjects, 30% had an estimated glomerular filtration rate (eGFR) <60 mL/minute/1.73m^2. Waist circumference (WC) [measured by the National Institutes of Health (NIH) protocol] had the strongest association with increased albuminuria (r = 0.540; p-value < 0.001) as well as reduced eGFR (r = 0.460; p-value < 0.001).

Conclusion: All the components of MetS, for example, increased WC, hypertension, increased fasting glucose, raised triglyceride (TG), and low high-density lipoprotein (HDL), have statistically significant correlations with increased urine albumin-to-creatinine ratio (ACR) and decreased eGFR, signifying glomerular injury and renal dysfunction, respectively.

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Introduction

Metabolic syndrome (MetS) is considered to be a significant risk factor for cardiovascular disease.[1] and is linked prospectively to diabetes mellitus,[2] cerebrovascular events, fatty liver,[3] hyperuricemia,[4] polycystic ovarian syndrome, and sleep disorder. The prevalence of MetS varies widely according to the definition used, but it has steadily increased with economic development and growth in the last 2 decades. However, along with the aforementioned risks, the current literature search also suggests that MetS is frequently associated with the development of albuminuria.[5] In our study, we have looked at the association of increased urine albumin-to-creatinine ratio (ACR) along with decreased estimated glomerular filtration rate (eGFR) with MetS.

Materials and Methods

The study was done in the Department of Medicine and Obesity and Lifestyle Diseases clinic in a tertiary care hospital over a period of 2 years. Around 100 individuals diagnosed with MetS (classified according to MetS International Diabetes Federation (IDF) guidelines for the South Asian population) between the age of 18 and 60 years were taken as cases.

Inclusion Criteria

Metabolic syndrome was classified as per MetS IDF guideline for the South Asian population that includes people with the following criteria—central obesity [waist circumference (WC) ≥90 cm for males and ≥80 cm for females) plus any two of the following four factors—(1) triglyceride (TG) ≥150 mg/dL, (2) high-density lipoprotein (HDL) <40 mg/dL in males and <50 mg/dL in females, (3) systolic blood pressure (SBP) ≥130 or diastolic blood pressure (DBP) ≥85, and (4) fasting plasma glucose (FBS) ≥100 mg/dL.

Exclusion Criteria

Pregnancy, those with secondary causes of MetS like Cushing's syndrome, acromegaly, secondary causes of chronic kidney disease (CKD) not directly related to MetS like systemic lupus erythematosus, drug-induced, glomerulonephritis, vasculitis, decompensated chronic liver disease, decompensated heart failure, known smokers, alcoholics, fever, menstruation, urinary tract infection, and those who did not give consent. An equal number of gender and age-matched normal weight controls were taken. All cases and controls were evaluated with the following anthropometric and biochemical parameters—(1) age and gender; (2) general examination and vitals; (3) body mass index (BMI), WC [measured by World Health Organization (WHO) and National Institutes of Health (NIH) protocol); (4) complete hemogram; (5) urea and creatinine; (6) liver function tests, lipid profile; (7) fasting blood glucose; (8) urinary albumin to creatine ratio; (9) eGFR using CKD-EPI equation.

$$CKD-EPI\ creatinine = A \times (Scr / B) \times 0.993^{age} \times (1.159\ if\ black)$$

where A, B, and C are the following:

females: if Scr ≤ 0.7 A = 144 B = 0.7 C = −0.329 if Scr > 0.7 A = 144 B = 0.7 C = −1.209

males: if Scr ≤ 0.9 A = 141 B = 0.9 C = −0.411 if Scr > 0.9 A = 141 B = 0.9 C = −1.209); and (10) ultrasonography of kidney, ureter, and bladde.

Statistical Analysis

Statistical analysis was done using Excel Stat and Statistical Package for the Social Sciences

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(SPSS) (version 29) in terms of descriptive statistics, analytical statistics, and parametric and nonparametric tests.

Results

Our study revealed that the gender distribution of our cases had a female preponderance, with 66% being females.

The mean age was 38.82 ± 10.4 (Fig. 1), and the mean BMI was 32.92 ± 10.4 kg/m^2. The distribution of other variables is shown in Table 1.

A total of 43 cases had impaired glucose tolerance, 57 were hypertensive, 66 had raised TG, and 76 had low HDL.

The control was age- and sex-matched with a mean BMI of 21.027 kg/m^2.

Microalbuminuria (urine ACR 30–300 µg/mg) was documented in 24%, while 42% of the cases had macroalbuminuria (urine ACR >300 µg/mg). The mean ACR was 562.96 µg/mg, ranging between 4356 and 3.6 µg/mg. The difference in albuminuria with controls was statistically significant, with only 7% manifesting microalbuminuria and no macroalbuminuria.

The mean eGFR among cases was documented to be 90.47 mL/minute/1.73 m^2, and 30% had an eGFR <60 mL/minute/1.73 m^2. This was significantly higher than the corresponding value (5%) among controls.

Both increased urine ACR and decreased eGFR were found in 23% of the cases.

All the components of MetS as in WC (measured by WHO and NIH protocol), SBP, DBP, FBS, HDL, and TG had a statistically significant strong positive correlation with increased urine ACR in the cases (Table 2) (Fig. 2) but in the controls, no such correlation was found. On a similar note, all the components of MetS, except HDL, shared a statistically significant correlation with decreased eGFR (Table 2) (Fig. 3), in sharp contrast to the controls.

Discussion

Our study conforms to the findings of many previous studies with patients of MetS. Klausen et al. stated that albuminuria was found in significantly high numbers in individuals with MetS,[6] while Chen et al. concluded that MetS was an important risk factor for decreased eGFR.[5] As for the combined presence of increased urine ACR and decreased eGFR 23 among the cases, only one among the controls was implicated. The study of Lin et al. predicted MetS to be associated with both decreased eGFR and increased albuminuria.[7]

The study performed by He et al. showed WC had an odds ratio of 1.12 (95% CI, 1.08–1.16) and it is superior to BMI in association with CKD,[8] while Quan et al.

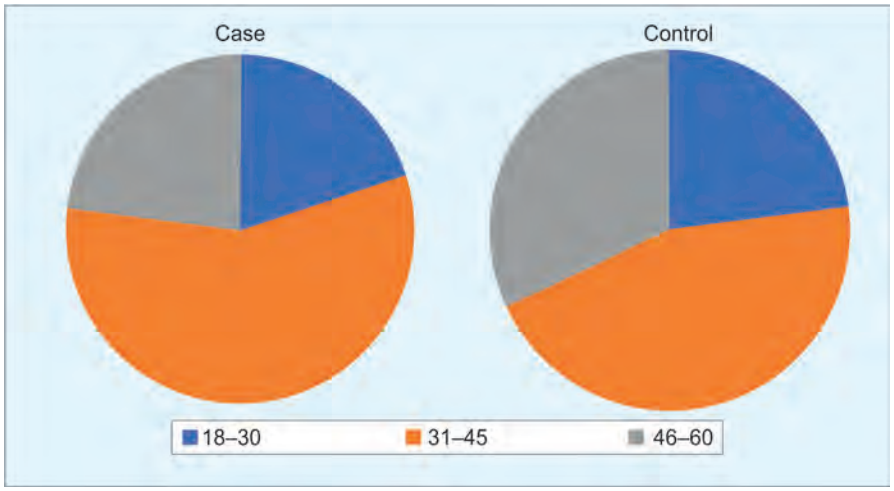

Fig. 1: Pie chart showing the distribution of age in cases and controls

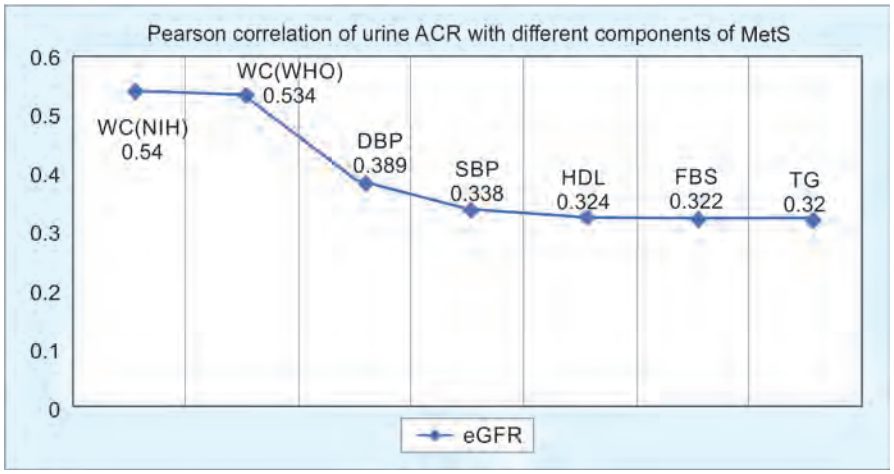

Fig. 2: Line diagram showing the correlation of urine ACR with different components of MetS

Table 1: Variable distribution among cases (MetS) and controls

	Case	*Control*
WC (WHO protocol)	105.627 ± 13.868	76.435 ± 1.882
WC (NIH protocol)	109.40 ± 13.909	76.43 ± 1.882
SBP	130.30 ± 16.799	114.38 ± 10.478
DBP	81.22 ± 13.232	73.32 ± 6.992
FBS	100.841 ± 26.845	96.89 ± 32.524
HDL	41.523 ± 9.065	52.50 ± 4.58
TG	165.699 ± 60.460	101.18 ± 16.167

Table 2: Correlation of urine ACR and eGFR with components of MetS among cases (MetS)

Components	*Urine ACR*	*eGFR*
WC	r = 0.534, p-value <**0.001**	r = –0.459, p-value <**0.001**
WC	r = 0.540, p-value <**0.001**	r = –0.460, p-value <**0.001**
TG	r = 0.320; p-value **0.001**	r = –0.384; p-value **0.001**
SBP	r = 0.338; p-value **0.001**	r = –0.322; p-value **0.001**
DBP	r = 0.389; p-value <**0.001**	r = –0.401; p-value <**0.001**
FBS	r = 0.322; p-value **0.001**	r = –0.349; p-value **0.001**
HDL	r = –0.324; p-value **0.001**	r = 0.126; p-value >0.05
BMI	r = 0.384, p-value <**0.001**	r = –0.314, p-value **0.001**

r-value showing the Pearson coefficient with r > 0.3 being strong correlation and p-value < 0.05 being statistically significant; Bold values represent that associations are significant

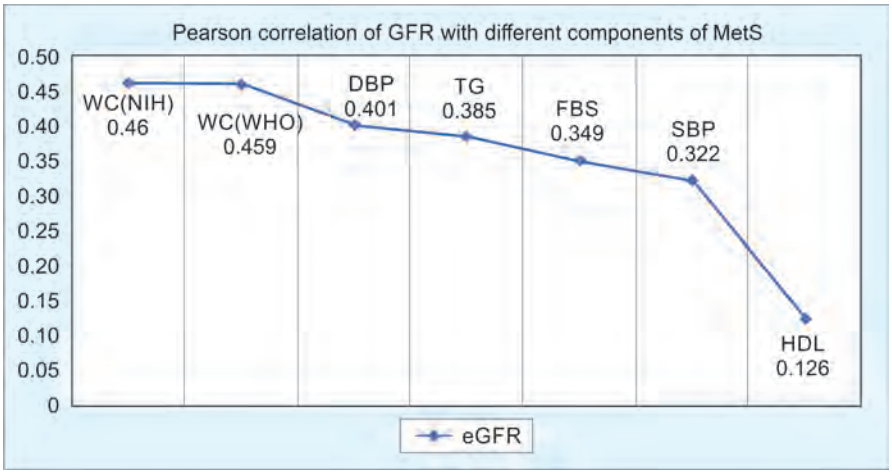

Fig. 3: Line diagram showing the correlation of eGFR with different components of MetS

quoted that central obesity may be a better predictor for renal function decline than BMI.[9] Supportive data were also found in our study.

Also, in our study, increased fasting blood sugar has a moderately strong positive correlation ($r = 0.322$) with increased urine ACR in the cases (MetS) that is also reflected in the studies of Jiang et al.[10] and Fujikawa et al.[11]

Huang et al. and Russo et al. showed that increased TG levels and low HDL-cholesterol were independent risk factors for the development of renal dysfunction.[12,13] However, though TG had a statistically significant moderately positive correlation ($r = 0.320$; p-value = 0.001) with increased urine ACR and a statistically significant moderately negative correlation ($r = -0.385$ p-value <0.001) with decreased eGFR in MetS cases HDL had no statistically significant correlation with decreased eGFR. This was an important deviation from established studies in our cases.

Limitation

The results of this study cannot be extrapolated to the larger population, as the sample size is small. This study was conducted with patients attending a special outdoor clinic at a tertiary care hospital. So, the ethnic distribution of the population is not diverse. The representation of male patients in the study is small. The preponderance of female patients in this study is observed as the overwhelming majority of female patients attended the obesity and lifestyle diseases clinic during that time period. Obesity is a chronic disease, so its complications cannot be assessed in an 18 months-snapshot. A prospective study rather than a correlational study would be better for assessing the effects of obesity-related health.

Conclusion

Our study revealed that 30% of the patients of MetS had renal dysfunction as measured by decreased eGFR, and 66% had a glomerular injury as measured by increased albuminuria. Components of MetS, for example, increased WC, hypertension, increased fasting glucose, and raised TG, had a statistically significant positive correlation with increased urine ACR and decreased eGFR. Individual components of MetS are independently associated with glomerular injury and renal dysfunction, but these associations become even stronger when a number of these individual components are clustered in MetS. WC, reflecting central obesity, among all the components of MetS, is most significantly associated with renal dysfunction. Hence, it is of prime importance that all MetS patients be followed up on in clinical practice at regular intervals for preventive measures, early detection of renal impairment, and prompt intervention.

Declaration

I beg most respectfully to state that I am a final-year postgraduate trainee in the Department of General Medicine at the Institute of Post Graduate Medical Education & Research (IPGMER), Kolkata, West Bengal, India. I am hereby sending you my original work, "A Study of the Prevalence of Renal Function Abnormalities and Their Association with the Individual Components of Metabolic Syndrome." This article has not been published or submitted in any other journal. I also declare that the order of authorship as placed in the manuscript is final and accepted by all. I also understand that the decision of the authority is final.

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ORIGINAL ARTICLE

Evaluation of Inflammatory Markers and Demographic Profile of Type 2 Diabetes Mellitus Patients among the Ethnic Communities Attending Central Referral Hospital, East Sikkim

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder and inflammation plays a key role in the pathogenesis of the disease. Ethnic variations have been linked with an increased prevalence of diabetes. This pilot study was designed to evaluate the inflammatory markers and demographic characteristics in T2DM patients among the ethnic group of Sikkim.

Materials and methods: A total of 100 type 2 diabetic patients and 50 healthy controls were enrolled in the study. Demographic characteristics were recorded among the patients and inflammatory markers [high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6)], body mass index (BMI), glycemic status, fasting blood sugar (FBS), and postprandial blood sugar (PPBS) level were compared between the cases and controls. Inflammatory markers were correlated with BMI, glycemic status, and duration of diabetes.

Results: Type 2 diabetes mellitus was found to be highest in between the age-group of 45 and 55 years with males being mostly affected. Among the ethnic group, Nepalis (57%) comprised the highest with diabetes. No significant correlation was found between inflammatory markers with BMI, glycemic status, and duration of diabetes.

Conclusion: Our study showed that T2DM increases as age progresses with males being mostly affected. The Nepalese community showed a high proportion of the disease mostly living in the urban residences. Though we included patients on statin therapy, its specific roles and relationship were not in the scope of the current study, but further studies should be conducted at the community level to understand the role and relationship of statins among type 2 diabetic patients and the possibilities of ethnic differences in the levels of biomarkers due to variation in the body fat distribution.

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Introduction

Type 2 diabetes mellitus (T2DM) **is** the most common metabolic disorder comprising 90% of all diabetic cases which is further accompanied by microvascular and macrovascular complications.[1] With rapid urbanization and socioeconomic evolution, the burden of diabetes has increased worldwide causing a serious public health concern.[2,3] In a developing country like India, most diabetic patients encounter a considerable economic burden and the lack of insurance policies further escalates the cost.[4] According to International Diabetes Federation (IDF), in 2019, about 463 million world's population were suffering from diabetes to 80% were from low- and middle-income countries (LMICs).[5] India has the second highest diabetic patients (73 million) after China and the figure is expected to double up to 134 million by 2045.[5] The National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) reported Sikkim with the highest number of diabetic cases in the country (13.67%).[6]

Though the cause is not well understood, the incidence and prevalence of T2DM varies geographically with race/ethnic group.[7] During the early stages, T2DM goes underdiagnosed in more than one-third of diabetic patients as the disease remains asymptomatic.[8] However, increasing evidence has shown that inflammatory mediators like C-reactive protein (CRP) and interleukin-6 (IL-6) have a key regulatory role in the pathogenesis of T2DM[9] owing to genetic predisposition associated with increased calorie intake and lack of physical activity resulting in adipose tissue dysfunction and release of inflammatory substances.[10] In this regard, the term "diabesity" was adopted due to the strong association between obesity and T2DM.[11] Obesity, classified as body mass index (BMI) ≥30 kg/m^2 could be used for lifestyle modification in diabetic patients by clinical practitioners as the risk of developing T2DM is stronger in people with higher BMI relative to people with lower BMI.[12]

With the emerging role of inflammation in T2DM and other metabolic diseases, we aim to explore the relationship of inflammatory markers [high sensitivity C-reactive protein (hs-CRP) and IL-6] with glycemia, BMI, and duration of diabetes along with the demographic profile among the ethnic communities of Sikkim.

Materials and Methods

Study Design

A hospital-based, cross-sectional study was conducted in the Department of Biochemistry at Sikkim Manipal Institute of Medical Sciences (SMIMS) from November 2015 to February 2016. Approval from the Institutional Ethics Committee (IEC/366/15-089) at SMIMS was obtained before commencing the study. One hundred fifty participants who met the eligibility criteria and were willing to participate were enrolled. The participants included 100 cases and 50 age- and sex-matched healthy controls.

The cases were defined as individuals diagnosed with T2DM according to the World Health Organization criteria [fasting blood sugar (FBS) ≥126 mg/dL and 2 hours postprandial blood sugar (PPBS) ≥200 mg/dL and glycated hemoglobin (HbA1c) >6.5%].[13] The controls were defined as healthy individuals who were not suffering from any disease.

Inclusion and Exclusion Criteria

Adults of either sex between 45 and 65 years of age diagnosed with T2DM were included. Participants suffering from acute or chronic

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infections, type 1 diabetes mellitus, a history of myocardial infarction and angina, thyroid disease, severe anemia, hemochromatosis, gestational diabetes, women on hormone replacement therapy, any malignancy, and pregnancy were excluded from the study.

For the demographic characteristics (age-group, gender, ethnicity, income, BMI (w/h^2), history of smoking, history of alcohol, and duration of the disease) were recorded in a pretested questionnaire.

Body mass index was calculated as weight (kg) divided by the square of height (m^2). The participants were categorized as underweight (BMI <18.5 kg/m^2) normal, (BMI 18.5–24.99 kg/m^2) overweight (BMI 25.0–29.99 kg/m^2), or obese (BMI ≥30.0 kg/m^2) according to the current World Health Organization classification.[14]

To assess the monthly income of T2DM patients, the patients were divided into three categories: income with Rs. ≤4,999/month, Rs. 5,000–9,999/month, and Rs. ≥10,000/month.

Sample Collection

About 5 mL of fasting venous blood was collected under aseptic condition. About 2 mL of the sample was stored in an ethylenediaminetetraacetic acid vial for estimation of HBA1c. From the remaining 3 mL, serum separated after centrifugation was used to measure hs-CRP, IL-6, and FBS levels. Two-hour postprandial blood was collected for PPBS estimation. Estimation of fasting, PPBS, and HBA1c levels were done immediately after sample collection. IL-6 and hs-CRP samples were stored in appropriate conditions (–20°) till further processing and analyzed in batches.

Assay

The biochemical parameters were analyzed by the following methods:

- High sensitivity C-reactive protein was estimated by ELISA Kit (Biomerica Inc.) (reference range: 0.068–8.2 mg/L).[15]
- Interleukin-6 was estimated by Sandwich ELISA kit (Ray Biotech) (reference range: 3–1000 pg/mL).[16]
- Fasting blood sugar and PPBS were done by the glucose oxidase peroxidase method in ERBA EM200 (Transasia Biomedical Ltd.).[17]
- Glycated hemoglobin was estimated by the particle-linked immune turbidimetric method in ERBA EM200 (Transasia Biomedical Ltd.).[18]

Statistical Analysis

Statistical analysis was done using the Statistical Package for the Social Sciences version (SPSS) 16.0 (SPSS Inc, Chicago, Illinois, United States). Data were described as percentages (%) for sociodemographic characteristics (BMI, age, gender, ethnicity, smoking, alcohol intake, income distribution, and duration of the disease). The inflammatory markers were expressed as median, mean ± standard deviation (SD), and categorized into quartiles (25th, 50th, and 75th) for cases and controls. An Independent "*t*-test" was used to compare the difference between cases and controls. Spearman's correlation test was done to assess the relationship between the inflammatory markers (IL-6, hs-CRP) with glycemic status, BMI, and duration of the disease. $p > 0.05$ was considered significant.

Results

Our study included 100 T2DM patients and 50 healthy participants (n = 150). Table 1 represents demographic characteristics among T2DM patients. The mean age of the study population was 52.39 ± 8.635 years. The highest number of patients with T2DM were in between the age-group of 45 and 55 years (36%) and a similar percentage was observed in between the age-group of ≥56 and 65 years (35.3%). More males were found to be suffering from T2DM (n = 57, 57%) than females (n = 43, 43%). The predominant ethnic communities of Sikkim are Bhutias, Lepchas, and Nepalese. In the study, people suffering from diabetes come from the abovementioned ethnic background and race. Nepalese constituted the highest number of cases of diabetes (57%) where 41% of patients had a monthly income of ≥10,000 with the majority hailing from the urban residents (64%). Smoking increases the risk for cardiovascular complications among T2DM. We observed a high number of nonsmokers (74%) in diabetic patients than smokers (26%) and alcohol consumption (29%) was comparatively less than expected.

Biochemical parameters (FBS and PPBS, HbA1c), inflammatory markers (hs-CRP and IL-6), and BMI were compared between the cases and the control (Table 2). Obesity (≥30 kg/m^2) was found to be more in diabetic patients (24.13 ± 3.14 kg/m^2) than in the control groups (23.24 ± 3.23 kg/m^2) but was statistically not significant. About 52% of diabetes patients had normal weight and 3% belonged to obese class I, whereas in the control group, 28% were overweight and 3% had obesity (Table 1). The mean concentration of FBS and PPBS levels was significantly ($p < 0.001$) high in T2DM (FBS = 140 ± 57.41 mg/dL, PPBS = 230.17 ± 90.34 mg/dL) than in the healthy controls (FBS = 80.10 ± 9.34, PBS = 103.46 ± 18.37 mg/dL). We also observed a high ($p < 0.001$) HbA1c in the T2D patients (6.72 ± 5.88%) than in the healthy subjects (2.63 ± 0.69). Inflammatory markers like hs-CRP are an acute phase reactant secreted by the liver in response to any inflammation *via* IL-6-mediated pathway and are involved in the development of insulin resistance. The concentrations of hs-CRP in T2DM patients (median = 5.8) were higher compared to the controls (median: 1.55) ($p < 0.001$). Similarly, the blood concentration of proinflammatory cytokine IL-6 which is known to modulate glucose metabolism was also increased significantly in the cases (2.4) than the control (0.80) ($p < 0.001$). Both inflammatory markers (hs-CRP and IL-6) were found to be high in three quartiles (25th, 50th, and 75th) in the T2DM patients than the control (Table 3).

Table 1: Demographic characteristics of patients with T2DM and healthy controls

Characteristics	*Number of patients (%)*
Age (years)	
35–45	28.7%
≥46–55	36.0%
≥56–65	35.3%
Gender	
Male	57%
Female	43%
Ethnicity	
Bhutia	33%
Lepcha	10%
Nepali	57%
Income	
≤Rs. 4,999	34%
Rs. 5,000–9,999	25%
Rs. ≥10,000	41%
Duration of disease	
0–5 years	18%
≥6–10 years	41%
≥11–15 years	35%
≥16–20 years	4%
>20 years	2%
BMI (kg/m^2)	
<18.5	4%
18.5–24.9	52%
25–29.9	40%
30–34.9	3%
35–39.9	1%
Smoking	
Yes	26%
No	74%
Alcohol	
Yes	29%
No	71%
Residential area	
Urban	59.0%
Rural	41.0%

Table 2: Comparison of various biochemical parameters in T2DM and controls

Parameters	*Cases (n = 100) mean ± SD*	*Control (n = 50) mean ± SD*	*p-value*
BMI (kg/m^2)	24.13 ± 3.17*	23.24 ± 3.23	NS
FBS (mg/dL)	140.34 ± 57.41	80.10 + 9.34	<0.001***
PPBS (mg/dL)	230.17 ± 90.34	103.46 ±18.37	<0.001***
HbA1c (%)	6.72 ± 5.88	2.63 ± 0.69	<0.001***

*p (<0.05) significant; ***p (<0.001) highly significant; *p (>0.5) not significant (NS)

Table 3: Comparison of hs-CRP and IL-6 between T2DM patients and controls in quartiles, median and mean ± SD

	Hs-CRP		*IL-6*		*p-value*
	Case (100)	*Control (50)*	*Case (100)*	*Control (50)*	
Mean ± SD	6.85 ± 5.29***	1.83 ± 1.2	2.67 ± 1.92***	0.88 ± 0.53	<0.001***
Median	5.8	1.55	2.40	0.80	
25th	3.32	0.98	1.83	0.60	
50th	5.8	1.55	2.40	0.80	
75th	7.98	2.65	2.90	1.20	

*p (<0.05) significant; ***p (<0.001) highly significant; *p (>0.5) not significant (NS)

Table 4: Correlation of IL-6 and hs-CRP with HbA1c, BMI, and duration of the disease

Parameters	*IL-6*		*Hs-CRP*	
	r-value	*p-value*	*r-value*	*p-value*
HbA1c (%)	0.047	>0.05*	0.140	>0.05*
BMI (kg/m^2)	–0.102	>0.05*	0.055	>0.05*
Duration of disease (years)	–0.016	>0.05	0.057	>0.05*

***p (<0.001) highly significant; *p > 0.05 not significant

To understand the relationship between the duration of the disease with the inflammatory markers, the duration of the patients living with T2DM was categorized as 5-year class intervals. Our study recorded the highest number of patients living with diabetes for >5–10 years (41%) (Table 1). There was no significant correlation significant between the inflammatory makers (hs-CRP and IL-6) with the disease duration ($r = 0.057, -0.016$ and $p > 0.05$), BMI ($r = -0.102, p > 0.05$) and the glycemic status ($r = 0.047, p > 0.05$) (Table 4).

Discussion

In the present study, T2DM was mostly observed between 45 and 55 years of age, which is consistent with various studies suggesting that T2DM increases with age progression, ultimately leading to disturbances in metabolic homeostasis.[18,19]

Males are at a higher risk for the development of T2DM than females. This difference in risk may be attributed to a larger amount of visceral fat deposition or different sociocultural practices, such as varied forms of nutrition, lifestyles, and approaches towards prevention and treatment of the disease.[19] More males (57%) were diagnosed with T2DM than females (43%) and this is similar to a study reported from the neighboring northeast state of Assam.[20] Ethnicity and genetic and environmental factors are known to affect the risk related to the pathogenesis of T2DM. Among the ethnic communities, Nepalese (57%) were the highest with T2DM, and this is in proportion to the ethnic distribution of Sikkim as they account for the major ethnic group. Untreated diabetes is associated with an individual's work productivity which may further affect their income. T2DM was more observed in those with a monthly income ≥Rs. 10,000 which could be contributed to rapid social and economic transformation leading to unhealthy eating habits and a sedentary lifestyle.[2]

About 29% of diabetic patients consumed alcohol and only 26% were smokers among the cases. Epidemiological studies have demonstrated a strong correlation between cigarette smokers and the risk of T2DM[21] though limited studies have been conducted in the northeastern part of Sikkim.

It is estimated that up to 25% of diabetic patients have systemic inflammation which starts much earlier than the development of the disease suggesting the presence of inflammatory activity before the development of T2DM.[22] We observed 41% of patients had the disease for 6–10 years which was the highest in our study. None of the inflammatory makers were found to be correlated with the disease duration and the glycemic status and a similar result has been observed.[23] Patients on statin were included in the study and it is known to affect the level of inflammatory markers and glycemia status.[24]

Most T2DM patients are either overweight or obese. Intensive lifestyle modifications such as diet and physical activity can aid in the treatment and management of the disease. The study revealed a high percentage of overweight (52%) and obese (40%) T2DM patients. Obesity is closely associated with the pathogenesis of T2DM due to its role in inducing inflammation. The "Asian Indian Phenotype" is characterized by increased insulin resistance and high waist circumference despite low BMI levels, making this population more prone to diabetes.[25] The study reported a high BMI in diabetic patients than the controls but with no association which is consistent with the study done in Sikkim.[26]

Inflammation plays a key role in the impairment of glucose metabolism by decreasing insulin sensitivity and increasing inflammatory biomarkers. Association between these markers with T2DM has shown inconsistent results in multiethnic cohort studies.[27,28] We reported a high concentration of hs-CRP and IL-6 among the ethnic group with T2DM. This may suggest an ethnic variation in the levels of circulating CRP and IL-6 with T2DM which could be due to obesity and body fat distribution. Inflammation is closely associated with obesity caused due to high-fat diet which successively leads to T2DM which might be related to ethnic disparities.[28]

Limitations

The study employed an observational cross-sectional design rather than a classic case-control study. For logistic efficiency, 50 individuals without the disease in question were selected and compared with 100 individuals who met the diagnostic criteria for T2DM. This approach was adopted due to the time constraints of the MD student conducting the study and resource limitations preventing the inclusion of more controls. While an influence of monthly income on T2DM was observed, other socioeconomic variables such as occupation, family history, marital status, and educational qualifications were not included in the study.

Conclusion

This study aimed to estimate inflammatory markers and correlate them with the demographic characteristics of T2DM patients

belonging to the ethnic communities of Sikkim. T2DM incidence increases with age progression, with males being predominantly affected, and Nepalis comprised the largest ethnic group with the disease. Although patients on statin therapy were included, the specific roles and relationships of statins were not within the scope of the current study. However, we suggest further studies to understand the role and relationship of statins among patients and the potential ethnic differences in inflammatory marker levels due to variations in body fat distribution.

Acknowledgment

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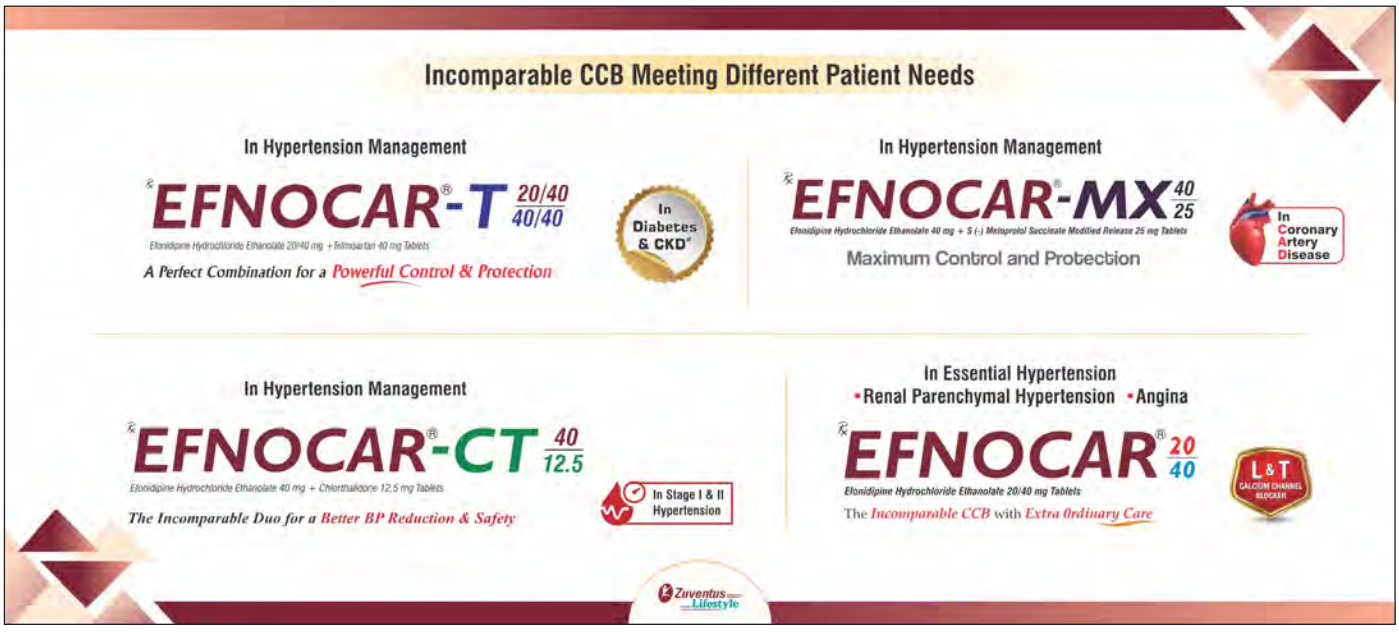

ORIGINAL ARTICLE

Evaluation of the SARC-F Questionnaire as a Diagnostic Tool for Sarcopenia in Geriatric Age-group in India

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Abstract

Introduction: With medical science advancing in leaps and bounds, average lifespan is now trending upward, and we are now facing an increasing prevalence of diseases of the elderly, sarcopenia being one of them. Unfortunately, sarcopenia, especially in India, remains to be frequently overlooked, underdiagnosed, and largely understudied. One of the greatest hindrances to the diagnosis of sarcopenia is high costs and limited availability of diagnostic modalities such as magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry (DEXA) scan. Accessible, feasible, and affordable means to diagnose sarcopenia is thus the need of the hour.

Materials and methods: We performed a cross-sectional observational study among 300 patients aged 65 years or above (including both outpatient and inpatient departments) at MM Institute of Medical Sciences, Mullana between June 2021 and June 2022. Patients were evaluated as per the European Working Group for Sarcopenia in Older People (EWGSOP) algorithm using bioelectrical impedance analysis (BIA) and the results were compared with results of the SARC-F questionnaire. Statistical analyses were then carried out using IBM Statistical Package for the Social Sciences (SPSS) Statistics version 26.

Results: Out of 300 patients, 56 (18.7%) were sarcopenic. Sarcopenia showed no significant association with sex ($p = 0.74$). SARC-F showed a sensitivity of 73.2% and a specificity of 37.3% with a positive predictive value of 86.51% and a negative predictive value of 32.84% in diagnosing sarcopenia. SARC-F showed good internal reliability with a Cronbach's $\alpha > 0.7$.

Conclusion: The SARC-F questionnaire can be used as a bedside screening tool for sarcopenia, especially in a developing country like India where diagnostic resources are frequently scarce.

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Introduction

Change is the only constant, and the era we live in is consistent with this notion in more ways than one. With the scope of healthcare jumping leaps and bounds, the demographic structure of the world is evolving. The median age of the world population is increasing year by year, and life expectancy has come a long way from what it used to be in the ides of 20th century.[1] A dilution to this bliss of longer life is the fact that scientific research, in this tangent, has somewhat been unkempt in the sense that though novel strategies and therapies for various diseases have been developed, the challenges of old age have been given somewhat of a cold shoulder. One obvious by-product of a greater lifespan is an increase in the prevalence of chronic diseases such as hypertension, diabetes mellitus, and cancer among others.[2] Extensive research in the domain of said diseases have put forth novel treatment strategies, enabling the patients to dodge the mortality and morbidity associated with these diseases for longer, but the road remains bumpy in dearth of a good quality of life. The blues of impending death have been deferred, but the pink of health still remains a pipe dream for most members of the geriatric population. A fruitful strategy in the domain of healthy aging and aging well is much warranted.

Though frailty has been studied and addressed as a complex geriatric syndrome, sarcopenia as an entity has received much less attention. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength and it is strictly correlated with physical disability, poor quality of life, and death.[3] It forms one of the founding stones that support the geriatric giant syndromes. While instability and immobility are obvious ramifications, there are studies that show a direct linkage between sarcopenia and cognitive status of community-dwelling elders. Various studies have shown an almost ubiquitous presence of sarcopenia in patients with atherosclerotic manifestations in the form of cardiovascular disease, ischemic stroke, and diabetes. Sarcopenia, by itself, has been shown to be an independent risk factor for mortality.[4–16]

Research workers and scientists have now recognized sarcopenia as an area that needs extensive research and much work is being done on the subject globally. However, there's a dearth of data and research on the topic. Studies to estimate the prevalence of sarcopenia among the geriatric population are needed to further quantify this relatively new entity and to study its effects on the Indian population. There is, however, a logistical fence when it comes to the diagnosis of this condition. Gold standard tests—computed tomography (CT) scan and magnetic resonance imaging (MRI) are expensive, nonportable and cumbersome, and dual energy X-ray absorptiometry (DEXA) scan is not readily available. Given the target geriatric age-group, there's a need for developing a reliable tool for bedside assessment of sarcopenia. Various tests and questionnaires have been developed for the bedside screening and diagnosis of sarcopenia, but the lack of data and adequate studies present a challenge in adopting a single method for diagnosis.

Materials and Methods

We adopted an observational cross-sectional design, and the study was conducted for a total duration of 1 year between June 2021 and June 2022 after seeking approval from the Institutional Ethics Committee. A total of 300 patients (from both inpatient and outpatient departments) meeting the inclusion criteria were enrolled in the study. Table 1 shows the inclusion and exclusion criteria for the study.

Sample Size

Sample size was calculated according to the formula, $4pq/d^2$, where p is the prevalence, q is 1 – p and d refers to the maximum permissible error.

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Though no large-scale studies were done to calculate the prevalence of sarcopenia in India, we took the prevalence as per the Sarcopenia-Chandigarh Urban Bone Epidemiological Study (Sarco-CUBES), and it was taken to be 20.1% and maximum permissible error was set at 5%. Extrapolating the values, the sample size came out to be 265, which was rounded off to 300.

Study Tools

We used the Omron HBF-222T body composition analyzer in the current study. The machine has an accuracy of ±0.4 kg (2.0–40.0 kg)/±1% (40.0–150 kg) while measuring body weight and an accuracy of 3.5% while measuring muscle percentage. Baseline Camry 90 kg digital handheld dynamometer was used in the study. The dynamometer has a least count of 100 gm.

SARC-F Questionnaire

The SARC-F questionnaire[17] (Fig. 1) was developed by Malmstrom and Morley as a rapid diagnostic tool for sarcopenia. The questionnaire consists of five questions which address the five domains of strength (S), assistance in walking (A), rising from a chair (R), climbing stairs (C), and history of falls (F). A score of four and above is diagnosed as sarcopenia.

Methodology

After approval from the Institutional Ethics Committee, five components—strength (S), assistance with walking (A), rising from a chair (R), climbing stairs (C), and falls (F) were self-recorded by the patient according to the SARC-F questionnaire (Fig. 2). We translated the SARC-F questionnaire to Hindi and produced a bilingual proforma (Appendix 1), keeping in mind the local demographic. Illiterate subjects or participants who were unable to read were interviewed. Subjects were then evaluated according to the European Working Group for Sarcopenia in Older People (EWGSOP) algorithm[18] (Fig. 2). First, the subject was asked to walk at a regular pace through a 6-m course—the subject accelerated in the first meter; the gait speed was measured in the mid-4-m zone and the subject decelerated in the final meter. After evaluation of gait speed, handgrip strength was measured with a handheld dynamometer with least count of 0.1 kg (Baseline Camry 90 kg dynamometer). Patient was asked to press the dynamometer with full force with the arm and shoulder extended in the dominant hand and maximum reading was recorded. A handgrip strength of <27 kg for males and <16 kg for females was deemed as dynapenic. Subject then underwent bioelectrical impedance analysis (BIA) for estimation of skeletal muscle mass (using Omron HBF-222T body composition analyzer). Appendicular skeletal muscle mass (ASM) (≤20 kg for males and ≤15 kg for females) was diagnosed as sarcopenia (cutoff values as suggested by the EWGSOP).

Table 1: Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
Elderly patients falling in the geriatric age-group (≥65 years) consenting to participate in the study.	Critically ill/hemodynamically unstable patients Patients suffering from any kind of malignancy/ cancer cachexia Patients unwilling to participate

The SARC-F Questionnaire

Each question is to be answered on a scale of 0–2, where,

0 refers to no difficulty,

1 refers to some difficulty, and

2 refers to inability

Question	Score		
	0	1	2
Q.1. How much difficulty do you have in lifting and carrying a weight of 10 pounds? **[S]**			
Q.2. How much difficulty do you have in walking across a room? **[A]**			
Q.3. How much difficulty do you have in transferring from a chair to bed? **[R]**			
Q.4. How much difficulty do you have in climbing a flight of 10 stairs? **[C]**			
Q.5. How many times have you fallen in the last year? (0 falls: 0/1-3 falls:1/>3 falls: 2) **[F]**			

A score ≥24 is diagnosed as Sarcopenia.

Fig. 1: The SARC-F questionnaire

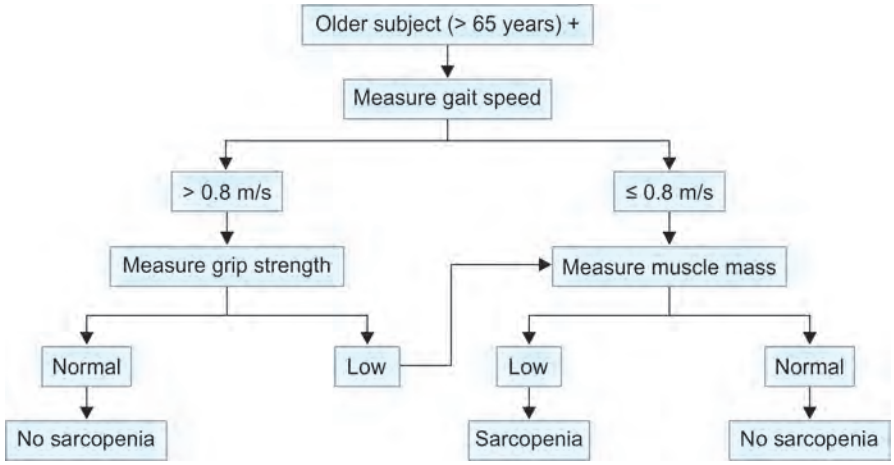

Fig. 2: The EWGSOP algorithm for diagnosis of sarcopenia; Source: Cruz-Jentoft et al.[18]

Results

A total of 300 patients aged 65 years or above were enrolled in the study of which 57.3% (n = 172) were males and 42.7% (n = 128) were females. Mean age (in years) was 71.49 ± 6.29, with a minimum of 65 years and maximum of 97 years. Characteristics of the study population are mentioned in Table 2.

Overall prevalence of sarcopenia was found to be 18.7% (N = 56) in the study population. A total of 25 females and 31 males were found to be sarcopenic (Fig. 3) and no significant relationship between sex and sarcopenia was seen (p = 0.74).

The prevalence of dynapenia as per the defined criterion was found to be 87% (n = 261) in the study population. About 95.3% (n = 122) of the enrolled females were found to be dynapenic while 80.8% (n = 139) males were found to be dynapenic (Fig. 4). Dynapenia was found to be significantly associated with sex (p = 0.00).

Mean score on the SARC-F questionnaire was 4.52 ± 2.26 across the study population, with a median score of 4. Females had a higher mean SARC-F score (5.4) than males (3.9). Question-wise analysis of frequency of responses to the SARC-F questionnaire is shown in Table 3 and Figure 5. Carrying a weight of 4.5 kg (p = 0.00), walking across a room (0.00) and climbing a flight of 10 stairs (0.02) showed a significant association with sarcopenia, while the relationship between sarcopenia and difficulty in transferring from a chair to bed was nonsignificant (p = 0.193). Sarcopenia was also found to be significantly associated with an increasing number of falls (p = 0.09).

At the recommended cutoff for diagnosis of sarcopenia, the SARC-F questionnaire predicted 64.67% (n = 194) of the subjects to be sarcopenic with a sensitivity of 73.2% and a specificity of 37.3% with a positive predictive value of 86.51% and a negative

Table 2: Characteristics of study population

Characteristic	*Cohort*	*Sarcopenic*	*Nonsarcopenic*
Age			
<70	131	24	107
70–80	148	25	123
>80	21	7	14
Sex			
Female	128	25	103
Male	172	31	141
Study variables			
Weight (kg)	59.43	45.65	62.59
Mean gait speed (m/second)	0.54	0.47	0.56
Mean handgrip strength (kg)	14.14	9.9	15.1
Mean skeletal muscle percentage (%)	36.5	30.72	37.87

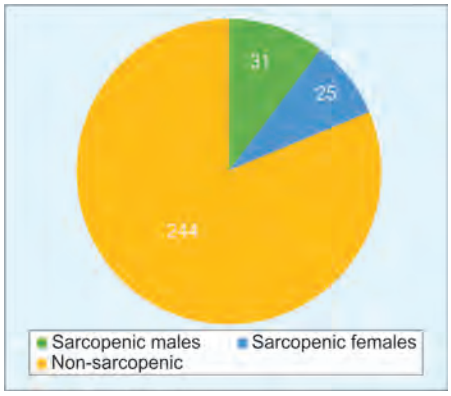

Fig. 3: Prevalence of sarcopenia in the study population

Table 3: Question-wise analysis of responses

Question	*Frequency of response*			*p-value*
	0 N (%)	*1 N (%)*	*2 N (%)*	
Difficulty in lifting and carrying a weight of ~4.5 kgs (10 lbs)	69 (23%)	148 (49.3%)	83 (27.7%)	**0.00**
Difficulty in walking across a room	72 (24%)	191 (63.7%)	37 (12.3%)	**0.00**
Difficulty in transferring from a chair to bed	94 (31.3%)	160 (53.3%)	46 (15.3%)	0.193
Difficulty in climbing a flight of 10 stairs	27 (9%)	161 (53.7%)	112 (37.3%)	**0.02**
Number of falls in past year	167 (55.7)	126 (42%)	7 (2.3%)	

kg: kilograms, lbs: pounds; Bold represents significant p values (<0.05)

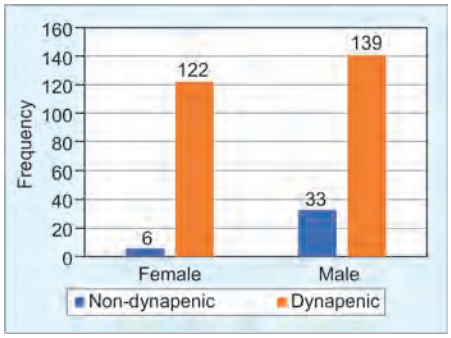

Fig. 4: Frequency of dynapenia according to sex

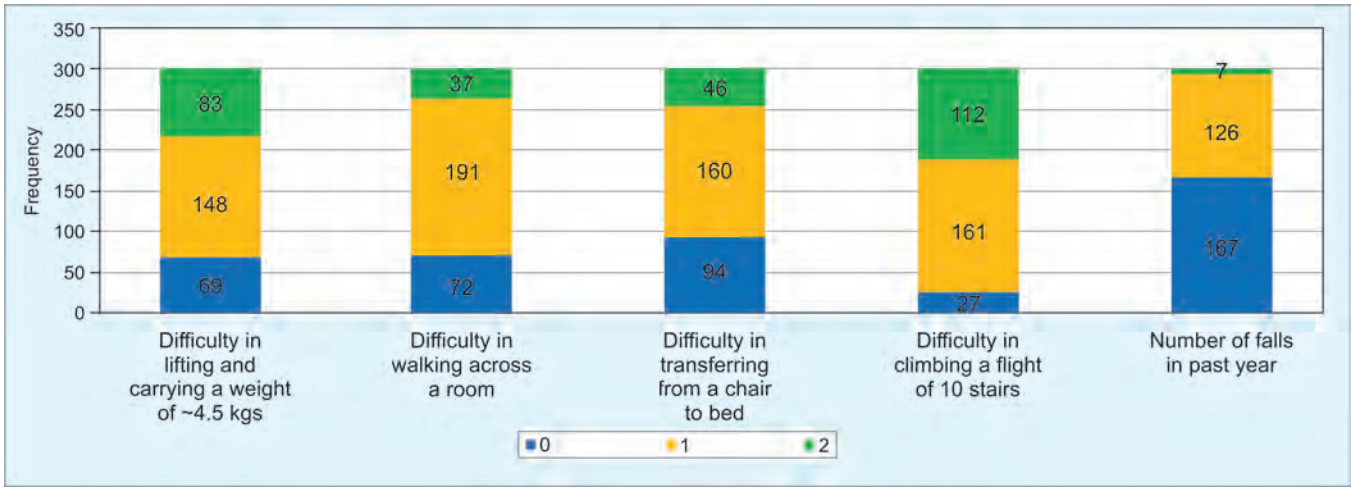

Fig. 5: Frequency of responses (question-wise) on the SARC-F questionnaire

predictive value of 32.84% (Table 4). Receiver operating characteristic (ROC) curve of SARC-F questionnaire is shown in Figure 6.

The area under the curve (AUC) was found to be 0.638. SARC-F questionnaire had a significant association with diagnosis of sarcopenia ($p = 0.00$) (Table 5).

Four out of five question of the SARC-F questionnaire showed high degree of correlation (Pearson coefficient, $r > 0.5$) while number of falls showed a moderate degree of correlation ($r = 0.46$). The questionnaire was validated for a maximum permissible error of 5% ($p < 0.05$ for each of the questions) (Table 6).

SARC-F questionnaire was found to have an acceptable reliability with a Cronbach's α of 0.767 (greater than 0.7 is acceptable).

Discussion

Not many studies have been conducted in India regarding sarcopenia. Our study estimated the prevalence of sarcopenia and dynapenia in the geriatric age-group and included admitted patients as well as patients visiting the outpatient department(s); no such study had been done till the time of writing this article. In a resource starved and overburdened healthcare setting like India, diseases of relatively novel interest such as sarcopenia are often overlooked. The unavailability of facilities such as MRI and DEXA in addition to their expensive costs and requirement for cumbersome equipment further pushes the interest into the abyss. Thus, a need for a mass-feasible and accurate method for diagnosis for sarcopenia is warranted. Studies to validate the SARC-F questionnaire have been conducted in Japan[19] and in other parts of the world,[20] but no such study regarding any of the available questionnaires (SARC-F, SARC-CalF, MSRA-5, MSRA-7, etc.) had been done in India. We selected the SARC-F questionnaire in our study as it was the most widely accepted and validated questionnaire worldwide.

We evaluated the SARC-F questionnaire against parametric data obtained by BIA. We chose BIA for our study as it is more readily available, relatively inexpensive, and acceptable by the patient. Facility for DEXA scan was not available at our institution at the time of our study and MRI, albeit available was expensive, time consuming, and not always consented to. BIA has been shown to be comparable to MRI for the diagnosis of sarcopenia.[21]

Mean gait speed (in m/second) was found to be 0.54 ± 0.28. Gait speed was found to be significantly related to handgrip strength ($p = 0.04$). This bodes well with the findings of a study conducted by López-Teros et al. in Mexico.[22] Sex was not found to be significantly associated with gait speed ($p = 0.054$).

Two studies were conducted in Southern India to estimate the prevalence of sarcopenia: In a study conducted by Shaikh et al. in elderly people aged 60 years and above in Dakshin Kannada district of Karnataka, prevalence of sarcopenia was found to be 14.2%.[23] This study used the Lee formula for calculation of ASM.[23]

$$ASM = [0.244 \times body\ weight\ (in\ kg)] + [7.8 \times height\ (in\ meters)] + (6.6 \times gender) - (0.098 \times age) + (race - 3.3)\ (use - 1.2\ for\ Asian\ race]$$

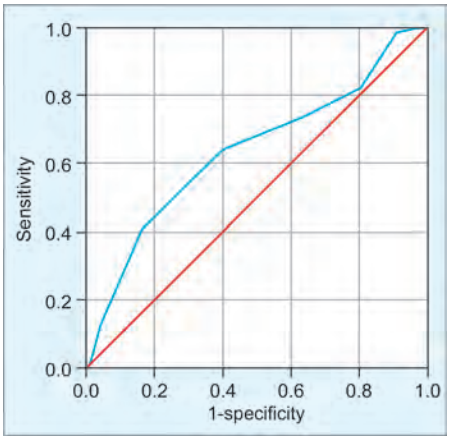

Fig. 6: Receiver operating characteristic curve of SARC-F questionnaire in the diagnosis of sarcopenia

Table 4: Sensitivity and specificity analysis of SARC-F questionnaire in detecting sarcopenia. Entries in bold correspond to the recommended cutoff

Positive if greater than or equal to	*Sensitivity*	*1—specificity*	*Specificity*	*Youden Index*
1	1.000	0.980	0.020	0.020
2	0.982	0.906	0.094	0.076
3	0.821	0.803	0.197	0.018
4	**0.732**	**0.627**	**0.373**	**0.105**
5	0.643	0.402	0.598	0.241
6	0.518	0.275	0.725	0.243
7	0.411	0.164	0.836	0.247
8	0.232	0.090	0.910	0.142
9	0.125	0.041	0.959	0.084
10	0.018	0.012	0.988	0.006

Bold represents the sensitivity and specificity values at the recommended minimum cut-off of 4 in the SARC-F questionnaire

Table 5: Area under the curve

Area	*Standard error*	*p-value*	*95% confidence interval*	
			Lower bound	*Upper bound*
0.638	0.044	**0.001**	0.551	0.724

p value highlighted in bold represents statistical significance

Table 6: Validity and correlations of the SARC-F questionnaire

		S	*A*	*R*	*C*	*F*	*SARC-F*
S	Pearson correlation	1	0.46**	0.48**	0.56**	0.17**	0.77**
	p-value		0.00	0.00	0.00	0.00	0.00
A	Pearson correlation	0.47**	1	0.60**	0.52**	0.23**	0.78**
	p-value	0.00		0.00	0.00	0.00	0.00
R	Pearson correlation	0.48**	0.60**	1	0.52**	0.22**	0.79**
	p-value	0.00	0.00		0.00	0.00	0.00
C	Pearson correlation	0.56**	0.52**	0.52**	1	0.14*	0.77**
	p-value	0.00	0.00	0.00		0.01	0.00
F	Pearson correlation	0.17**	0.23**	0.22**	0.14*	1	0.46**
	p-value	0.00	0.00	0.00	0.01		0.00

*, correlation is significant at the 0.05 level (two-tailed); **, correlation is significant at the 0.01 level (two-tailed); A, assistance in walking; C, difficulty in climbing stairs; F, number of falls; R, rise from chair; S, strength

No study to validate the use of Lee formula in the Indian population or to assess its accuracy against MRI could be found at the time of writing this article. In another study conducted by Rahman et al. in people aged 60 year and above, the prevalence was found to be as high as 39.2%.[24] This study utilized DEXA scanning for quantification of skeletal muscle mass. The study also found sarcopenia to be significantly associated with sex (males being at a higher risk than females).[24] Both these studies (Shaikh et al. and Rahman et al.)[23,24] utilized different methods for estimation of skeletal muscle mass and yielded vastly different results, even though both were conducted in the Southern part of India. Our study found the prevalence to be 18.7% and was conducted using a diagnostic modality comparable to MRI,[21] however, no statistically significant correlation of sex with sarcopenia was seen ($p = 0.74$). Our study had a larger sample size than any study conducted in India (aforementioned studies included) to determine the prevalence of sarcopenia and utilized BIA for the confirmation of sarcopenia while validating the SARC-F questionnaire. However, all these studies (present study included) utilized values from the European recommendations. Significant physical variations in the form of average weight, height, and cultural disparities with respect to staples and meals and socioeconomic backgrounds exist between India and the more developed European countries. Large scale studies to determine contextual Indian values for handgrip strength, gait speed and appendicular skeletal mass are required for a more accurate diagnosis of sarcopenia.

Dynapenia was found to be present in 92.3% ($n = 277$) of the study population. Handgrip strength was found to be significantly correlated with sex ($p = 0.00$) and females were more frequently found to be dynapenic than males (99.2 vs 87.2%).

The SARC-F questionnaire showed a sensitivity of 73.2% and a specificity of 37.3% in the current study. The questionnaire had a sensitivity of 41.1% and a specificity of 81.1% when the diagnostic cutoff point was set to greater than or equal to seven. The Cronbach's α for the SARC-F questionnaire was determined as 0.767, suggesting acceptable internal validity. In the Korean Frailty and Aging Cohort Study,[25] SARC-F showed a high specificity (96.6–98% in males, 85–87.7% in females), but poor sensitivity. In a study conducted by Ida et al.[26] in diabetic patients in Japan, a similar finding of poor sensitivity and high specificity was found. Similar findings were found in studies conducted in Hong Kong,[27] Mexico,[28] and France.[29] All these studies exhibited good internal validity except for the Mexican study by Parra-Rodríguez et al.[28] which had a Cronbach's α of 0.641. An interesting thing to note here is that in each of the abovementioned studies, majority of these SARC-F questionnaires were self-administered, whereas in the present study, which was conducted in a rural tertiary care center, majority of the subjects were illiterate and had to be interviewed, which could have introduced interviewer bias.

Conclusion

Sarcopenia continues to be an underdiagnosed condition in India. Tools for rapid, inexpensive, and accurate diagnosis are the need of the hour. Our study utilized the diagnostic criteria put forth by the EWGSOP and validated the SARC-F questionnaire for the Indian population. The SARC-F questionnaire, thus, can be used as a bedside screening tool for sarcopenia, but has its own shortcomings. Larger studies to define cutoffs for the Indian population are also recommended.

Disclosures

Human Subjects

Consent was obtained by all participants in this study.

Ethical Approval

Study was approved by the Institutional Ethics Committee.

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Appendix 1: Study proforma with bilingual questionnaire used in the study

TO EVALUATE THE VALIDITY OF THE SARC-F QUESTIONNAIRE IN THE DIAGNOSIS OF SARCOPENIA IN GERIATRIC POPULATION IN CONJUNCTION WITH HAND-GRIP STRENGTH AND BIOELECTRICAL IMPEDANCE ANALYSIS IN A RURAL TERTIARY CARE HOSPITAL

Proforma for participation in the study
अध्ययन में भाग लेने हेतु प्रपत्र

Name / नाम

Age / उम्र

UMR

Sex / लिंग

Hypertension (yes/no) उच्च रक्तचाप (हां/नहीं)	
Diabetes (yes/no) मधुमेह (हां/नहीं)	

Tick (✓) in the appropriate column
उचित स्थान पर (✓) का चिन्ह लगायें

Question	Level of difficulty		
	No difficulty कोई कठिनाई नहीं 0	Some difficulty कुछ कठिनाई 1	Unable असमर्थ 2
How much difficulty do you have in lifting and carrying a weight of 10lbs (~4.5 kgs)? लगभग 4.5 किलोग्राम वजन उठाने में आपको कितनी कठिनाई का सामना करना पड़ता है?			
How much difficulty do you have in walking across a room? आपको कमरे के एक कोने से दूसरे कोने तक चलने में कितनी कठिनाई होती है?			
How much difficulty do you have in transferring from a chair to bed? आपको कुर्सी से बिस्तर पर जाने में कितनी कठिनाई होती है?			
How much difficulty do you have in climbing a flight of 10 stairs? 10 सीढ़ियाँ चढ़ने में आपको कितनी कठिनाई होती है?			

How many times have you had a fall in the last year? पिछले एक साल में आप कितनी बार गिरे हैं?	

ORIGINAL ARTICLE

Neutrophil-to-lymphocyte Ratio as a Marker for Diagnosis and Prognostication of Sepsis

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Abstract

Purpose: Exploring the ideal marker for early diagnosis and prognosis of sepsis is crucial due to limitations of available sepsis indicators. Hence, we aimed to evaluate the neutrophil-to-lymphocyte ratio (NLR) as a diagnostic and prognostic marker of sepsis.

Materials and methods: This prospective case-control study was conducted at a tertiary care teaching public hospital. NLR values among cases and controls were compared for diagnosis. Among cases, serial trends in NLR values, outcome (survival or death), and various parameters [such as Sequential Organ Failure Assessment (SOFA) score, duration of intensive care unit (ICU) stay, etc.] were compared between survivors and nonsurvivors for prognosis. Analysis was performed using MS Excel and PSPP version 1.0.1.

Results: A total of 120 patients (60 cases and 60 controls) were analyzed. The NLR among cases was significantly higher ($p = 1.31 \times 10^{-16}$) than in controls. Using binary logistic regression, a high NLR was found to be a statistically significant predictor of sepsis category ($p = 2.25 \times 10^{-5}$). The association of various variables among survivors and nonsurvivors of cases showed statistically significant differences: NLR ($p = 5.29 \times 10^{-5}$), mean = 13.27, interquartile range (IQR) = 5.90, *z*-value = –4.042), C-reactive protein (CRP) ($p = 4.80 \times 10^{-7}$), mean = 74.40, IQR = 21.30, *z*-value = –5.034), D-dimer ($p = 4.32 \times 10^{-8}$), mean = 7.09, IQR = 0.88, *z*-value = –5.477), SOFA score ($p = 0.00118$, mean = 8.50, IQR = 3.00, *z*-value = –3.244), and duration of hospital stay ($p = 0.03578$, mean = 13.45, IQR = 8.00, *z*-value = –2.099).

Conclusion: The NLR emerges as a valuable marker for both diagnosis and prognosis in sepsis. Elevated NLR levels aid in diagnosing sepsis at very early stages, and the trend of NLR demonstrates a dynamic course throughout the disease process. Persistently elevated NLR and high NLR values correlate with poor outcomes in sepsis. Additionally, NLR can be correlated with other prognostic markers of sepsis and mortality. Therefore, we recommend the utilization of NLR as a quick, easy, and cost-effective marker for both early diagnosis and regular prognostication of sepsis.

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Introduction

Sepsis represents a complex disease continuum ranging from systemic inflammatory response syndrome (SIRS), through sepsis and septic shock, to multiorgan dysfunction syndrome (MODS), all of which carry a high risk of mortality. According to Sepsis-3 criteria, sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1] Millions of people are affected worldwide due to sepsis having very high morbidity and mortality.[2–4] Improving the mortality rate related to sepsis is a global challenge. In the Indian public health system, intensive care units (ICUs) face significant strain, with sepsis being a leading cause of high and prolonged bed occupancy, exacerbated by limited resources. Therefore, it is crucial to reduce sepsis-related morbidity and mortality. Prompt diagnosis and management are paramount, involving the implementation of sepsis bundle components and regular prognostication.

Numerous screening tools, markers, and scoring systems have been evaluated for the diagnosis, risk prediction, and outcome assessment of sepsis; however, they possess certain limitations. For instance, the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) exhibit poor sensitivity and specificity.[3,5,6] Procalcitonin, D-dimer, and CD14 are expensive and impractical options, while microbiological cultures are time-consuming and prone to high false-negative rates. The Modified Early Warning Score (MEWS), the Sequential Organ Failure Assessment (SOFA) score, or quick SOFA (qSOFA) include components that are not consistently measured, and their surveillance methods are complex and time-consuming.[3,4] Therefore, the search for an ideal marker that is quick, readily available, and applicable across various settings such as wards, emergency departments, and ICUs for the diagnosis and prognostication of sepsis continues.

The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory biomarker that reflects the dynamic balance of the immune system. It is defined as the absolute number of neutrophils divided by the absolute number of lymphocytes, calculated based on a complete blood count (CBC). NLR is purported to be one of the earliest indicators of systemic inflammation and is also used for monitoring prognosis.[5] It is a quick, simple, readily accessible biomarker derived from CBC which is performed routinely and adds no extra costs.[7–9] In adults, normal NLR values are 0.78–3.53, and beyond this, it can be a predictor and a marker of inflammatory or infectious pathologies.[8] The NLR has been studied for diagnosis and/or prognosis of various diseases including sepsis and results have been encouraging.[5–9] Some studies mention the role of NLR in predicting sepsis and related mortality remains controversial.[10,11] Hence, we aimed to evaluate NLR as diagnostic and prognostic marker of sepsis at tertiary care public institute. In this prospective case-control study, we compared the NLR among cases and controls for diagnosis, and we compared serial NLR values among cases along with other parameters with the outcome for the prognostication of sepsis.

Materials and Methods

This was a prospective, observational, case-control study initiated after obtaining permission from the Institutional Ethics and Research Committee (ECARP/2019/102), and valid written informed consent was obtained from all patients. The study was conducted for a period of 18 months at a tertiary care teaching public hospital. We included patients aged >18 years of both sexes admitted to the medical ICU and wards.

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Cases with suspected and newly diagnosed cases of sepsis as per the Sepsis-3 definition were enrolled in the study.[1,2]

Patients admitted to wards for annual check-ups, monitoring, and investigations unrelated to infection or sepsis were enrolled as controls. Pregnant females, individuals with known immunological diseases or hematological malignancies, and patients on steroids or immunosuppressive therapy for >5 days were excluded from the study.

The following data were collected from all participants: demographics (age, sex), associated conditions, vital parameters including temperature (T), pulse rate (PR), respiratory rate (RR), blood pressure (BP), and SOFA score. Laboratory parameters including CBC with white blood count (WBC), absolute neutrophil and lymphocyte counts, differential count, CRP, and D-dimer were noted. NLR was calculated from the CBC as the ratio of the total neutrophil count to the total lymphocyte count. The NLR of controls was studied only once on admission, while for cases, it was studied from the time of admission to the time of discharge or death on a regular basis. The normal range for NLR was determined to be 0.78–3.53, with an NLR above 3.53 used as a cutoff for inflammation marker and for diagnosis and prognosis of sepsis. In cases, we also noted the serial trend in NLR values, SOFA score, and duration of ICU stay. The outcome of the patient was categorized as survival or death. NLR and various noted parameters were compared among survivors and nonsurvivors for prognosis.

Sample size was calculated using formula $Z^2 \times [P \times (1 - P)]$ with Z of 1.96 and precision of 0.10, using sensitivity of 81.3% of NLR for diagnosis of sepsis.[7] Where Z: z-statistics for desired level of confidence (i.e., 0.05) (1.96 for 95% CI) Z—1.96, Z-square—3.8416, P (proportion): the estimate of expected proportion with the variable of interest in the population (0.813) 0.81, $1 - P$ is 0.19, E: the precision level—0.10, E-square—0.01, $P \times (1 - P)$ is 0.152031, $Z^2 \times [P \times (1 - P)] = 0.58$, hence, the sample size (n) = 58.40. Thus, the calculated sample size was 58.40. We enrolled minimum of 60 cases and 60 controls for the present study.

Appropriate statistical software, including but not restricted to MS Excel, PSPP version 1.0.1, was used for statistical analysis. Qualitative data were represented in the form of frequency and percentage. Among qualitative data, nominal data included group category (case and control), sex of the cases, NLR level (>3.53 and ≤3.53), etc. Association between qualitative variables was assessed by Chi-squared test, with continuity correction for all 2 × 2 tables and by Fisher's exact test for all 2 × 2 tables where Chi-squared test was not valid due to small counts. In the presence of small counts in tables with more than two rows and/or columns, adjacent row and/or column data was pooled and Chi-squared test reapplied. Continuity correction was applied for all 2 × 2 tables after pooling of data. Fisher's exact test was applied for all 2 × 2 tables where p-value of continuity correction was not valid due to small counts, despite pooling of data [e.g., association between sensorium and group category (case and control)]. Among qualitative data, ordinal data included SOFA score and was represented using mean ± SD and median and interquartile range (IQR). Comparison of SOFA score between cases and controls was done using Mann–Whitney U test.

Quantitative data were represented using mean ± SD and median and IQR. Quantitative data included age, WBC count, absolute neutrophil count, absolute lymphocyte count, NLR, pulse, systolic and diastolic BP, D-dimer, and duration of hospital stay, etc. Comparison of quantitative data measured between binomial qualitative variable [group category (case and control)] was done using unpaired t-test, if the data passed "Shapiro–Wilk test Normality test" or by Mann–Whitney U test if the data failed "normality" test (e.g., comparison of age between cases and controls). Binary logistic regression was used to assess predictors of group category (case and control) as dependent variables and age, systolic BP, and NLR as independent (predictor) variables. Results were graphically represented where deemed necessary. Graphical representation was done in MS Excel package included in Microsoft Office 365. An alpha value (p-value) of ≤0.05 was used as the cutoff for statistical significance.

Table 1: Neutrophil-to-lymphocyte ratio among cases and controls

NLR level		*Group*		*Total*
		Case	*Control*	
>3.53	No.	49	4	53
	%	81.7%	6.7%	44.2%
≤3.53	No.	11	56	67
	%	18.3%	93.3%	55.8%
Total	No.	60	60	120
	%	100.0%	100.0%	100.0%
Chi-squared tests	Value	Degrees of freedom (df)	*p*-value	Association is—
Pearson Chi-square	68.431	1	1.31E-16	Significant
Continuity correction	65.424	1	6.04E-16	Significant

Results

A total of 120 participants with 60 cases and 60 controls fulfilling the inclusion criteria were analyzed in this study. Both cases and controls were comparable with respect to demographics. There was a male preponderance in sepsis cases with 43 (71.7%) males and 17 (21.3%) females, and the mean age of males was 42.883 years while that of females was 45.47 years.

A value of NLR above 3.53 was used as a cutoff for diagnosing sepsis. On comparison of NLR among cases and controls, 49 (81.7%) cases had an NLR >3.53 compared to 4 (6.7%) controls, and the mean value of NLR among cases was 8.87 ± 7.54, while among controls, it was 1.96 ± 0.73. Thus, NLR among cases was significantly higher ($p = 1.31 \times 10^{-16}$) than the control group (Table 1). There was a significantly higher WBC count among cases compared to controls (p-value $= 2.73 \times 10^{-22}$). Comparison of various parameters among cases and controls are depicted in Table 2.

Using binary logistic regression to assess predictors of group category, which is case and control, between dependent variables and age, systolic BP, and NLR as independent (predictor) variables, high NLR was found to be a statistically significant predictor of sepsis case group category with a p-value ($p = 2.25 \times 10^{-5}$) (Table 3).

On evaluating the association of NLR with the outcome of cases, namely survival and death, a significant difference was demonstrated [Chi-squared test ($p = 0.036$) and Fisher's exact test ($p = 0.043$)] between outcomes in cases with NLR >3.53 and in cases with NLR ≤3.53 (Table 4). Among sepsis patients, serial values of NLR were analyzed, and we observed that a rising NLR trend was associated with a poor outcome, while a decrease in NLR was associated with a better outcome. The mean value of NLR is 13.27 and 6.32 among cases which did not survive and cases which recovered, respectively.

Association of various variables with survivors and nonsurvivors of cases was evaluated, and a statistically significant difference was found between the following parameters: NLR ($p = 5.29 \times 10^{-5}$, mean = 13.27, median = 5.33, IQR = 5.90), CRP ($p = 4.80 \times 10^{-7}$, mean = 74.40, median = 32.50, IQR = 21.30),

D-dimer ($p = 4.32 \times 10^{-8}$, mean = 7.09, median = 1.01, IQR = 0.88), SOFA score (p = 0.00118, mean = 8.50, median = 4.00, IQR = 3.00), and duration of hospital stay (p = 0.03578, mean = 13.45, median = 11.00, IQR = 8.00).

Mean value of absolute neutrophil count and absolute lymphocyte count showed a significant difference among the survivors and nonsurvivors of the cases group (Mann–Whitney *U* test, *z*-value = –2.270, *p*-value = 0.02319), (unpaired *t*-test, *t*-value = –3.868, *p*-value = 0.00028), respectively. A higher mean value of NLR, D-dimer, SOFA score, and duration of hospital stay was associated with a poor outcome of cases. On applying Mann–Whitney *U* test, a significant difference was found between the mean values of NLR (*z*-value = –4.042, *p*-value = 5.29×10^{-5}), CRP (*z*-value = –5.034, $p = 4.80 \times 10^{-7}$), D-dimer (*z*-value = –5.477, *p*-value = 4.32×10^{-8}), SOFA score (z = –3.244, p-value = 0.00118), and duration of hospital stay (*z*-value = –2.099, *p*-value = 0.03578) among the survivors and nonsurvivors of the cases group (Table 5).

Table 2: Various parameters among cases and controls

Parameters	*Groups*	*Statistic*						*Shapiro–Wilk*		
		Mean	*Standard deviation*	*Median*	*IQR*	*95% confidence interval for mean*		*Statistic*	*df*	*Significance*
						Lower bound	*Upper bound*			
Age (years)	Case	43.62	13.849	42.00	20	40.04	47.19	0.985	60	0.66563
	Control	48.27	17.648	47.50	31	43.71	52.83	0.961	60	0.05488
WBC count	Case	20130.83	8517.492	18850.00	10828	17930.53	22331.13	0.907	60	0.00025
	Control	7120.92	2120.937	6950.00	3520	6573.02	7668.81	0.955	60	0.02557
Absolute neutrophil count	Case	16210.00	7380.174	15356.00	8422	14303.50	18116.50	0.955	60	0.02557
	Control	4276.72	1565.053	4029.00	2181	3872.42	4681.01	0.898	60	0.00011
Absolute lymphocyte count	Case	2306.75	943.573	2146.00	1325	2063.00	2550.50	0.971	60	0.17214
	Control	2277.85	737.626	2230.00	833	2087.30	2468.40	0.960	60	0.04736
NLR	Case	8.870	7.5432	8.050	6.6	6.921	10.818	0.703	60	1.0342E-009
	Control	1.962	0.7345	1.870	0.7	1.772	2.151	0.856	60	4.6517E-006
Temperature (F)	Case	98.80	1.335	99.00	2	98.45	99.14	0.919	60	0.00068
	Control	98.09	0.719	98.00	1	97.90	98.28	0.833	60	1.0184E-006
Pulse (/minute)	Case	104.63	12.297	102.00	15	101.46	107.81	0.970	60	0.15129
	Control	82.00	8.706	81.00	14	79.75	84.25	0.954	60	0.02296
SBP (mmHg)	Case	106.27	15.108	109.00	30	102.36	110.17	0.942	60	0.00677
	Control	117.23	9.518	120.00	10	114.77	119.69	0.943	60	0.00734
DBP (mm Hg)	Case	68.63	8.624	70.00	20	66.41	70.86	0.765	60	2.0098E-008
	Control	75.20	5.695	80.00	10	73.73	76.67	0.747	60	8.0702E-009
RR (/minute)	Case	22.20	6.385	20.00	8	20.55	23.85	0.857	60	4.9902E-006
	Control	14.57	1.064	14.00	2	14.29	14.84	0.816	60	3.3586E-007
CRP	Case	49.895	26.8419	43.000	37.8	42.961	56.829	0.902	60	0.00016
DDIMER	Case	3.3282	4.23738	1.6150	3.07	2.2335	4.4228	0.675	60	3.0046E-010
SOFA score	Case	6.15	3.965	4.50	6	5.13	7.17	0.865	60	8.4972E-006
Duration of hospital stay (days)	Case	13.25	11.156	10.00	10	10.37	16.13	0.776	60	3.5850E-008

CRP, C-reactive protein; DBP, diastolic blood pressure; IQR, interquartile range; RR, respiratory rate; SBP, systolic blood pressure; SD, standard deviation; df, degree of freedom

Table 3: Binary logistic regression with "group" as dependent variable and a set of predictor variables; dependent variable encoding

Group	*Internal value*				
Case	1				
Control	0				
Model summary step 1: –2 log-likelihood	Cox and Snell R^2	Nagelkerke R^2			
61.342	0.583	0.778			
Variables	B	Standard error	Wald	*p*-value	Exp(B)
Age (years)	–0.033	0.022	2.279	0.131	0.968
NLR	1.500	0.354	17.967	**2**.25E-05	4.482
SBP (mm Hg)	–0.015	0.029	0.269	0.604	0.985
Constant	–1.730	3.681	0.221	0.638	0.177

Table 4: Association of NLR with outcome of cases

NLR level		*Outcome*		*Total*
		Not survived	*Recovered*	
>3.53	No.	21	28	49
	%	42.9%	57.1%	100.0%
≤3.53	No.	1	10	11
	%	9.1%	90.9%	100.0%
Total	No.	22	38	60
	%	36.7%	63.3%	100.0%
Chi-squared tests	Value	df	*p*-value	Association is—
Pearson Chi-square$	4.411	1	0.036	Significant
Continuity correction$	3.076	1	0.079	Not significant
Fisher's exact test			0.043	Significant

Table 5: Association of various variables with outcome of cases

Variables	*Outcome*	*Mean*	*SD*	*Median*	*IQR*	*t-value*	*p-value*
WBC count^	Not survived	22756.82	10188.35	18250.00	8375.00	−1.618	0.106
	Recovered	18610.53	7091.91	19750.00	12725.00	Difference is not significant	
Absolute neutrophil count^	Not survived	19084.95	7757.70	13980.00	8881.00	−2.270	0.02319
	Recovered	14545.55	6703.41	17915.00	11488.00	Difference is significant	
Absolute lymphocyte count	Not survived	1749.91	743.41	2588.00	1473.00	−3.868	0.00028
	Recovered	2629.13	902.74	1630.50	805.00	Difference is significant	
Age (years)	Not survived	48.68	14.00	40.50	20.00	2.227	0.029864
	Recovered	40.68	13.06	45.00	21.00	Difference is significant	
Systolic BP (mm Hg)^	Not survived	93.91	10.91	115.00	11.00	−4.771	1.83E-06
	Recovered	113.42	12.37	90.00	12.00	Difference is significant	
C-reactive protein^	Not survived	74.40	25.14	32.50	21.30	−5.034	4.80E-07
	Recovered	35.71	15.05	78.50	41.80	Difference is significant	
NLR^	Not survived	13.27	10.00	5.33	5.90	−4.042	5.29E-05
	Recovered	6.32	3.98	10.53	6.50	Difference is significant	
D-dimer^	Not survived	7.09	5.14	1.01	0.88	−5.477	4.32E-08
	Recovered	1.15	0.62	5.28	9.52	Difference is significant	
SOFA score#	Not survived	8.50	4.66	4.00	3.00	−3.244	0.00118
	Recovered	4.79	2.75	7.50	8.00	Difference is significant	
Duration of hospital stay (days)^	Not survived	13.45	15.38	11.00	8.00	−2.099	0.03578
	Recovered	13.13	8.01	6.50	13.00	Difference is significant	

Unpaired *t*-test applied. ^, data failed "normality" test, hence, Mann–Whitney *U* test applied. *T*-value replaced by *Z*-value. #, ordinal data. Hence, Mann–Whitney *U* test applied. BP, blood pressure; IQR, interquartile range; SD, standard deviation

Discussion

The innate response to sepsis is highly dynamic and multifaceted, comprising humoral and cellular reactions, inflammatory, anti-inflammatory, and circulatory aberrations. Early, time-sensitive diagnosis and stratification of the severity of sepsis are vital. Due to limitations of available sepsis indicators, exploration for the ideal marker, which is quick, easy, and cost-effective for the accurate diagnosis and prognostication of sepsis, is essential. NLR is calculated from the CBC, which is the most basic, cheap, rapid laboratory investigation done in the emergency and provides numerous parameters. It is the ratio of absolute neutrophil count and absolute lymphocyte count, having a normal range of 0.78–3.53. There is the release of various inflammatory markers (tumor necrosis factor α, interleukin-6, interleukin-1β) in the early and late phase of sepsis, leading to a rise in the NLR.[9,12–15] Studies have found that NLR is an easily measurable parameter that can be used in the diagnosis of sepsis and predicting the severity of bacteremia and prognosis of sepsis.[5,7,9,13] Authors mentioned that in the early phase of sepsis, due to immune system stress, NLR elevations occur, and it may serve as the earliest marker of sepsis.[9] This was a prospective, case-control study conducted on 60 sepsis cases and 60 controls to evaluate the role of NLR as a diagnostic and prognostic marker of sepsis and to assess the association of NLR with the severity and outcome of sepsis.

An NLR of 3.53 was considered a cutoff for severe sepsis and for poor prognosis of sepsis. In the current study, we observed that maximum cases (49, 81.7%) had an NLR >3.53, and there was a significant difference ($p = 1.31 \times 10^{-16}$) between the NLR of cases and controls groups. The mean value of NLR among cases was significantly higher (8.87 ± 7.54) than controls (1.96 ± 0.73). We also observed significant leukocytosis (*p*-value = 2.73×10^{-22}), neutrophilia (*p*-value = 0.02319), and lymphocytopenia (*p*-value = 0.00028) among cases compared to controls. This was consistent with the studies by Jiang et al. and Kaushik et al.[6,7] In the present study, it

was reaffirmed that NLR in the early phase of sepsis was significantly higher compared to controls, and the higher the NLR value, the more likely the patient belonged to the sepsis group. This was proved by Binary Logistic Regression among Cases and Controls that NLR was a statistically significant predictor of the sepsis group category ($p = 2.25 \times 10^{-5}$). De Jager et al. concluded that NLR can predict bacteremia better than conventional infection markers.[5] Zahorec demonstrated that NLR was an easy, daily measurable parameter during sepsis.[9] Many researchers established the sensitivity and specificity of NLR for diagnosis of sepsis as dynamic variations of NLR occurs much before overt clinical manifestation of sepsis and, thus, may act as earliest warning signal.[6–9,12–16] Hence, we may recommend this quick, easy, and cost-effective marker for the early diagnosis of sepsis.

For prognostication, sepsis cases were followed up until discharge or death, and an appraisal of various parameters and serial values of NLR were done among survivors and nonsurvivors. In our study, among cases, mortality was 22 (36%). Globally, the mortality rate for sepsis, severe sepsis, and MODS is diverse, heterogeneous, and still very high in low-resource settings.[2–4,17] In the current study, we observed a significant association of NLR >3.53 with poor outcome-mortality [Chi-squared test ($p = 0.036$) and Fisher's exact test ($p = 0.043$)]. A higher mean WBC count (p-value = 0.106), and a higher mean absolute neutrophil count (z-value = –2.270, p-value = 0.02319) were associated with a poor outcome, while a higher mean absolute lymphocyte count was associated with a better outcome (t-value = –3.868, p-value = 0.00028). We also observed that a serial NLR trend gave us valuable information. A rising NLR trend was associated with a poor outcome, as the majority of cases with persistently very high NLR expired. While a decrease in NLR was associated with a better outcome, as among survivors, NLR came down significantly in the late phase. Thus, a decreasing trend in NLR may help in deciding de-escalation therapy. This is consistent with the studies by Kaushik et al. and Liu et al., in which a higher mean NLR was associated with an unfavorable outcome.[7,18] Literature mentions NLR as a good predictor of sepsis. High NLR level in the early phase is associated with a poor outcome. Also, NLR is a cheap and reliable biomarker and is directly proportional to disease severity with good sensitivity and specificity.[5–9,13–16,18–20] Similar results echoed in the present study, and hence, NLR can be considered an easily available, reproducible, and prognostic marker of sepsis.

We evaluated the association of various parameters among survivors and nonsurvivors. In patients who expired, the mean value of NLR was very high (13.27) compared to survivors (6.32) (z-value = –4.042, p-value = 5.29×10^{-5}). Also, a statistically significant difference was found among them between the following parameters: CRP (z-value = –5.034, $p = 4.80 \times 10^{-7}$), D-dimer (z-value = –5.477, p-value = 4.32×10^{-8}), SOFA score (z = –3.244, p-value = 0.00118), and duration of hospital stay (z-value = –2.099, p-value = 0.03578). A recent meta-analysis showed that in sepsis, higher NLR was associated with a poor prognosis, and it was higher in nonsurvivors than in survivors.[13] de Jager et al. observed NLR as a better predictor of severity and outcome in bacteremia than conventional markers without added costs.[65]There are various proven prognostic markers of sepsis like raised levels of D-dimer, CRP, SOFA score, longer ICU stay, etc., which are associated with increased morbidity and mortality.[18–22] In the present study, NLR correlated with other prognostic markers of sepsis and poor outcome. However, few studies mention that large studies are required to determine the prognostic role of NLR in septic patients.[10,11] Authors demonstrated NRL is an easily available predictive biomarker which can be used to categorize the patients at an early stage and high NLR was reliable indicator of the disease severity and mortality in COVID-19 disease.[12,23–25] Research established the sensitivity and specificity of NLR for diagnosis as well as correlated with early recognition of sepsis, disease severity scores, and sepsis-related mortality, and can be considered part of the decision-making processes. Regular follow-up NLR shows its dynamic course in sepsis and has strong predictive value.[7,13–16,18] Buonacera et al. affirmed that NLR to be an easily measurable and having better correlation with sepsis severity and mortality.[15] Thus, NLR is quick, affordable, simple, and easily available parameter of inflammation which may give new dimension to sepsis management and its use of NLR for diagnosis and prognostication of sepsis should be emphasized. The present study had certain limitations due to being observational, single-center, partaking small sample size; hence, strong recommendations cannot be made.

Thus, from this prospective case-control study at a tertiary care public institute, we may conclude that NLR is elevated early in sepsis and can help suspecting and diagnosing sepsis at a very early stage. Persistently elevated NLR and high values of NLR are associated with a poor outcome in sepsis, making it a useful marker to determine prognosis in patients with sepsis. The trend of NLR shows its dynamic course in sepsis, and decreasing values indicate a better outcome. NLR correlates with other prognostic markers of sepsis like raised levels of D-dimer, CRP, SOFA score, longer ICU stay, increased morbidity, and increased mortality, and overall poor outcome. Hence, we may recommend this quick, easy, and cost-effective marker for the early diagnosis and regular prognostication of sepsis.

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ORIGINAL ARTICLE

Evolution of Metabolic Syndrome in Newly Diagnosed Type 2 Diabetes Mellitus Asian–Indian Patients Over the Last 15 Years using Adult Treatment Panel III of the National Cholesterol Education Program, World Health Organization, and International Diabetes Federation Criterion

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Abstract

Aim: A retrospective observational study was undertaken to assess the changing trends in the incidence of metabolic syndrome (MetS) in Asian–Indian patients with newly diagnosed type 2 diabetes (T2D) using Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATP III), World Health Organization (WHO), and the International Diabetes Federation (IDF) criteria. The overall and gender-wise pattern of MetS and its components were also evaluated.

Materials and methods: Newly diagnosed T2D patients (n = 10,950)visiting Dr Panikar's Diabetes Care Centre from 2004 to 2019 with retrievable electronic medical records were selected. The incidence of MetS in these patients was studied using NCEP-ATP III, WHO, and IDF criteria in three separate timelines, namely, group I (2004–2008), group II (2009–2013), and group III (2014–2019). Overall and gender-wise, the incidence of various components of the MetS was also studied and compared across the three groups. All data were analyzed by using the Statistical Software Statistical Package for the Social Sciences (SPSS) version 10.0. Continuous variables were summarized by the number of observations (mean, standard deviation or median with minimum and maximum) and categorical values (calculating frequencies with percentages). Chi-square was used to estimate the incidence of MetS using different criteria and gender-wise patterns of the MetS components for the three periods. Other variables, such as mean body mass index (BMI), were assessed by applying variance analysis (ANOVA test). All values were reported based on a two-sided ANOVA test, and all the statistical tests were interpreted at a 5% level of significance.

Results: In the current study, the overall incidence of MetS observed among the study population was 80.9, 65.4, and 69.8% using NCEP-ATP III, WHO, and IDF criteria, respectively. The incidence of MetS across the three timelines (i.e., from 2004 to 2019) with all the diagnostic criteria showed a steady increase. An analysis of the individual components of MetS revealed a high incidence of central obesity across all subgroups, followed by hypertension and dyslipidemia. Central obesity was prevalent in nearly 85.9% of patients in 2014–2019 vs 78.6% in the 2004–2008 subgroup. Similarly, the incidence of hypertension and overall dyslipidemia [i.e., high triglycerides (TGs) and low high-density lipoprotein-cholesterol (HDL-C)] was 77.8% and 68.2% in the former vs 67.9% and 59.6% in the latter, respectively. The incidence of all three MetS components, along with fasting sugar, showed a statistically significant and progressive increase over the years, with prevalence in group III (2014–2019) being the highest. Women were found to be more centrally obese and more dyslipidemic compared to men, whereas men were found to be more hypertensive.

Conclusion: The study shows a high incidence of MetS in Asian–Indian patients with newly diagnosed T2D. The incidence of MetS was significantly higher with the NCEP-ATP III diagnostic criteria than with WHO and IDF criteria. A steady rise in the incidence of MetS was observed over the study period of 2004–2019. Among the components of MetS, the incidence of central obesity, elevated TG levels, and low HDL-C were found to be higher in the female population than in males, whereas the incidence of hypertension was higher in males. Stringent lifestyle measures, along with appropriate pharmacological management, might help mitigate the risks associated with MetS.

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Introduction

Metabolic syndrome (MetS), characterized by a cluster of cardiometabolic abnormalities, is a significant global public health concern.[1,2] MetS significantly increases the risk of cardiovascular disease (CVD), type 2 diabetes (T2D) and premature mortality and is represented by the complex interconnection of several disorders, including insulin resistance or dysglycemia, dyslipidemia [increased levels of triglycerides (TGs) and decreased levels of high-density lipoprotein-cholesterol (HDL-C)], obesity (especially central obesity), and high blood pressure.[1,3] Many of these conditions are linked to poor lifestyle choices, such as sedentary habits, unhealthy diet, and inadequate physical fitness.[3]

The complexity and clustering of risk factors constituting MetS in adults have resulted in various diagnostic criteria being proposed by multiple organizations, such as the World Health Organization (WHO, 1998), the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATP III, 2001) and the International Diabetes Federation (IDF, 2005) along with a consensus between the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and IDF (Join Interim Statement, 2009).[4]

The definitions for MetSin adults proposed by NCEP-ATP III, WHO, and IDF are given in Table 1.[4] The WHO definition necessitates the markers of insulin resistance, whereas the IDF makes central obesity an obligatory component of the MetS cluster. Overall, the presence of three abnormal findings out of the five components qualifies a person as having MetS.[3] In addition to these,

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Table 1: Different diagnostic criteria for MetS in adults (adapted from Kassi et al.)[4]

Components	*WHO (1998)*	*NCEP-ATP III (2001)*	*IDF (2005)*
Absolute requirement	Insulin resistance (T2D, IFG, and IGT)	None	Central obesity [defined as waist circumference* >90 cm (men) and >80 cm (women)] or BMI >30 kg/m^2
Along with	Any 2 of the following	Any ≥3 of the following	Any 2 of the following
Abdominal obesity	Waist-to-hip ratio >0.9 in men or >0.85 in women, or BMI >30 kg/m^2	Waist circumference >102 cm in men, >88 cm in women	–
Dyslipidemia (mg/dL)	TG ≥150 and/or HDL-C <40 (men) and <50 (women)	TG ≥150 or HDL-C <40 (men) and <50 (women)	TG ≥150 or HDL-C <40 (men) and <50 (women)
BP (mm Hg)	≥140/90	≥135/80	≥135/80
Microalbuminuria	Urinary AER ≥20 µg/min or ACR ≥30 mg/g	–	–
FBG (mg/dL)	–	≥100	≥100

*for South Asians, Chinese, and Japanese; for Europeans, it is >94 cm in men and >80 cm in women; ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein-cholesterol; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MetS, metabolic syndrome; NCEP-ATP III, Adult Treatment Panel III of the National Cholesterol Education Program; T2D, type 2 diabetes; TGs, triglycerides; WHO, World Health Organization

other factors that may contribute to MetS in varying proportions include advancing age, a proinflammatory state, certain genetic and progenetic factors, and female gender.[5]

MetS is usually correlated with accelerated atherosclerotic CVD, chronic kidney disease, obstructive sleep apnoea and hyperuricemia/gout.[6] It also increases the risk of ischemic heart disease (IHD) and T2D by 2–3 times and 5 times, respectively. The worldwide prevalence of MetS is around 20–25% and is on the rise.[5] A recent meta-analysis of global data involving 28 million individuals showed that the prevalence of MetS and its components ranged from 12.5% (95% CI: 10.2–15.0) to 31.4% (29.8–33.0), depending on the definition considered.[1] According to the Centers for Disease Control (CDC) and Prevention, its prevalence in United States adults rose by >35%, from 25.3% (1988–1994) to 34.2% (2007–2012).[7] Epidemiological studies undertaken across India have shown that nearly one out of every four adults have MetS, with greater prevalence observed with increasing age and in the female population.[5] A cross-section of studies across India suggests that the prevalence of the MetS is higher in patients with diabetes with a higher preponderance in the female sex.[8–10]

According to many experts, central obesity is a major driving force behind the rising prevalence of MetS.[11] The recent Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study showed that the individual components of MetS are highly prevalent in India, with over 11% of the adult population being affected by diabetes and >15% by prediabetes. Additionally, dyslipidemia, hypertension, generalized obesity and abdominal obesity were present in 81.2, 35.5,28.6, and 39.5% of the population. Interestingly, low HDL-C was present in nearly 66.9% of the studied population.[12]

With this background, the current retrospective observational study seeks to assess the changing trends in the incidence of MetS over 15 years among Asian–Indian patients newly diagnosed with T2D who attended a private tertiary care centre in India using the NCEP-ATP III, WHO, and IDF criteria.

Materials and Methods

This was a retrospective, observational study involving newly diagnosed T2D patients attending a private tertiary care centre in India. Patients with preexisting diabetes (either type 1 or type 2) were excluded from the study. All patients (n = 10,950) were screened for MetS, and its incidence was assessed using NCEP-ATPIII, WHO, and IDF criteria. Moreover, MetS incidence over three timelines, that is, 2004–2008, 2009–2013, and 2014–2019 was also assessed. The incidence of various components of MetS in the overall population and their gender-wise distribution was also studied and compared across the three timelines.

Data Analysis

All the data in this study were analyzed by using the Statistical Software Statistical Package for the Social Sciences (SPSS) version 10.0. Continuous variables were summarized by the number of observations (mean, standard deviation, or median with a range of minimum and maximum) and categorical values (calculating frequencies with percentages).

The Chi-squared test was used to assess the incidence of MetS using the three different diagnostic criteria and the gender-wise individual components of MetS across the three timelines. Depending on the period under assessment, the groups included—group I (2004–2008), group II (2009–2013), and group III (2014–2019). Other variables, such as mean body mass index (BMI), were evaluated by applying analysis of variance (ANOVA test). All values were reported based on a two-sided ANOVA test, and all the statistical tests were interpreted at a 5% level of significance.

Results

Baseline Data

Out of the 10,950 patients included in the study, over 60.7% (n = 6647) were male, and 39.3% (n = 4,303) were female, with an overall mean age of 46.74 years (12–94 years). A similar age and gender distribution was seen across the three periods assessed, and the mean BMI was also comparable across subgroups (Table 2). The mean age of onset of diabetes showed a reduction of 1.40 years between groups I and III. A similar reduction was seen between males and females, but it was not statistically significant.

Incidence of Metabolic Syndrome

In the overall population of newly diagnosed T2D patients, the incidence of MetS varied based on the diagnostic criteria applied and was 80.9, 65.4, and 69.8% as per NCEP-ATP III, WHO, and IDF definitions, respectively (Fig. 1).

When assessed across the three timelines, a consistent and steady increase in the incidence of MetS was evident. The incidence was highest with the NCEP-ATP III criteria, followed by IDF and then the WHO (Fig. 2).

Individual Components of Metabolic Syndrome

An analysis of the individual components of MetS revealed a high incidence of central obesity across all subgroups, followed by hypertension and dyslipidemia. The incidence

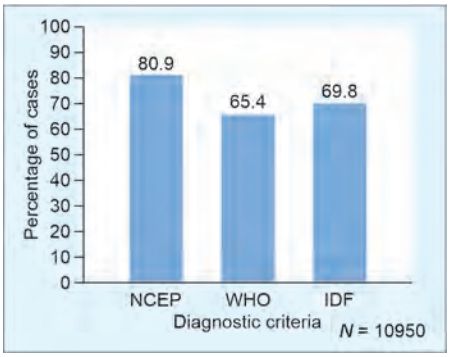

Fig. 1: Incidence of MetS; NCEP vs WHO vs IDF $p < 0.05$ by Chi-squared test; significant

of all three components, along with fasting sugar, showed a statistically significant and progressive increase over the years, with prevalence in group III (2014–2019) being the highest (Fig. 3).

Impact of Gender on Individual Components

Gender-based analysis of the individual components (Figs 4 and 5) showed a statistically significant and progressive increase in the incidence of all components over the years. There was a significant female preponderance in the case of central obesity and dyslipidemia (both in terms of high TGs and low HDL-C). On the contrary, the incidence of hypertension increased progressively in the male population (Fig. 4).

Discussion

The incidence of MetS is increasing worldwide in both developing and developed countries and across ethnic groups. The incidence of MetS often parallels the incidence of obesity and T2D. It also increases the risk of other disabling disorders, such as CVDs and stroke. The global prevalence of MetS is

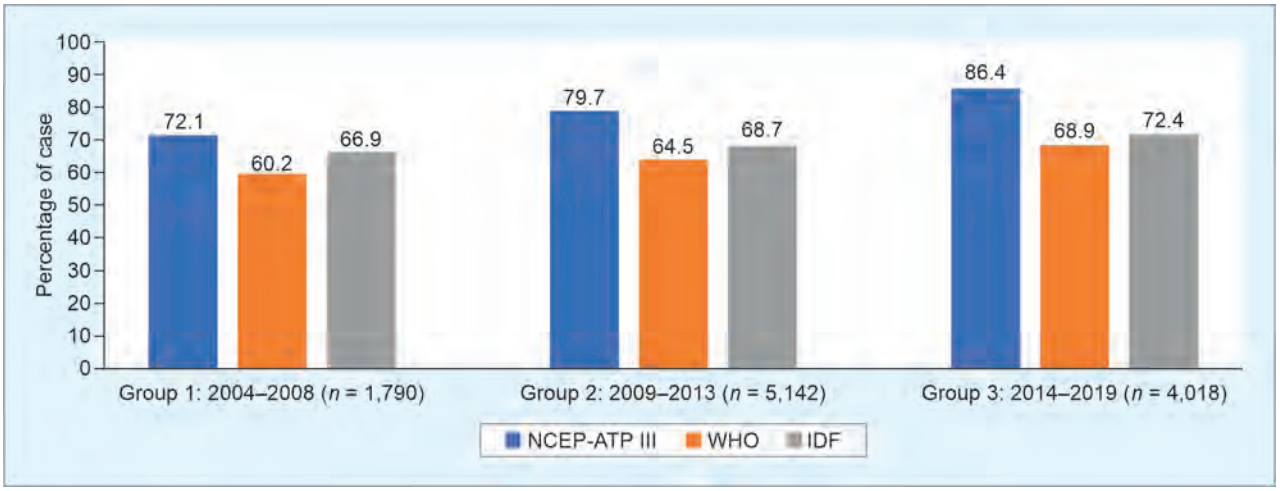

Fig. 2: Incidence of MetS for NCEP and WHO criteria—group I vs group II vs group III; $p < 005$ by Chi-squared test; significant for IDF criteria—group I and group II vs group III; $p < 0.05$ by Chi-squared test; significant

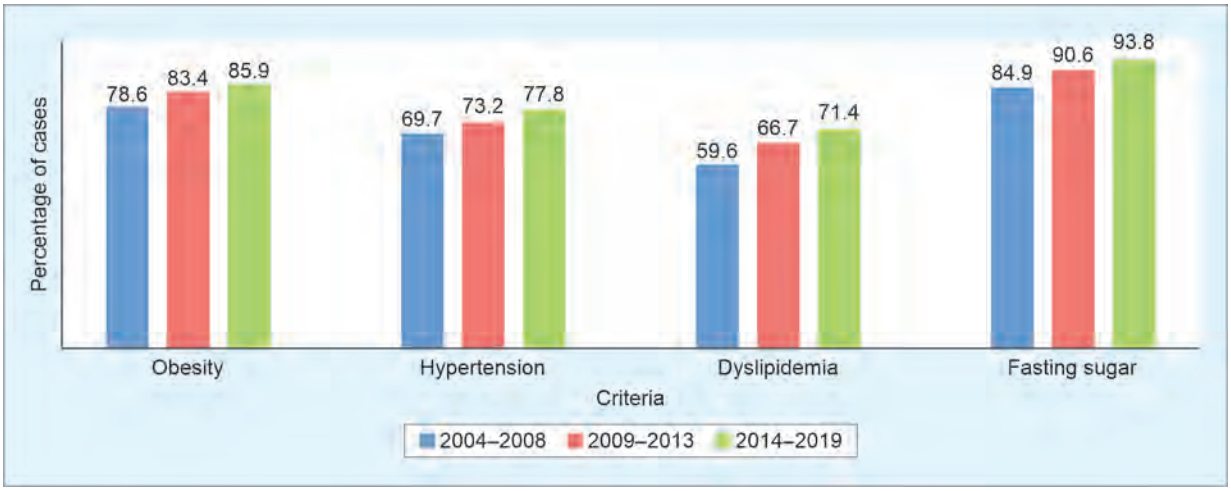

Fig. 3: Components of the MetS for all criteria; group I vs group II vs group III $p < 0.05$ by Chi-squared test; significant

Table 2: Baseline data

Newly diagnosed T2D patients	*Overall*	*Group I (2004–2008)*	*Group II (2009–2013)*	*Group III (2014–2019)*
Total patients (*n*)	10,950	1,790	5,142	4,018
Mean age and range (years)	46.74 (SD 12.9); 12–94	47.84 (SD 12.62); 12–84	46.59 (SD 12.96); 12–94	46.44 (SD 12.91); 12–94
Males (*n*; %)	6,647 (60.7)	1,122 (62.7)	3,124 (60.8)	2,415 (60.1)
Females (*n*; %)	4,303 (39.3)	668 (37.3)	2,018 (39.2)	1,603 (39.9)
BMI (kg/m^2; mean ± SD)	27.60 ± 5.08	27.31 ± 5.25	27.64 ± 5.07	27.67 ± 5.02

$p < 0.05$ by ANOVA, not significant by Chi-squared test

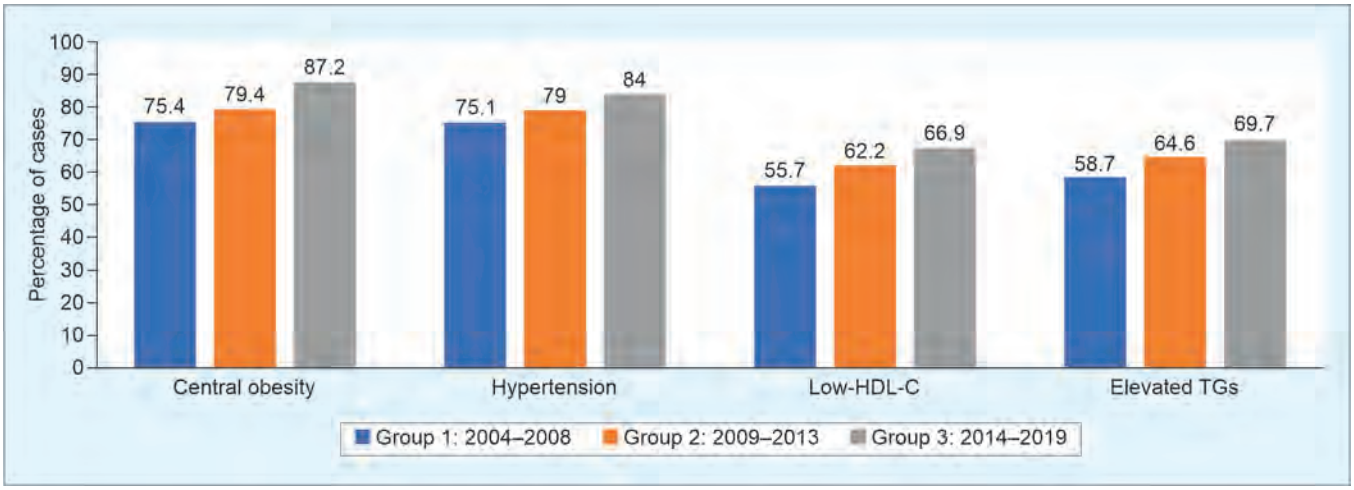

Fig. 4: Components of MetS in males for all criteria—group I vs group II vs group III $p < 0.05$ by Chi-squared test; significant

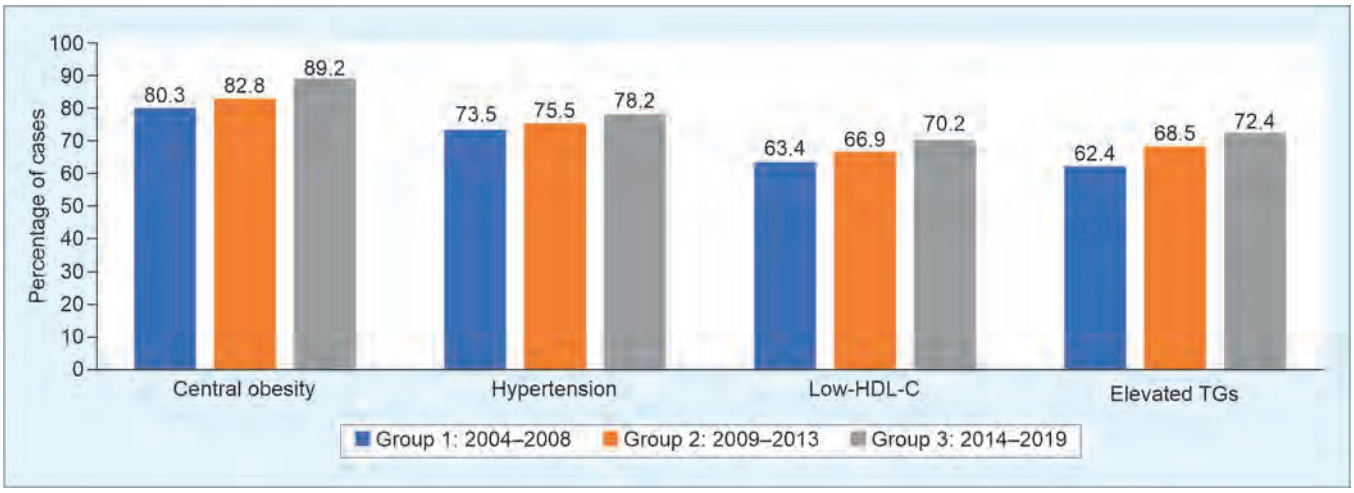

Fig. 5: components of MetS in females central obesity, low HDL-C and elevated TG—group I vs group II vs group III $p < 0.05$ by Chi-squared test; significant hypertension—group I and group II vs group III $p < 0.05$ by Chi-squared test; significant

around 20–25%, with variations observed in the Asian (12–37%) and European (12–26%) populations.[13]

Data from a CDC study (2017) showed that nearly 30.2 million adults (≥18 years), that is, 12.2% of the adult population in the United States, had T2D. Moreover, a quarter of this population was unaware of their condition. The prevalence of MetS was about three times more, translating into nearly a third of the adults in the United States.[14]

In Chinese adults (≥20 years), the prevalence of MetS (2015–2017) was 31.1%, with its components, such as high blood pressure, low HDL-C and greater waist circumference present in 49.4, 41.1, and 40.8% of the population, respectively.[15]

According to the CoLaus study—a single centre cross-sectional study including a random sample of 6188 extensively phenotyped Caucasian subjects aged 35–70 years living in Lausanne, Switzerland—the prevalence of overweight, obesity, hypertension, hyperlipidemia, diabetes, and microalbuminuria was 36.6, 15.7, 36.7, 34.2, 6.6, and 6.3%, respectively. In this population, the prevalence was greater in men than women across all categories.[16]

The prevalence estimates vary based on the criteria used for the definition of MetS. For example, a national survey in Iran in 2007 showed the prevalence of MetS was about 34.7% based on ATP III criteria, 37.4% based on the IDF definition, and 41.6% based on the ATP III/AHA/NHLBI criteria. In another Middle Eastern country, Tunisia, the prevalence was 45.5% based on IDF criteria but 24.3% based on ATP III criteria. However, in all the Middle Eastern countries, the prevalence was much higher among women than men.[17]

The overall incidence of MetS in our study was 80.9, 65.4, and 69.8% using NCEP-ATP III, WHO, and IDF criteria, respectively. As seen in earlier studies, the prevalence estimates were variable, based on the criteria used for defining MetS, with the highest incidence seen with the NCEP-ATP III criteria. The incidence of MetS was also significantly higher in females, similar to that seen in the Middle East and Africa.[17,18]

Furthermore, the incidence of all components of MetS (central obesity, hypertension, and dyslipidemia) was found to be highest in the 2014–2019 subgroup, which clearly points toward the increasing prevalence of MetS in recent years. Lifestyle changes have been contributory factors to this rapid rise of MetS in the population. Studies indicate that inadequate physical activity, along with the daily consumption of a Western diet, including meat, fried food items, and excessive salt, is linked to the prevalence of MetS.[19]

Among the individual components, the incidence of central obesity was highest across all periods. It was also higher in females compared to males in every subgroup. Moreover, the prevalence of central obesity was highest in the 2014–2019 subgroup, suggesting a steady rise. The increased prevalence of obesity has become a major health problem worldwide,[20] and the accumulation of abdominal body fat, the most frequently observed component of MetS, is associated with insulin resistance.[21]

In our study, the incidence of hypertension was found to be higher in males compared to females across all subgroups, while the incidence of elevated TGs and low HDL-C (representing a dyslipidemic state) was higher in females vs. males in every subgroup. A somewhat similar pattern was observed in the ICMR-INDIAB-17 study, wherein a significantly greater proportion of the female population had generalized and abdominal obesity, hypercholesterolemia, low HDL-C, and low-density lipoprotein cholesterol compared to males.[12] Overall, the incidence of all MetS components showed a progressive increase across the three time periods.

Conclusion

This retrospective study suggests that the incidence of MetS in newly diagnosed T2D Asian–Indian patients is high and on the rise, especially in the female population. Upon assessment with multiple diagnostic criteria, the incidence of MetS is significantly higher with the NCEP-ATP III criteria than with WHO and IDF criteria. Among the individual components of the syndrome, the incidence of central obesity is highest, followed by hypertension and then dyslipidemia. Incidence of central obesity, elevated triglyceride levels and low HDL levels are higher in females compared to males, and the incidence of hypertension is higher in males compared to females. The persistent increase in the incidence of MetS in newly diagnosed T2D patients makes them more vulnerable to complications, which can have a far-reaching impact on the patient's quality of life. Early detection of coexisting MetS, appropriate medication and implementation of stringent lifestyle measures, such as a nutrient-rich diet and physical activity, may help mitigate the risks associated with T2D in Asian–Indian patients.

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ORIGINAL ARTICLE

Long-term Outcome of Coronavirus Disease-associated Mucormycosis: 1-year Follow-up Study from India

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Abstract

Importance: Invasive fungal infections have recently become a public health problem, particularly in India following the second wave of coronavirus disease 2019 (COVID-19). India harbors the world's largest population of patients suffering from diabetes. What prompted the sudden spike of mucormycosis infections in the COVID pandemic needs investigation.

Objective: To determine if COVID-19 infection prompted the spike in invasive fungal infections in diabetic population. To determine the long-term outcome of COVID-associated mucormycosis. To determine if COVID-19 infection causes diabetes mellitus transiently.

Design: The study was a prospective cohort study comprising patients suffering from mucormycosis. The study was planned from 20 May 2021, until 30 November 2022, to investigate the long-term follow-up (1 year) of mucormycosis patients.

Setting: The study setting was a referral hospital.

Participants: All the consecutive patients admitted to this hospital for treatment of mucormycosis were included in the study who consented to it.

Intervention(s) (for clinical trials) or exposure(s) (for observational studies): All patients suffering with mucormycosis underwent treatment at this hospital with surgery and injectable systemic antifungal drugs alongside diabetes management.

Main outcome(s) and measure(s): Primary outcome measurement was in the form of survival with cure of mucormycosis. Hypothesis being tested was formulated during data collection.

Results: The data of 98 participants was collected, but analysis was done after excluding the case of cutaneous mucormycosis (infant patient). Mean age for patients was 55.5 years, varying from 28 to 88 years. In our study, 63.3% of patients with mucormycosis were males and 37.8% were females, of which 55.7% (34) and 58.3% (21) were known diabetics, respectively. Previous history of diabetes mellitus was identified as an underlying comorbid condition in 56.7% of patients, while the rest were diagnosed with new-onset diabetes mellitus. Sugar levels ranged (on admission) from 112 to 494 mg/dL (median 212 mg/dL) for known diabetics and from 132 to 356 mg/dL (median 204 mg/dL) for newly diagnosed diabetics. Other comorbidities included hypertension (19.5%), ischemic heart disease (8.2%), chronic renal illness (3.09%), and one case (1.03%) of postoperative renal cell carcinoma (disease-free). The majority of cases (91.8%) were not vaccinated for COVID-19, while only two patients reported a history of vaccination with two doses, and six others had received only a single dose. At the 1-year follow-up, 57.7% of cases were disease-free, 30.9% had expired, and 11.3% were lost to follow-up. The mean glycated hemoglobin (HbA1c) at the time of admission was found to be statistically significant when compared between known diabetics and newly diagnosed ones [confidence interval (CI)—95%, $p \leq 0.01$]. A total of seven patients from the newly diagnosed diabetic group no longer required medicines for diabetes at the end of 1 year (CI—95%, $p \leq 0.01$).

Conclusions and relevance: Diabetes mellitus, particularly with poor glycemic control, was the single most important factor associated with and predictor of outcome. Contrary to the popular hypothesis, industrial oxygen and oxygen masks were not the reasons for the mucormycosis pandemic. Additionally, immunization against COVID provided protection not only from severe COVID but also from COVID-associated mucormycosis. It is recommended that patients with mucormycosis be followed for longer periods as a few patients could be suffering from transient diabetes, particularly against the backdrop of a pandemic.

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Introduction

Systemic invasive fungal infections, which were never a concern for public health authorities, left them baffled with a sudden spike in reports of once rare mucormycosis infections, especially following the second wave of coronavirus disease 2019 (COVID-19) in India and other middle- and low-income countries.[1] In India, during the first wave of the COVID-19 pandemic, sporadic reporting of mucormycosis cases was made from hospitals in the national capital. Following the subsidence of the first wave, in the final month of 2020, the actual number was very low to raise any concern.[2] With no substantiated treatment protocols, various repurposed and experimental therapies in association with prolonged intensive care unit (ICU) stays, COVID-19 infections can get complicated by secondary infections, commonly bacterial. However, it was the rise in potentially fatal invasive fungal infections caused by mucormycetes that created an epidemic of its own. The commonly reported type of mucormycosis was *Rhizopus oryzae*, which was responsible for 90% of cases. Other species reported with lower incidence were *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Absidia*.[3] Among various reasons purported that allowed mucormycosis to reach epidemic proportions with poor outcomes were improper management, late diagnosis, and misleading unsupervised treatment. As high mortality is associated with mucormycosis, effective treatment requires early detection of the condition followed by surgical debridement with metabolic corrections and systemic antifungal therapy.[4]

The rapid surge in fungal infections, a recent trend, is a growing concern worldwide, particularly in India. Mucormycosis prevalence ranges from 0.005 to 1.7 per million people worldwide; however, it is almost 80 times higher (0.14 per 1000) in India. The COVID-19 pandemic brought mucormycosis to the forefront in India, accounting for 80% of the global burden of COVID-19-associated mucormycosis (CAM).[5,6]

Several risk factors such as hematological disorders, neutropenia, organ transplant, metabolic acidosis, intravenous drug abuse, renal insufficiency, broad-spectrum antibiotic usage, increased serum iron levels, malnutrition, etc., have been associated with mucormycosis.[7] COVID-19 infection and the use of corticosteroids in its treatment

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make patients vulnerable to mucormycosis infection.[8] Steroids are known to increase blood sugar levels and create an acidic body environment, which favors the growth of mucor. This is further complicated when steroids are used in uncontrolled diabetes.[9]

The scientific data published during the mucormycosis epidemic primarily followed patients for very short periods, ranging from 7 days to 3 months. Additionally, these studies demonstrated a relatively better outcome in terms of survival among patients with mucormycosis compared to data from previous studies conducted before the COVID-19 pandemic. Since no studies have reported the long-term results in CAM, this study, as a continuation of the authors' previously published research, aims to understand the long-term outcomes, with a special emphasis on newly diagnosed diabetics, and to examine the phenomenon of transient diabetes.

Materials and Methods

The prospective study was initially proposed as an observational study at a teaching hospital in India, scheduled to run from 20 May 2021 to 15 July 2021. However, it was later extended until 30 November 2022 to facilitate long-term follow-up. The study protocol was approved by the Institutional Ethics Committee (SNMC/IEC/2021/35). The present study aims to provide insight into the demographic profile of patients admitted to the hospital with mucormycosis, various comorbid conditions, COVID-19 immunization status, disease staging, fungal profile, and the outcomes of patients with mucormycosis at or beyond a year from the initiation of treatment. Mucormycosis diagnosis was established using the Smith and Krichner criteria or by demonstrating fungi with broad ribbon-like aseptate hyphae in the tissue through direct microscopy. Diabetes mellitus diagnosis was based on the 2021 guidelines of the American Diabetes Association.

The patients were treated with injection amphotericin B (liposomal) along with oral posaconazole therapy. Nasal endoscopies were conducted periodically every week, coupled with radiological evaluations, and progressive debridement was carried out as required. Patients with orbital lesions additionally received transcutaneous amphotericin B (TRAMB) injections, with a dosage of 1 mL of a 3.5 mg/mL solution, for 5–7 days as necessary. All patients received management with oral hypoglycemic agents and insulin, as required, to maintain strict control of blood sugar levels.

Statistical Analysis

The compiled data from Microsoft Excel was analyzed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 23.0 (Armonk, New York: IBM Corp). Descriptive statistics such as mean and standard deviation were calculated, and Chi-squared tests were performed. A *p*-value of ≤0.05 was considered statistically significant.

Results

The data of 98 participants was collected and barring one neonate all others were suffering with rhino-cerebral-orbital mucormycosis (RCOM); hence, only 97 were analyzed, as the infant suffered from cutaneous mucormycosis, of which 11 patients were lost to follow-up at the end of 1 year. Mean age for patients was 55.5 years, varying from 28 to 88 years. In our study, 63.3% of patients with mucormycosis were males and 37.8% were females, of which, 55.7% (34) and 58.3% (21) were known diabetics, respectively. Approximately, 42% of study subjects belonged to rural background and rest were from urban areas. Previous history of diabetes mellitus was identified as underlying comorbid condition in 56.7% patients, and rest were diagnosed as new-onset diabetes mellitus. Sugar levels ranged (on admission) from 112 to 494 mg/dL (median 212 mg/dL) for known diabetics; and 132–356 mg/dL with median value of 204 mg/dL for newly diagnosed diabetics. Other comorbidities were hypertension (19.5%), ischemic heart disease (8.2%), chronic renal illness (3.09%) and one case (1.03%) of postoperative renal cell carcinoma (disease free). Majority of cases (91.8%) were not vaccinated for COVID-19, while only two patients gave history of vaccination with two doses, six others had received only single dose. History of recent COVID infection was documented in 41 (42.2%) cases and rest had no test reports to suggest COVID infection. Forty-eight (49.4%) patients had history of taking steroids recently, however, its use was not statistically significant for outcome, $p > 0.05$. Forty-two patients (43.2%) were on oxygen therapy recently but no distinction could be ascertained about it being industrial or medical grade. In our study participants, the cause of death could be determined for those who expired while undergoing treatment in our hospital and a few of those who died elsewhere. Three patients died of anesthesia-related complications, one patient died of cerebrovascular accident (CVA), six of systemic sepsis, for 11 patients mucormycosis was the immediate cause of death; for others the cause of death couldn't be ascertained precisely.

The long-term outcome of patients with mucormycosis after treatment resulted in 57.7% of cases being disease free at 1-year follow-up since initiation of treatment, 30.9% of cases had expired and 11.3% were lost to follow-up (Table 1).

The mean HbA1c at the time of admission was found to be statistically significant when compared between known diabetics and newly diagnosed ones ($p \leq 0.01$). Another important observation after a year-long follow-up was that a total of seven patients from the newly diagnosed diabetic group no longer required medicines for diabetes; in other words, they were no longer diabetic ($p \leq 0.01$) (Table 1).

All the cases (97) had rhino-cerebral-orbital mucormycosis (RCOM), majorly in clinical stage 2 (Fig. 1). Microbiological species identification could be done for 83.5% cases only, and majority belonged to genus *Rhizopus* (Table 2 and Fig. 2).

Table 1: Comparative data for known and newly diagnosed diabetics suffering with mucormycosis

Parameters		*Overall (n = 97)*	*Known DM (n = 55)*	*New DM (n = 42)*	*p-value*
Age (years)		50.5 ± 13.8	52.1 ± 14.1	48.3 ± 12.2	–
Sex	Male	61	34	27	0.80
	Female	36	21	15	
H/o corticosteroid use in COVID illness		48	31	17	0.12
Admission Hba1c (mean)		9.05 ± 2.05	9.5 ± 2.14	7.9 ± 1.8	**0.01**
Nonsurvivors		30	19	11	0.30
Survivors (excluding loss to follow-up)		56	29	27	
Lost to follow-up		11	7	4	0.62
No longer suffering with DM (beyond 1 year)		7	0	7	**0.01**

Bold values represent statistically significant values

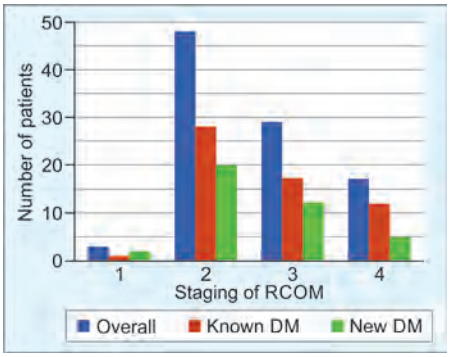
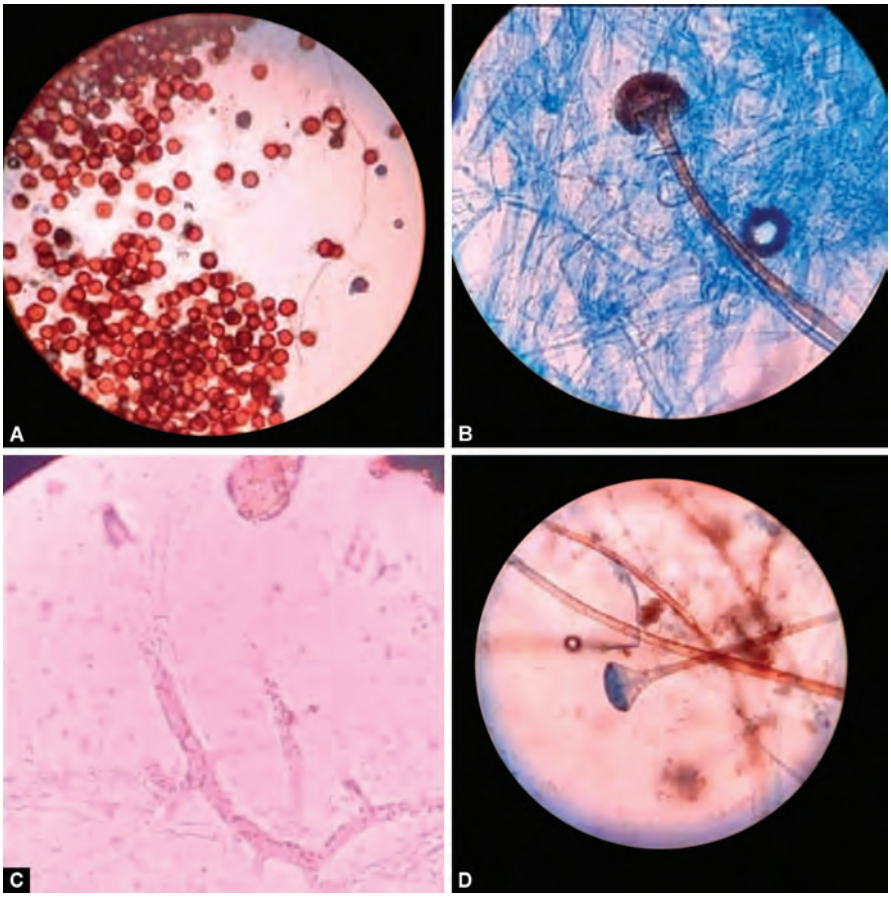


Fig. 1: Frequency distribution of clinical staging of RCOM

Table 2: Mycological profile of specimens subjected for identification

Mycological profile	
Total species identification	81
Rhizopus arrhizus	62
Rhizopus microsporus	7
Rhizopus homothallicus	2
Mucor	2
Mucor with aspergillosis	2
Apophysomyces	3
Rhizomucor	1
Cunninghamella	1
Lichtheimia	1



Figs 2A to D: Fungal microscopy; (A) lactophenol cotton blue (LPCB) mount of *R. homothallicus*; (B) LPCB mount: *Rhizopus* spp.; (C) KOH mount: broad aseptate fungal filament; (D) LPCB mount: *Apophysomyces* spp.

Discussion

Due to microangiopathy, altered healing dynamics, suppressed immune system, acidosis, and raised sugar in tissue fluid providing a nutritive medium, diabetes has proved to be an inseparable entity when mucormycosis is discussed. In the study by Yang et al., during the SARS pandemic, a spike in new-onset diabetes was noted.[10] The silent burden of diabetes mellitus can get unmasked during an illness like COVID, resulting in increasingly common new-onset DM. Similar findings were published by Jali and Shankar with varicella infections[11]; and Muthukrishnan et al. and Waizel et al. too reported cases of new onset diabetes mellitus with COVID-19 infection.[12,13]

Diabetes is the single most common comorbidity associated with mucormycosis in India, accounting for about 73.5% of cases.[14] However, only 17% of mucormycosis infections in Western nations are linked to diabetes.[15] In our study, all the patients suffered from raised blood sugars, with 56.7% being known diabetics and 43.3% newly diagnosed ones. Diabetes was associated with poor control, as suggested by mean fasting blood glucose levels ranging (at admission) from 112 to 494 mg/dL with a median value of 212 mg/dL for known diabetics, and 132 to 356 mg/dL with a median value of 204 mg/dL for newly diagnosed diabetics. In a study by Chakrabarti et al., uncontrolled diabetes mellitus was the single largest risk factor (in 50% of cases) in RCOM; odds ratio (OR) = 9.3; $p \leq 0.001$.[16]

Another observation after a year-long follow-up in our study was that seven patients from the newly diagnosed diabetic group no longer required medicines for diabetes control; in other words, they were no longer diabetic ($p \leq 0.01$). They were probably the case of transient diabetes/hyperglycemia likely due to the direct insult of beta cells of the pancreas by the delta variant of COVID, sympathetic response to inflammation, steroid use, or some other unknown drug interactions, as polytherapy was prevalent during the COVID pandemic.

In the study by Mishra et al., the prevalence of CAM was predominantly rhino-orbital in 19 out of 32 cases (59.4%), while others had sinonasal mucormycosis.[17] Of all patients, the majority were in clinical stage 2 (Fig. 1). The pattern of involvement is similar to previous reports with the predominant risk factor in the form of diabetes.[16,18]

In terms of outcome of patients with mucormycosis, in a study by Mishra et al., 4/32 (12.5%) patients did not survive in the study period of 7 weeks,[17] though the reported mortality of rhino-cerebral mucormycosis in patients with diabetes is 40–50%.[18] Improved prognosis is suggested by Mishra et al., to be due to early diagnosis and surgical debridement. However, the majority of 23/32 (71.8%) of patients in their study were still under treatment and the conclusive outcome was still to be assessed. Their better outcome may be due to very short follow-up period of 7 weeks. In our study, reporting the longest follow-up in literature, 30.9% participants died, and 11.3% were lost to follow-up which is similar to studies by Roden et al., Singh et al., and Chakrabarti et al.[16,18,19] In our study, three patients did not recover from anesthesia to expired within 48 hours due to anesthesia-related complications as they suffered with cardiopulmonary complications of COVID sequelae. Survival rate as reported in one of

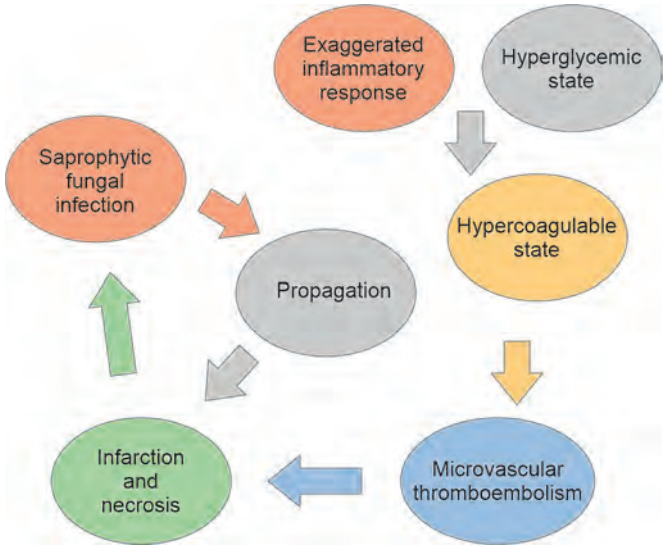


Fig. 3: Hypothesis for saprophytic fungal infection (mucormycosis)

the largest series by Roden et al. was 3% for cases that were untreated, 61% for patients treated with amphotericin B, 57% for patients treated only surgically, and 70% for patients treated with antifungal therapy and surgery both.[18]

In our study, 63.3% of patients with mucormycosis were males and 37.8% were females, while a total of 65% of all zygomycetes infections were reported in males in a study by Roden et al.[18] It is unknown why males have a greater frequency of zygomycetes infections. Estrogen plays a preventive function in paracoccidioidomycosis infections, though it has not yet been determined if oestrogen may have a protective function in zygomycetes infection.[20]

In a meta-analysis of 600 series and 851 patients, diabetes mellitus has been identified as single most important and independent risk factor for RCOM, with a death rate of 46% overall, *Rhizopus* species were the most frequently isolated species.[21]

Ever since amphotericin B was introduced about 40 years ago, the overall mortality has not changed much.[22] Early three-pronged intervention with antifungal therapy, surgical debridement, and better glycemic control may improve the outcome of this devastating infection. In a study by Greenberg et al., patients not tolerating amphotericin therapy, when switched to posaconazole therapy, experienced partial to complete response. Their patients also underwent surgical debridement alongside systemic antifungal therapy. This response may be attributed to the long half-lives of polyenes in tissue fluids working synergistically with posaconazole therapy. In our study, all patients were given oral posaconazole as an adjuvant therapy. Further evaluation is needed to assess the potential added benefit of posaconazole therapy for mucormycosis.[23]

In a review by Erener, severe COVID infection has been found to be strongly associated with a heightened risk for developing venous thromboembolism.[24] Multiple-site systemic vascular coagulation is recognized to be activated in response to infections, triggering inflammatory reactions in the host and activation of the coagulation cascade.[25] Excessive coagulation occurs as a result of severe inflammatory response, likely due to the phenomenon of "cytokine storm" in a few patients of COVID. Since individuals with diabetes are at risk for a profound inflammatory response, they may be predisposed to a hypercoagulable state. It is also noteworthy that individuals with diabetes have significantly upregulated markers of hypercoagulation and fibrinolysis in plasma.[26,27] Also, in an experimental study by Stegenga et al., hyperglycemia was found to amplify coagulation and increased insulin to impair fibrinolytic response during systemic inflammation.[28]

In our cohort, intraoperatively, well-defined areas of infarction or necrosis were observed in many patients within the areas supplied by branches from the maxillary artery system. Similar observations were made by Ahmed et al. and Abou-Ismail et al.[29,30] It is our hypothesis that this necrosis led to saprophytic fungal infection which caused further propagation of necrosis (Fig. 3).

Conclusion

Ours is the first study to document the long-term follow-up of COVID-associated mucormycosis. Diabetes mellitus was the single most important factor associated and predictor of outcome. Contrary to popular belief, industrial oxygen and masks were not the cause of the mucormycosis pandemic, as observed in various previously published studies. Additionally, immunization against COVID did provide protection not only from severe COVID but also from COVID-associated mucormycosis. It is recommended that patients with mucormycosis be followed for longer periods, as a few patients could be suffering from transient diabetes, particularly when associated with COVID. Further epidemiological studies may be needed to identify reasons for the predominance of mucormycosis in the Indian subcontinent.

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Dr. Agam C Vora
Hon. General Secretary

ORIGINAL ARTICLE

Addition of Mask to High-flow Nasal Oxygen: A Strategy to Improve Oxygenation in Hypoxemic Respiratory Failure Secondary to COVID-19

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Abstract

Purpose: High-flow nasal cannula (HFNO) reduces the need for invasive mechanical ventilation in COVID-19 patients with hypoxemic-respiratory failure. During HFNO entrainment of room air dilutes the delivered fractional inspiratory oxygen (FiO_2), thereby preventing improvement in oxygenation. The placement of a mask over HFNO to improve oxygenation has provided conflicting results. We aimed to determine and compare the effect of placing various mask types over HFNO on oxygen saturation (SPO_2).

Materials and methods: In this prospective physiological study 40 patients with COVID-19-associated hypoxemic respiratory failure on HFNO with O_2 concentration <92% were included. The effect of placing different masks over HFNO on oxygenation, respiratory rate, heart rate, blood pressure, patient comfort, and partial pressure of carbon dioxide level (pCO_2) was recorded after a prespecified time interval.

Results: We observed a significantly higher mean SPO_2 and lower mean respiratory rate on using various study masks over HFNO compared to HFNO alone. On comparing various mask types, the use of N95 masks and nonrebreather (NRB) masks with O_2 showed a significant increase in O_2 concentration and reduction in respiratory rate compared to surgical mask (SM) and NRB without O_2. The proportion of patients who achieved SPO_2 of >92% was higher with the use of N95 masks (47.5%) or NRB with O_2 (45%) over HFNO compared to SM (35%) and NRB without O_2 (35%). No significant change was observed in heart rate, blood pressure, and CO_2 level with the use of any mask over HFNO.

Conclusion: This study demonstrates improvement in oxygenation and reduction in respiratory rate with the use of various masks over HFNO in patients of COVID-19-related hypoxemic-respiratory-failure. Significantly greater benefit was achieved with the use of N95 or NRB with O_2 compared to SM or NRB without O_2.

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Introduction

The spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ranges from asymptomatic to critical illness. Nearly 15% of cases of COVID-19 have severe disease and require hospitalization; while 5% of cases progress to critical disease and require admission and management in intensive care. Among patients with critical illness, intubation rates vary between 5 and 88%.[1] Respiratory support and O_2 supplementation using conventional oxygen therapy (COT) devices, a high-flow nasal cannula (HFNO), noninvasive (NIV), and invasive ventilation form the cornerstone for the management of hypoxemic respiratory failure in COVID-19. However, due to the rapid increase in case burden during the current pandemic, the major concern in the management of severe to critical COVID-19 patients has been the insufficient availability of beds in intensive care units.[2]

High-flow nasal cannula (HFNO) has been successfully used in the management of hypoxemic respiratory failure in patients with COVID-19. Although comparable to NIV, its use reduces the need for invasive mechanical ventilation as well as a reduction in the duration of intensive care unit (ICU) stay when compared to COT.[3–7] However; entrainment of room air while using HFNO reduces the delivered fractional inspiratory oxygen (FiO_2) and prevents improvement in oxygenation.[8] In addition, there is a potential risk of aerosol dispersion and disease transmission to healthcare workers.[9]

Use of mask over HFNO may reduce both entrainment of room air as well as aerosol dispersion. In two recent observational studies that used SM and nonrebreather (NRB) over HFNO in patients with hypoxemic respiratory failure, significant improvement in oxygenation was observed with SM only.[10,11] There is a paucity of literature regarding the potential benefit of placing a mask over HFNO in terms of improvement in oxygenation. With this background, we aimed to determine the effect of placing various types of masks over HFNO on oxygenation in patients with hypoxemic respiratory failure due to COVID-19.

Materials and Methods

This prospective physiological study was conducted at Sher-i-Kashmir Institute of Medical Sciences, a tertiary care center in North India. The center serves as a referral center for the management of severe and critically ill COVID-19 patients in the union territory of Jammu and Kashmir. The study protocol was approved by the Institutional Ethical Committee.

Study Population

Patients aged ≥18 years with documented SARS-CoV-2 infection based on positive nasopharyngeal RT-PCR and hypoxemic respiratory on HFNO were assessed for inclusion in the study. Patients with oxygenation saturation (SPO_2) <92% on HFNO despite maximum flow and FiO_2 were included. Those with hemodynamic instability requiring inotropic support, impairment in consciousness, or required NIV ventilation, or urgent intubation were

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excluded. A written informed consent was obtained from all the participants.

Study Objectives

The primary objective of the study was to determine the effect of using SM, N95, NRB, and NRB/O_2 (15 L/minute) over HFNO on SPO_2 as measured by pulse oximeter. The secondary objectives were to determine the effect on heart rate, blood pressure, level of consciousness [Glasgow Coma Scale (GCS)], respiratory rate, the partial pressure of carbon dioxide level (pCO_2), and patient comfort using a visual analog scale (VAS). VAS ranges from 0 to 10, where "0" indicates no discomfort and "10" maximum discomfort.[12]

High-flow O_2 was provided by using the Airvo2 high-flow nasal system manufactured by Fisher & Paykel Healthcare. Proper use of HFNO was confirmed in each patient. HFNO settings (flow and FiO_2) were adjusted to target SPO_2 of >92% and were kept constant throughout the study period. The study design comprised five sequential sessions of 30 minutes each as represented in the flowchart (Fig. 1). In the first session patients fulfilling the study inclusion criteria were explained the study protocol and consent for study participation was obtained. Demographic profile, disease severity, and comorbid illnesses from each patient were noted. Study parameters including the level of consciousness (GCS), heart rate, blood pressure, respiratory rate, oxygen saturation, and VAS score were obtained and noted down. In addition, a venous blood sample was drawn for the estimation of CO_2 concentration. This was followed by the next session in which an N95 mask was placed over HFNO. After 30 minutes of observation, study parameters were recorded. During the third session, N95 was replaced by SM. Proper fit and tight seal of SM mask over HFNO was ensured. Study parameters were recorded after 30 minutes of observation. In the last two sessions, NRB followed by NRB/O_2 at 15 L/minute were used over HFNO, each for a period of 30 minutes, to obtain the study parameters.

Statistical Analysis

Categorical variables were represented by a number of cases and percentages while quantitative data as mean ± standard deviation or median with interquartile range whichever was applicable. The difference in means of various parameters between study groups was analyzed by using analysis of variance with Bonferroni correction for multiple comparisons. Dunnett's multiple comparison was used to compare the means of the control group (HFNO alone) from various experimental groups (HFNO plus various types of masks). The *p*-value of <0.05 was considered significant. Data was entered on Microsoft Excel 2019. Statistical analysis was done by using IBM Statistical Package for the Social Sciences statistics (SPSS) version 26.0 whereas graphs were built using IBM SPSS statistics version 26.0 and graph pad prism version 8.0.1.

Results

The study recruited a total of 40 patients with hypoxemic respiratory failure due to COVID-19. The mean age of the study population was 59.33 ± 13.72 years. Females constituted 62.5% (*n* = 25) of total participants. Hypertension (57.5%) followed by diabetes (37.5%) were the common comorbid illnesses observed among participants. All patients had bilateral lung involvement on chest computed tomography (CT) with a mean CT severity index (CTSI) of 13.8 ± 3.0. The majority of the patients (*n* = 22; 55%) had critical COVID-19 illness. The median Sequential Organ Failure Assessment (SOFA) score was 2 [interquartile range (IQR) 2–3] with a major contribution from severe hypoxemia. The median World Health Organization grade (representing the severity of COVID-19) was 5 (IQR 5–5) (Table 1). Various clinical and laboratory parameters of patients while on HFNO alone and after placing different types of masks on HFNO are given in Table 2.

All patients on HFNO received 100% FiO_2 at a flow rate of 60 L/minute. The mean SPO_2 while patients were receiving HFNO alone was 82.72 ± 8.14. We observed significant improvement in SPO_2 with the use of each type of mask over HFNO compared to HFNO alone. Mean SPO_2 increased to 89.77 ± 6.45, 87.67 ± 6.54, 89.67 ± 5.98, and 87.55 ± 6.68 on placing N95, SM, NRB, and NRB/O_2, respectively over HFNO (Fig. 2A).

On comparing the effects of various mask types used on SPO_2, a significant increase in oxygenation concentration was observed

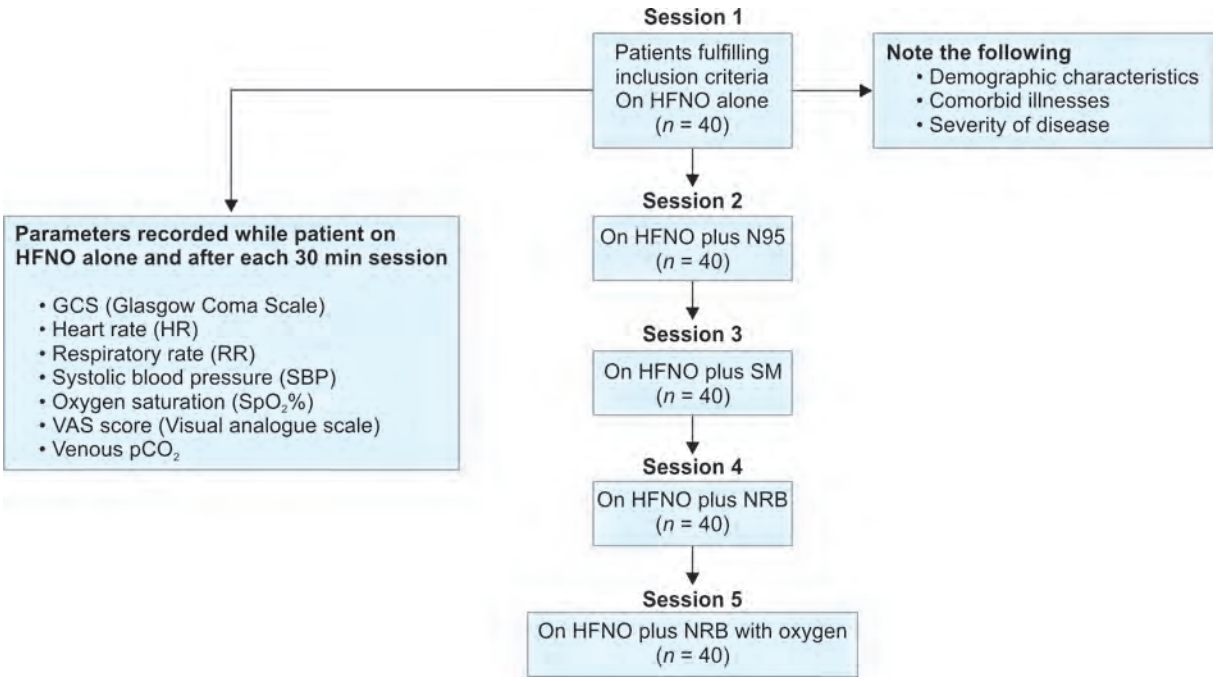


Fig. 1: Study design

with the use of N95 and NRB/O_2 over HFNO compared to SM and NRB without O_2. The mean increase in SPO_2 was 7.05 ± 3.87 with the use of N95 and 6.95 ± 3.44 with NRB/O_2, while it was 4.82 ± 3.27 and 4.95 ± 3.10 with SM and NRB, respectively (Table 2 and Fig. 3A). However, no significant difference was observed on comparing N95-mask with NRB/O_2 with each other. We also observed that the proportion of patients who achieved SPO_2 of >92% was higher when N95 or NRB/O_2 was added to HFNO (47.5%, *n* = 19 with N95, 45%, *n* = 18 with NRM/O_2, 35%, *n* = 14 with NRB and 35%, *n* = 14 with SM) (Fig. 4).

The mean respiratory rate was significantly lower while using various mask types over HFNO compared to HFNO alone (Table 2 and Fig. 2B). It was noted that a significant reduction in mean respiratory rate was achieved with use N95 mask and NRB/O_2 compared to NRB without O_2 and SM over HFNO (Table 2, Fig. 3B). Respiratory rate as well as patient comfort measured by VAS was significantly reduced with addition of each type of mask over HFNO, thus, reflecting improvement in respiratory failure.

No significant change in CO_2 level was observed with the addition of different masks to HFNO. Likewise, we did not observe any significant change in other study parameters including heart rate, blood pressure, and level of consciousness (Table 2).

Table 1: Baseline characteristics of patients

Baseline characteristics	*(n = 40)*
Age in years (mean ± standard deviation)	59.33 ± 13.72
Gender, *n* (%)	
Males	15 (37.5)
Females	25 (62.5)
Comorbid illnesses, *n* (%)	
Hypertension	23 (57.5)
Diabetes	15 (37.5)
Hypothyroidism	5 (12.5)
Lung diseases (COPD, ILD, Asthma)	4 (10)
CKD	1 (2.5)
Duration of illness (mean ± standard deviation)	21.15 ± 9.7
Severity COVID-19 on presentation, *n* (%)	
Severe	18 (45)
Critical	22 (55)
SOFA score, median (IQR)	2 (2–3)
CT severity index (CTSI)	13.8 ± 3.0
WHO grade of illness, median (IQR)	5 (5–5)

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CTSI, computed tomography severity index; ILD, interstitial lung disease; IQR, interquartile range, SOFA, sequential organ failure assessment

Discussion

Our study demonstrated a significant increase in SPO_2 in severely hypoxemic COVID-19 patients on HFNO with the addition of different types of masks. The highest improvement in SPO_2 was achieved with the use of an N95 mask or NRB/O_2 at 15 L/minute over HFNO compared to SM and NRB.

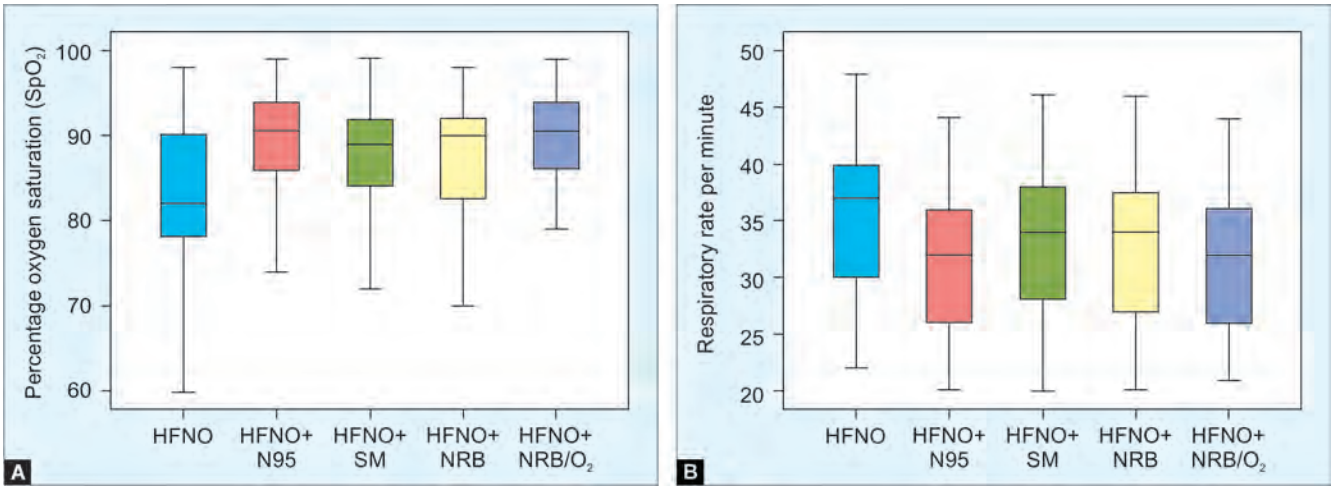
Te HFNO has been utilized in the management of hypoxemic respiratory failure secondary to severe COVID-19. In resource-constrained areas, the use of HFNO in the non-ICU environment has been found feasible, and nearly half of the patients with severe COVID-19 escape the need for mechanical ventilation.[5,6] However, a higher flow rate required by patients with hypoxemic respiratory failure exceeding the flow provided by HFNO as well as open-mouth breathing favors entrainment of room air that results in reduced delivery of FiO_2 and failure to improve SPO_2. Patients who fail on HFNO and need invasive ventilation pose a challenge to collapsing healthcare systems, especially in the developing world. Using a mask over HFNO is proposed to reduce entrainment of room air and thus augment oxygenation achieved by HFNO.[10] In addition, the positive end expiratory pressure (PEEP) generated with HFNO which depends upon the presence and extent of leaks around nostrils and mouth may also be maintained or augmented with the use of a well-fitting mask.[13]

Montiel et al. were the first to demonstrate improvement in SPO_2 with the use of SM on HFNO. He included 21 hypoxemic COVID-19 patients with a mean SPO_2 of 91.8 ± 1%. The use of SM over HFNO significantly increased SPO_2 (mean SPO_2 94.4 ± 1% on HFNO plus SM).[10] Our study included more severely hypoxemic patients with a mean SPO_2 of

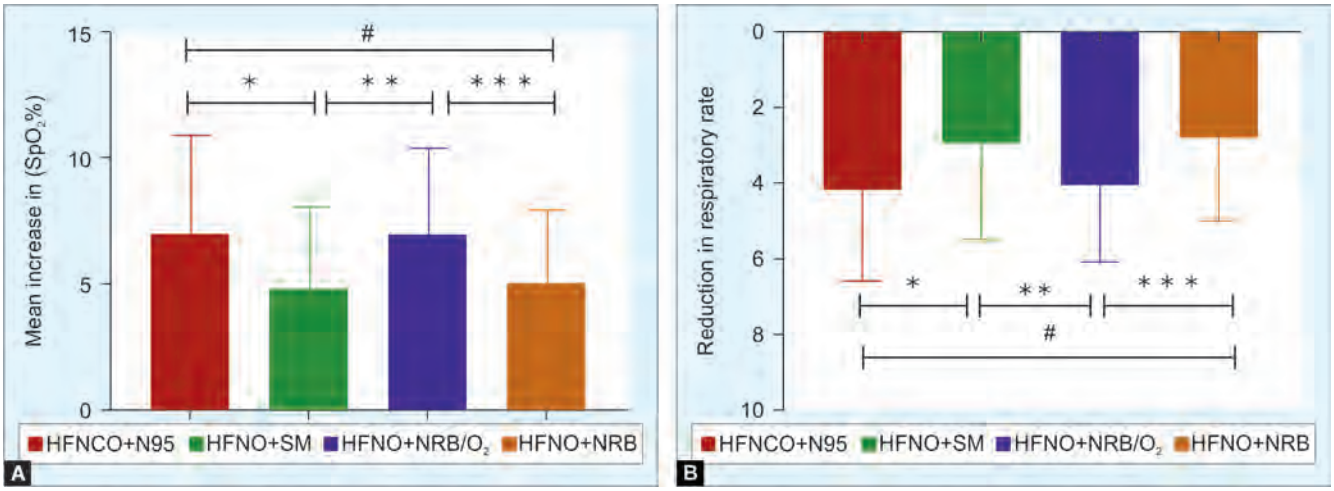
Table 2: Various clinical and laboratory parameters on HFNC alone and HFNC with different types of masks

Patient parameters	*HFNO alone*	*HFNO plus SM*	*HFNO plus N95*	*HFNO plus NRB*	*HFNO plus NRB with O_2*	*p-value*
GCS, median (IQR)	15 (15–15)	15 (15–15)	15 (15–15)	15 (15–15)	15 (15–15)	–
HR/minute, mean ± SD	100.4 ± 15	92.40 ± 19.64	93.37 ± 14.07	95.37 ± 13.61	94.65 ± 14.02	–
SBP mm Hg, mean ± SD	125.15 ± 9.3	122 ± 11.36	121 ± 10.32	121 ± 10.57	122.15 ± 11.33	–
RR/minute, mean ± SD	35.95 ± 6.75	32.9 ± 6.45	31.75 ± 6.24	33.12 ± 6.35	31.87 ± 6.18	*
SPO_2, mean ± SD	82.72 ± 8.14	87.55 ± 6.68	89.77 ± 6.45	87.67 ± 6.54	89.67 ± 5.98	**
pCO_2 mm Hg, mean ± SD	36.91 ± 4.2	33.47 ± 6.47	36.15 ± 11.86	28.77 ± 7.7	39.77 ± 10.96	–
VAS, median (IQR)	7 (6–8)	6 (5–7)	6 (5–6.75)	6 (5–7)	6 (5–6)	***
Change in SPO_2, mean ± SD#	–	4.28 ± 3.27	7.05 ± 3.87	4.95 ± 3.10	6.95 ± 3.44	–
Change in respiratory rate/minute, mean ± SD#	–	2.9 ± 2.5	4.2 ± 2.4	2.82 ± 2.19	4.07 ± 2.03	–

GCS, Glasgow Coma Scale; HR, heart rate; NRB, nonrebreather mask; NRB/O_2, nonrebreather mask plus oxygen supplementation; pCO_2, partial pressure of carbon dioxide; RR, respiratory rate; SBP, systolic blood pressure; SM, surgical mask; VAS, visual analog scale; **p*-value between groups for respiratory rate; HFNO vs HFNO plus SM = 0.039, HFNO vs HFNO plus N95 = 0.004, HFNO vs HFNO plus NRB/O_2 = 0.005, HFNO vs HFNO plus NRB = 0.05; ***p*-value between groups for SPO_2; HFNO vs HFNO plus SM = 0.015, HFNO vs HFNO plus N95 = 0.001, HFNO vs HFNO plus NRB/O2 = 0.001, HFNO vs HFNO plus NRB = 0.012; ****p*-value between groups for VAS; HFNO vs HFNO plus SM = 0.048, HFNO vs HFNO plus N95 = 0.009, HFNO vs HFNO plus NRB/O2 = 0.008, HFNO vs HFNO plus NRB = 0.042



Figs 2A and B: Box and Whisker plot. (A) SPO_2; (B) Respiratory rate (RR/minute) on HFNO alone and HFNO with different types of masks. SM, surgical mask; NRB, nonrebreather mask; NRB/O_2, nonrebreather mask plus oxygen supplementation



Figs 3A and B: (A) Mean increase in SpO_2(%) with HFNO in the presence of different types of masks. *p = 0.022, **p = 0.035, ***p = 0.049, #p = 0.032; (B) Mean reduction in respiratory rate (RR/minute) with HFNO in the presence of different types of masks. *p = 0.018, **p = 0.034, ***p = 0.016 and #

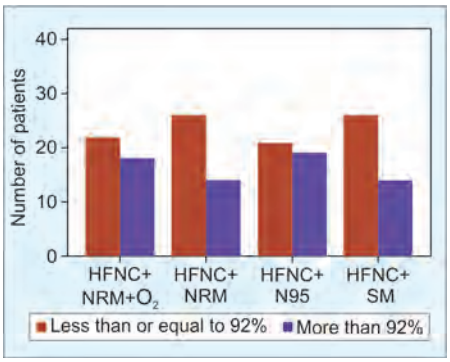


Fig. 4: Proportion of patients with SpO_2 of >92% on HFNO plus various mask types

82.72% on HFNO alone. The use of SM over HFNO significantly increased SPO_2 (mean SPO_2 87.67 ± 6.45) compared to HFNO alone. Out of 40 patients with hypoxemic respiratory failure 35% (n = 14) achieved target SPO_2 of ≥92% on the addition of SM to HFNO compared to only 12.5% (n = 5) patients on HFNO alone.

On comparing SM with N95, significant improvement in oxygenation was attained with the use of an N95 mask over HFNO (mean SPO_2 89.77 ± 6.45). In addition, a significantly higher proportion of patients (47.5%, n = 19) was achieved.

Recommended target SPO_2. These results may be attributed to better seal achieved with the use of N95 which further reduces entrainment of room air.

In an observational study, the use of NRB over HFNO in patients with hypoxemic respiratory failure resulted in a mean increase in SPO_2 by 1.79% (mean SPO_2 of 92.23% on HFNO alone and 94.01% after adding NRM; p = not significant).[11] We observed a significant increase in mean oxygenation by 4.95% with the use of NRB over HFNO. Also, with the use of NRB over HFNO, 35% (n = 14) of patients achieved a target saturation of ≥92%. In addition, on supplementing O_2 at 15 L/minute *via* NRB, there was an increase in both oxygenation (increase in mean SPO_2 by 6.95%) as well as the proportion of patients who attained target saturation ≥92% (n = 18,45%). These findings were almost similar to what was observed with the use of N95 mask over HFNO. Better oxygenation achieved with supplementation of O_2 *via* NRB could be explained by the compensatory effect of O_2 supplementation to the improper seal of mask around the face making it insufficient to prevent entrainment of room air.

Montiel et al. reported a decrease in respiratory rate from a mean of 27.8/minute–26.2/minute (p < 0.05) with the use of SM over HFNO.[10] In our study, a significantly lower respiratory rate was achieved with the use of an N95 mask over HFNO compared to other mask types. However, a significantly higher reduction in respiratory rate was achieved with the use of an N95 mask and NRB with O_2 over HFNO compared to SM and NRB without O_2. A greater increase in SPO_2 with the use of

N95 or NRB/O_2 over HFNO compared to other masks may explain these results.

There is a concern that the use of face masks impairs gas exchange, resulting in hypoxemia and/or hypercarbia. However, observational studies on healthy adult volunteers have not reported any significant effect on gas exchange (hypoxemia and/or hypercarbia) with the use of SM or N95 mask.[14,15] In our study no significant change in pCO_2 was observed with the use of any type of masks over HFNO. Similarly, Montiel et al. did not report retention of CO_2 on placement of SM over HFNO in patients with hypoxemic respiratory failure related to COVID-19.[10] It has been shown that prolonged use of masks is associated with discomfort among healthcare workers.[16] However, we observed a significant improvement in comfort level in patients with respiratory failure on the addition of various masks over HFNO compared to HFNO alone, reflecting improvement in respiratory failure associated with the addition of various types of masks. In addition, our study used masks for a shorter period of time (only for 30 minutes) which may not be enough to perceive discomfort related to wearing a mask over HFNO.

Arterial blood gas is routinely used in monitoring patients with respiratory failure; however, the procedure is painful and technically demanding. In our study patients with respiratory failure were monitored by using finger pulse oximetry and estimation of venous CO_2 level. In a study by Koul et al., that included 100 patients with respiratory failure, venous estimation of pH, pCO_2, HCO_3 plus digital SPO_2 significantly correlated with corresponding arterial blood gas analysis.[17] Therefore, the use of finger oximetry and venous CO_2 estimation can obviate the need for more invasive and painful arterial blood gas sampling.

Based on the available scientific data there is no evidence of an increased risk of aerosol generation and dispersion during HFNO devices compared to other high-flow O_2 therapy.[18] However, the addition of a surgical mask to HFNO is believed to reduce the dispersion of infected aerosols.[19] N95 mask having better filterability for infected aerosols compared to other masks may serve an added advantage to contain the possible spread of COVID-19 to healthcare workers.[20–22]

Limitation

Since our study was an observational physiological study, the effect of wearing different mask types over HFNO on patient outcome in terms of the need for mechanical ventilation or mortality was not studied. Only a few patients with chronic obstructive pulmonary disease (COPD) without respiratory acidosis were included, therefore the findings of the study may not be applicable in patients with severe COPD. As various masks were used only for shorter periods of time, we didn't observe significant patient discomfort and retention of CO_2, however, studies with a larger number of patients to be observed over a prolonged period of time are required to see these effects. Lastly, the effect on arterial oxygenation and P/F ratio was not evaluated as only venous blood was drawn for estimation of pCO_2 to avoid patient discomfort.

Conclusion

This study demonstrates an improvement in oxygenation and a decrease in respiratory rate without a concomitant increase in discomfort or pCO_2 on wearing a mask with HFNO. Maximum improvement was documented with the use of an N95 mask followed by NRB with supplemental O_2. This is the first study to document improvement in respiratory failure in patients with severe to critical COVID-19 with the addition of an N95 mask over HFNO. Furthermore, the use of NRB with or without supplemental O_2 in addition to HFNO has never been studied previously and our study is novel to introduce such a concept and document improvement in respiratory failure in critical COVID-19 subjects. Thus, adding a mask, preferably N95 to HFNO should be considered in a subset of patients who remain hypoxemic despite HFNO.

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ORIGINAL ARTICLE

Statin Usage in Peripheral Arterial Disease Patients

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Abstract

Objectives: Atherosclerotic cardiovascular disease (ASCVD) events have been shown to occur at higher frequency in patients with peripheral arterial disease (PAD). In this study, our aim is to evaluate whether statin is being used appropriately in patients with PAD and also evaluate its usage with the number of vascular beds involved.

Materials and methods: This retrospective cross-sectional study reviewed data of patients with a confirmed diagnosis of PAD based on invasive or noninvasive imaging. Demographic, clinical, laboratory, and treatment data collected were described using descriptive statistics. Multiple logistic regression analysis was conducted to determine the predictors for the prescription of statins (HIS). High-intensity statin therapy was defined as atorvastatin ≥40 mg per day, rosuvastatin ≥20 mg per day, or simvastatin ≥80 mg per day, according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.

Results: We analyzed data from 166 patients who met the inclusion criteria. The mean age was 63.34 years. The most common comorbidity was diabetes mellitus (DM) (68.86%). Statins were used in 82% of patients, among whom only 39% were on high-intensity statins.

Multiple logistic regression analysis revealed that patients with cerebrovascular disease (CVD) [odds ratio (OR) = 0.19, 95% confidence interval (CI) = 0.06–0.61, p = 0.005], on oral anticoagulants (OAC) (OR = 0.16, 95% CI = 0.04–0.62, p = 0.008) and on dual antiplatelet therapy (DAPT) (OR = 0.20, 95% CI = 0.08–0.47, p < 0.000) had lower odds of receiving lower extremity revascularization (LIS) therapy.

Conclusion: Despite having a high risk of future adverse cardiac events, patients with PAD are less likely to receive appropriate statin therapy. Involvement of more vascular beds was associated with higher chances of initiating high-intensity statin.

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Introduction

Peripheral arterial disease (PAD) affects more than 202 million patients worldwide.[1] Atherosclerotic cardiovascular disease (ASCVD) events have been shown to occur at a higher frequency in patients with PAD.[2] Previous studies have suggested that statin usage among PAD patients is low.[3] In this study, our aim is to evaluate whether statin is being used appropriately in patients with PAD and also evaluate its usage with the number of vascular beds involved.

Review of Literature

Peripheral arterial disease (PAD) refers to atherosclerotic disease involving the upper and lower extremities as per the recommended nomenclature for peripheral vascular disease by Atherosclerotic Peripheral Vascular Disease Symposium II of the American Heart Association (AHA).[4] PAD most commonly affects lower limbs. Estimates of PAD are derived from ankle brachial pressure index (ABI) screening programs. An ABI of ≤0.9 indicates a stenosis of ≥50% in peripheral arteries.[5] Using this definition in a cross-sectional study in the United States of America prevalence of PAD in a population aged ≥40 years was found to be around 5.9%.[6]

In India, based on ABI data, PAD is prevalent among patients with diabetes mellitus (DM). It was found to be around 7.6%.[7] The prevalence of PAD is known to increase with age, and registry data among the older population aged 60–79 years in the state of Kerala, India, showed that 26.7% of them had PAD.[8] Prior studies suggest that the presence of PAD, whether asymptomatic or symptomatic, is associated with an increased risk of future ASCVD events.[9,10] Hence, appropriate preventive strategies and treatment of risk factors are paramount in reducing the cardiovascular disease burden. Furthermore, evidence suggests that patients with PAD have more extensive atherosclerosis compared to patients who have coronary heart disease (CHD) or cerebrovascular disease (CVD).[9,11] Patients with PAD are recommended to be on high-intensity statin (HIS) therapy [low-density lipoprotein cholesterol (LDL-C) of <70 mg/dL or ≥50% reduction].[12] Several studies have shown that statins improve walking distance,[13,14] limit adverse limb events,[15] and improve the cardiovascular prognosis[14,16] in patients with PAD.

However, previous studies indicate that compared to patients with CHD and CVD, the prescription of stains in patients with PAD is low.[2,3,17] As the PAD carries significant future ASCVD events, this can indicate a major shortcoming in risk preventive strategies. There have not been any studies evaluating the appropriate usage of statin in PAD patients in India. In this study, we plan to evaluate the appropriate use of statin in patients with PAD. We will also compare the statin usage with the presence of PAD, CHD, and CVD.

Aims

- To evaluate the appropriate usage of statin in PAD patients.
- To analyze the usage of statin in patients with PAD and disease in other vascular beds.

Materials and Methods

A retrospective cross-sectional study was conducted, which reviewed data from adult (aged >18 years) patients admitted to a teaching hospital between 2017 and 2020 with a confirmed diagnosis of PAD based on invasive or noninvasive imaging. Demographic, clinical, laboratory, and treatment data collected were described using descriptive statistics. Multiple logistic regression analysis was conducted to determine the predictors for the prescription of statins. High-intensity statin therapy was defined as atorvastatin ≥40 mg per day, rosuvastatin ≥20 mg per day, or simvastatin ≥80 mg per day according to American College of Cardiology (ACC)/AHA guidelines.[18]

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Table 1: General characteristics of patients

Parameters	*No. of patients/166*	*%*
Hypertensive (HTN)	100	59.88%
Diabetic (DM)	115	68.86%
CAD	57	34.13%
CKD	33	19.76%
DLP	24/158	15.19%
CVD	25/166	15.06%
On aspirin	127/162	78.40%
On P2Y12i	56/162	34.57%
On angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker	45/162	27.78%
On β-blocker (BB)	58/162	35.80%
On OAC	15/162	9.26%
On cilostazol	25/162	15.43%
On pentoxifylline	2/162	1.23%
LDL-C >130	16/166	9.64%
DAPT	78/166	46.98%

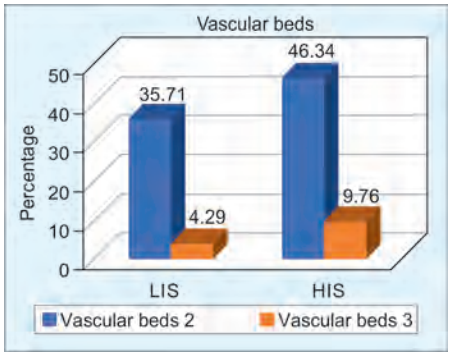

Fig. 1: Statin use in PAD with other vascular beds involvement

Table 2: Characteristics of statin usage

Parameters	*No. of patients*	*Percentage*
On statins	137/167	82.04%
On high statin use	54/137	39.41%
On low statins	83/137	60.58%

Table 3: Gender distribution

Parameters	*No. of patients*	*Percentage*
Males on HIS	45/137	32.84%
Females on HIS	9/30	30%

HIS, high-intensity statin

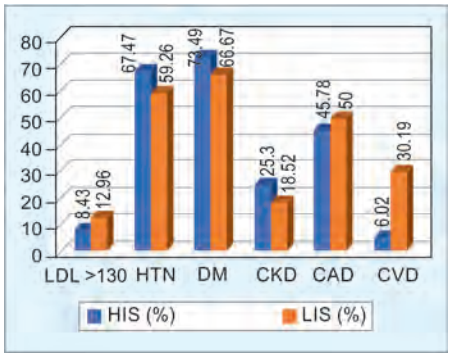

Fig. 2: Statins used in comorbidities

Results

We analyzed data from 166 patients who met the inclusion criteria of the study. The mean age of patients was 63.34 years, standard deviation (SD) = 14.085. A total of 82% of the study population was male. Table 1 contains the general characteristics of the patients included.

The most common comorbidity was DM, which was seen in 68.86% of patients. This was followed by hypertension and coronary artery disease at 59.88 and 34.13%, respectively. Other comorbidities seen were dyslipidemia (DLP), chronic kidney disease (CKD), and CVD. Aspirin was used in more than two-thirds of patients (78.4%), followed by P2Y12 inhibitors in a third of patients. Furthermore, the usage of cilostazol and pentoxyfylline was found to be low at around 15 and 1%, respectively. About half of the patients were on dual antiplatelet therapy (DAPT). The percentage of patients with LDL cholesterol of >130 mg/dL was low at 9.64%.

Statin Usage

Statins were used in 82% of patients, indicating that 18% of those who could have benefited from them were not initiated on these drugs. Of the patients who had been prescribed statins, only 39% were on high-intensity statins, and almost two-thirds of them were on low-intensity statins (Table 2).

There was no difference in HIS usage among males and females (Table 3).

The mean age was similar in both groups of lower extremity revascularization (LIS) and HIS patients. The mean LDL level also was similar in both groups. More number of patients who had two or more vascular beds involved were put on HIS. Among patients on HIS, 46% had two vascular beds involved, and 9.76% of patients had three vascular beds involved (Fig. 1). A greater proportion of patients who had CVD and who were on DAPT and oral anticoagulants (OAC) were on HIS than other comorbidities. Other comorbidities and usage of other drugs were similar in both groups (Fig. 2).

Multiple logistic regression analysis revealed that patients with CVD [odds ratio (OR) = 0.19, 95% confidence interval (CI) = 0.06–0.61, $p = 0.005$], on OAC (OR = 0.16, 95% CI = 0.04–0.62, $p = 0.008$) and on DAPT (OR = 0.20, 95% CI = 0.08–0.47, $p < 0.000$) had lower odds of receiving LIS therapy.

Discussion

The current analysis reveals that patients who have PAD, despite being at high risk of future atherosclerotic events, are less likely to be on appropriate statin therapy. PAD indicates that there is systemic atherosclerosis, and this could be masked as these patients may have difficulty ambulating and exercising. Hence, appropriate statin therapy is a cornerstone in the prevention of future atherosclerotic events. As observed in this study, 82% of patients with PAD were on statins. That means 18% of patients were not on a statin which can help in limiting adverse events and improving morbidity and cardiovascular prognosis.

Among the patients who were on statins, almost 60% were not on guidelines-directed high-intensity statins. In spite of this, only 8.4% of patients on LIS had uncontrolled LDL as compared to 12.9% in the HIS group. This suggests that the dose of statins is still being intensified on the basis of LDL values rather than based on the presence of disease as directed by guidelines. More awareness is required among health care providers for initiation of HIS regardless of cholesterol values as is done in acute coronary syndrome (ACS) patients, which being more discussed disease has better adherence to guidelines directed management. Involvement of more vascular beds was also associated with high-intensity statin initiation. Among patients on HIS, around 50% had more than one vascular bed involved. Although

Table 4: Characteristics of LIS and HIS

Parameters	*LIS (83)*	*HIS (54)*
Mean age (SD)	64.72 (SD: 14.84)	62.29 (SD: 11.28)
Vascular beds (2)	25/70 = 35.71%	19/41 = 46.34%
Vascular beds (3)	3/70 = 4.29%	4/41 = 9.76%
Median LDL	76 mg/dL	77 mg/dL
LDL-C >130	7/83 = 8.43%	7/54 = 12.96%
HTN	56/83 = 67.47%	32/54 = 59.26%
DM	61/83 = 73.49%	36/54 = 66.67%
CKD	21/83 = 25.30%	10/54 = 18.52%
CAD	38/83 = 45.78%	27/54 = 50%
CVD	5/83 = 6.02%	16/53 = 30.19%
DAPT	16/83 = 19.28%	31/54 = 57.41%
ACEi/ARB	27/83 = 32.53%	17/54 = 31.48%
BB	29/83 = 34.94%	27/54 = 50%
Cilostazol	15/83 = 18.07%	7/54 = 12.96%
Pentoxifylline	1/83 = 1.20%	1/54 = 1.85%
OAC	4/83 = 4.82%	9/54 = 16.67%

among these groups also many were on LIS (Table 4).

There is no difference in terms of age or gender with regard to the usage of high-intensity statin therapy. Furthermore, PAD patients who have CVD and those who are on DAPT and OAC are less likely to receive LIS. However, this association was not found in patients with CAD. This could suggest that when patients come in contact with specialties dealing with these comorbidities, they are more likely to receive appropriate statin therapy. This indicates that there is a need to intensify the secondary prevention strategies with statins among all specialties dealing with these patients. Patients in this study are likely to be sicker and with many comorbidities; hence the actual usage of appropriate statin among all patients may be much lower than what has been shown in the study. The study has limitations as it is a single-center study, and all patients were those who were admitted to different departments.

Conclusion

Despite having a high risk of future adverse cardiac events, patients with PAD are less likely to receive appropriate statin therapy. Involvement of more vascular beds was associated with higher chances of initiating high-intensity statin. More awareness is required among healthcare providers for initiation of HIS regardless of cholesterol values, as is done in ACS patients.

What is already known?

Patients with PAD are recommended to be on high-intensity statin therapy (LDL-C of <70 mg/dL or ≥50% reduction)

What does this study add?

Patients with PAD are less likely to receive appropriate statin therapy, and more awareness is required among healthcare providers for initiation of HIS regardless of cholesterol values, as is done in ACS patients

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Abridged Prescribing Information

Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets **Indication:** For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycaemic control. **Dosage and Administration:** The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed. **Adverse Reactions:** For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur; allergic reactions or pseudo allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in Vit B12 absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders. **Warnings and Precautions:** For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly. **Contraindications:** Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma). Severe renal failure (GFR<30ml/min). In pregnant women. In lactating women.Acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents); acute or chronic disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock); hepatic insufficiency; acute alcohol intoxication; alcoholism. **Use in a special population:** Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
Additional information is available on request.
Last updated: March 13, 2023

For the use of registered medical practitioner, hospital or laboratory.*

*In case of any adverse events, kindly contact: pv@usv.in

*In **T2DM** Uncontrolled on **dual FDCs**,*

Uptitrate with

UDAPA-Trio

Dapagliflozin 10 MG + Sitagliptin 100 MG + Metformin 500 MG XR

UDAPA-Trio Forte

Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 1000 mg XR

CONTROL
COMPLIANCE
Turn Towards Improved

CARDIO RENAL CARE

Abridged Prescribing Information

UDAPA-TRIO Forte UDAPA-TRIO Dapagliflozin, Sitagliptin & Metformin Hydrochloride Extended Release Tablets Composition: Dapagliflozin 10 mg, Sitagliptin 100 mg & Metformin Hydrochloride Extended Release 1000 mg tablets Dapagliflozin propanediol monohydrate eq. To Dapagliflozin 10 mg Sitagliptin Phosphate Monohydrate IP Eq. Sitagliptin 100 mg Metformin Hydrochloride IP (as Extended Release) 1000 mg Dapagliflozin10 mg, Sitagliptin 100 mg & Metformin Hydrochloride Extended Release 1000 mg tablets Dapagliflozin propanediol monohydrate eq. To Dapagliflozin 10 mg Sitagliptin Phosphate Monohydrate IP Eq. Sitagliptin 100 mg Metformin Hydrochloride IP (as Extended Release) 500 mg Indication: It is indicated as an adjunct to diet and exercise to improve Glycemic Control adults with type 2 diabetes mellitus Recommended Dosage: As directed by the physician. Method of Administration: Oral Adverse Reactions: Most common adverse reactions reported are: Dapagliflozin - Female genital mycotic infections, Nasopharyngitis, Urinary tract infections. Sitagliptin - Upper respiratory tract infection, nasopharyngitis and headache. Metformin - Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Warnings and Precautions: Dapagliflozin: Volume depletion; Ketoacidosis in patients with Diabetes Mellitus; Urosepsis and Pyelonephritis; Hypoglycemia; Genital mycotic infections Sitagliptin: General: Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of Diabetic Ketoacidosis. Acute pancreatitis: Hypoglycemia is used in combinations when combined with other anti-hyperglycemic medicinal product; Renal impairment: Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions - Steven johnson syndrome; Bullous pemphigoid Metformin Hydrochloride: Lactic acidosis; In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Contraindications: Hypersensitivity to the active substance of Dapagliflozin, Sitagliptin & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma; Severe renal failure (eGFR < 30ml/min); Acute conditions with the potential to alter renal function such as: Dehydration, Severe infection, Shock; Acute or chronic disease which may cause tissue hypoxia such as: Cardiac or respiratory failure. Recent myocardial infarction, Shock, Renal Impairment, Acute intoxication, Alcoholism. Use in special population: Pregnant women: Due to lack of human data, drugs should not be used during pregnancy. Lactating women: It should not be used during breastfeeding. Pediatric patients: The safety and efficacy of drugs has not yet been established. No data is available. Geriatric Patients: In patients >65 years, it should be used with caution as age increases. For Additional Information/full prescribing information, please write to us: USV Private Limited, Arvind Vithal Gandhi Chowk, B.S.D Marg, Govandi, Mumbai - 400088
Last updated on 02/04/2024.

USV Private Limited Corvette Team

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UDAPA

Dapagliflozin 5mg & 10mg

TURN TOWARDS IMPROVED METABOLIC HEALTH

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USFDA ANDA Approval

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- Bioequivalent & Therapeutically Equivalent to Innovator
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Introducing

Intensify Diabetes Therapy in uncontrolled PwD

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Reduce insulin requirement by **17.2%**[1]

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Reference: 1.Ponssen HH, Elte JW, Lehert P, Schouten JP, Bets D. Combined metformin and insulin therapy for patients with type 2 diabetes mellitus. Clin Ther. 2000;22(6):709-718. doi:10.1016/S0149-2918(00)90005-5
2.Ref b: Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle H-J. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2012;14(6):565-574.

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In uncontrolled T2DM patients with HbA1c <8%

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℞ UDAPA-M XR

Dapagliflozin 5mg/10mg + Metformin Extended Release Tablets (500mg/1000mg)

Better ↑ Turn with superior Weight + A1c reduction

Better outcomes than other first line monotherapies and metformin combinations

Better weight reduction 3.3 kg +

Better A1c reduction 2.1% +

Weight reduction[1]

HbA1c reduction[2]

Improves insulin sensitivity

CV risk reduction

Also Available

UDAPA-S 10/100

Dapagliflozin 10 mg + Sitagliptin 100 mg Tablets

↑ turn to a life 'IN RANGE'

Ref.
1. Clamp, L. et al. Enhanced insulin sensitivity in successful, long-term weight loss maintainers compared with matched controls with no weight loss history. Nutr. Diabetes 7, e282 (2017)
2. Hu Y. Advances in reducing cardiovascular risk in the management of patients with type 2 diabetes mellitus. Chronic Dis Transl Med. 2019 Mar 15;5(1):25-36.

ABDOMINAL AORTIC ANEURYSM (AAA)

INFORMATION FOR HEALTH CARE PROVIDERS

AAA is a localized ballooning of the aorta. If an AAA rupture occurs, overall mortality is 75–90%, making it the third leading cause of sudden death in men over 60. For this reason, it is very important to diagnose and preventatively treat AAAs.

Normal Aorta

Aorta with Large Abdominal Aneurysm

TREATMENT

Current AAA size criteria indicate repair once the aneurysm has reached 5 cm. If treatment is required for AAA, there are two options currently available:

Open surgical repair—Open surgical repair has been in practice since the 1950s with a great deal of success. However, some patients are not suitable candidates for invasive surgery due to age and common chronic co-morbidities that greatly increase their risks.

Endovascular repair (EVAR)—EVAR is less invasive than open surgical repair and is appropriate for well over half of patients with AAA, allowing for AAA repair in patients that are otherwise inoperable patients. Through a catheter-based system, EVAR utilizes small incisions in the femoral artery to deliver a self-expanding graft into the abdominal aorta. Benefits of the EVAR treatment include low incidence of complications, a very low morbidity rate, less loss of blood during the procedure, shorter hospital stays and shorter recovery times.

PREVALENCE AND RISK FACTORS

- Male gender
- Age 60+
- History of smoking
- Hyperlipidemia
- Coronary artery disease
- Hypertension
- Chronic obstructive pulmonary disorder (COPD)
- Prior coronary artery bypass graft (CABG)

SYMPTOMS

Patients suffering from AAA are usually asymptomatic.

- Vague, constant or throbbing abdominal pain
- Intense pain if AAA is rapidly expanding

DIAGNOSE EARLY

- Consider AAA risk factors
- A tender, pulsatile mass may be palpable upon examination
- If AAA is suspected, it can be confirmed via ultrasound, CT scan, MRI and angiography

Disclaimer:
The information Provided are generic and for educational purpose only and is not a part of any Promotional/Marketing activity.

ORIGINAL ARTICLE

Pattern of Medical Device Adverse Events in a Tertiary Care Hospital in Northern India: An Ambispective Study

Saifuddin PK[1], Ajay Prakash[2*], Ram Samujh[3], Sunil Kumar Gupta[4], Vanita Suri[5], Rohit Manoj Kumar[6], Siddhartha Sharma[7], Bikash Medhi[8*]

Received: 08 November 2022; *Accepted:* 03 July 2023

Abstract

Background: Knowledge about the pattern of adverse events caused by medical devices (MDs) is limited in India. We aimed to assess the pattern of MD adverse events (MDAEs) in a tertiary hospital in Northern India.

Materials and methods: This descriptive study was conducted ambispectively at various clinical departments of PGIMER, Chandigarh. We followed the guidelines edged by the Materiovigilance Program of India (MvPI) to conduct this study. The prospective study (PS) was done from January to December 2020, with a concurrent retrospective study (RS) proceeding to 3 years to learn more about the reporting culture, demographics, notification status, risk class of defective devices, and the type of adverse events.

Results: We received 224 MDAE in the PS and identified 413 MDAE in the RS. Reporting of adverse events to the national MvPI was negligible in the RS. In the PS, nurses reported the majority of MDAEs (65%), followed by doctors (30%). The occurrence of MDAE was higher in males (PS; 52%, RS; 57%) and age groups between 21 and 30 years (PS; 19.1%, RS; 23.2%) in both studies. MDAEs were frequent in low- to moderate-risk devices (class B: 66%) in the PS, while it was documented only for high-risk devices (class C: 51% and class D: 49%) in the RS. Most of the serious adverse events (SAEs) were reported among moderate to high-risk devices, and an increased frequency of SAE (60.4%) was observed among nonnotified MDs. The overall incidence of near-miss events was 14%.

Conclusion: Knowledge of MDAEs and reporting of defective devices to regulatory authorities is essential to prevent further incidence. Adverse events caused by MDs are ubiquitous irrespective of their risk classification, notification status, and patient demographic factors. Accelerated reporting of MDAE by all cadre of healthcare professionals is urgently required to safeguard the health of Indians.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0424

Introduction

Medical devices (MDs) are an integral part of the healthcare delivery system and contribute to patient care enormously. The MDs represent "all instruments, apparatus, implants, *in vitro* reagents, or software intended for disease diagnosis or treatment in humans."[1] It is estimated that a multispecialty hospital uses over 5000 various categories of MDs for routine procedures.[2] However, in certain circumstances, it can cause MD adverse events (MDAEs) ranging from serious to non-serious adverse events (non-SAEs).[3] The true public health impact of MDAEs is unclear, and reported cases could be an iceberg of all MDAEs.[4] It is estimated that as little as 0.5% of all MD adverse events were reported to the United States Food and Drug Administration (FDA).[5] A study by Porte et al. described that 2.8% of the admissions in Dutch hospitals were associated with MDAEs.[6] The following are some SAEs reported from India. A patient received an electrical burn injury as a result of defibrillator failure,[7] metal ions were found in the blood and soft tissue of patients following hip replacement surgery,[8] and a newborn baby died after the overheating of an incubator[9]. In addition to serious outcomes, MDAEs also increase the cost of hospitalization.[10]

Although MDs are causing adverse events and economic burdens, the studies on MDAEs are limited compared to adverse drug reaction studies because of the complexity of the field and the difficulty in the classification of MDs. Drugs can be classified according to their intended purposes, like antihypertensive, antifungal, etc.; however, a MD could not be classified in this manner. To bring uniformity in regulatory approval and postmarketing surveillance (PMS), the Global Harmonization Task Force (GHTF) classified MDs into four classes (classes A, B, C, and D) where class A indicate low risk, class B indicates low to moderate risk, class C indicates moderate-high risk, and class D devices present a higher risk to patients.[11]

The impact of MDAEs varies based on the complexity, intended purpose, and invasive nature of the MDs.[12] Commonly, noninvasive and simple MDs are likely to cause non-SAEs, while invasive and complex devices are likely to cause SAE.[13] An adverse event is labeled as an SAE if it leads to hospitalization or prolongation of existing hospitalization, disability, congenital abnormality, or death.[14] The safety of licensed MDs is ensured by implementing PMS.[15] Even though manufacturers are largely responsible for PMS, regulatory authorities have specific roles at various levels.[16] Globally, 65% of countries have established regulatory authority for executing PMS.[17] As per the World Health Organization directive, The Government of India launched the Materiovigilance Program of India (MvPI) in July 2015 and designated the Indian Pharmacopoeia Commission (IPC) to implement MvPI. IPC has to report the analysis of MDAEs to the Central Drug Standard Control Organization (CDSCO), which is the regulatory authority of drugs and MDs in India.

The criterion for the regulatory framework of PMS of MDs varied among implemented countries. Since the Government of India has adopted the same classification of MDs given by the GHTF and framed a MD rule accordingly in 2017 (MDR-2017),[18] studies from the Indian perspective might apply to the global perspective. One drawback of MDR-2017 is that its regulatory status is limited to MDs that are periodically notified by the Government of India. As of 1st January 2020, only 37 MDs are notified (Supplementary Material 1), and many MDs are out of this notified list. Frequently used non-notified

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MDs include oxygen masks, infusion pumps, ventilators, incubators, etc. Previous studies from other countries have shown adverse events, including SAE, with these nonnotified MDs.[19,20] So, the present study was undertaken to characterize the MDAEs reported in a tertiary-level teaching hospital (PGIMER, Chandigarh) according to GHTF risk classification and to identify the notification status of causative MDs. An ambispective study was designed to have more insight by comparing the adverse events pattern and to identify the gap in the documentation and reporting of adverse events.

Materials and Methods

Design and Settings

This descriptive study was designed as a single-centre ambispective study, which includes prospective and retrospective studies done concurrently. Data collection for the prospective study (PS) was done from 1st January 2020 to 31st December 2020 by visiting various medical and surgical departments. Data collection for the retrospective study (RS) was done for the preceding 3 years of the PS, from 1st January 2017 to 31st December 2019, by reviewing patients' records. The study was approved by the Institutional Ethics Committee (IEC) of the PGIMER, Chandigarh, vide order INT/IFC/2020/SPL-407/2020. Collecting and reporting of MDAE were performed according to the relevant guidelines and regulations given by MvPI.

Inclusion/Exclusion Criteria

All reported MDAEs in hospitalized and outpatient departments (OPD) attending patients were included irrespective of age, gender, diagnosis, or treatment.

Sample Size

We had included all relevant cases of MDAE reported within the timeframe.

Materials

Medical device adverse events (MDAE) reporting form downloaded from www.ipc.gov.in (Supplementary Material 2) was used as a case record file, and the notification released by CDSCO as of 01/01/2020 was followed (Supplementary Material 1).

Data Collection

We employed active and passive surveillance for data collection. The passive method involved spontaneous targeted reporting in which we conducted an awareness program for doctors, nurses, and technicians regarding MvPI and how to report MDAE in a prescribed format. Every month, we send reminders to the healthcare workers through social media messages and emails to report MDAE, if any. Active surveillance was done by personally visiting outdoor and indoor departments to identify any AE. Patients using MDs were screened and documented if any adverse events were observed. For retrospective data collection, screening of registers kept at various operation theaters (OTs) and patient case files kept at the medical record department (MRD) was done.

Statistical Analysis

All the data collected during the study period were entered into the master sheet through Microsoft Excel software (Microsoft Co., United States of America). The categorization of data was done both qualitatively and quantitatively as applicable, and Poisson distribution was applied. The results were expressed in absolute numbers and percentages. The correlation between the incidences of SAEs with notification status of MDAE was executed with the Chi-squared test along with the Yates correlation, and a p-value of <0.05 was considered statistically significant.

Results

In total, 637 MDAEs were reported retrospectively and prospectively, out of which 413 cases were identified based on retrospective records and 224 cases were reported from a PS.

For the RS, we screened 30142 records in which it was identified that 23892 cases were having an implant *in situ*. The hospitalization of these patients with implant-related adverse events was taken as a sample, and 413 cases were identified (Fig. 1). Among these implant-related adverse events, nearly half of the adverse events were reported from the orthopedic dept (orthopedic implants: n = 203, 49.1%) followed by the gynaecology department (copper T: n = 116, 28%) and ophthalmology department [intraocular lens (IOL): n = 94, 22.9%]. However, in the PS, MDAEs were reported across all departments through spontaneous reporting. The MDAE pattern was further broken down into various categories given below.

Healthcare Professionals Reported MDAE

In the PS, nurses reported most of the AEs (65%), followed by doctors (30%). Reporting by medical technical staff (2%) and other healthcare workers (3%) were very few, and by biomedical engineers was negligible (Fig. 2).

Demographic Profile and Pattern of MDAE

A slightly higher incidence of MDAE was reported among male patients compared to female patients in both (M: 234, 57%,

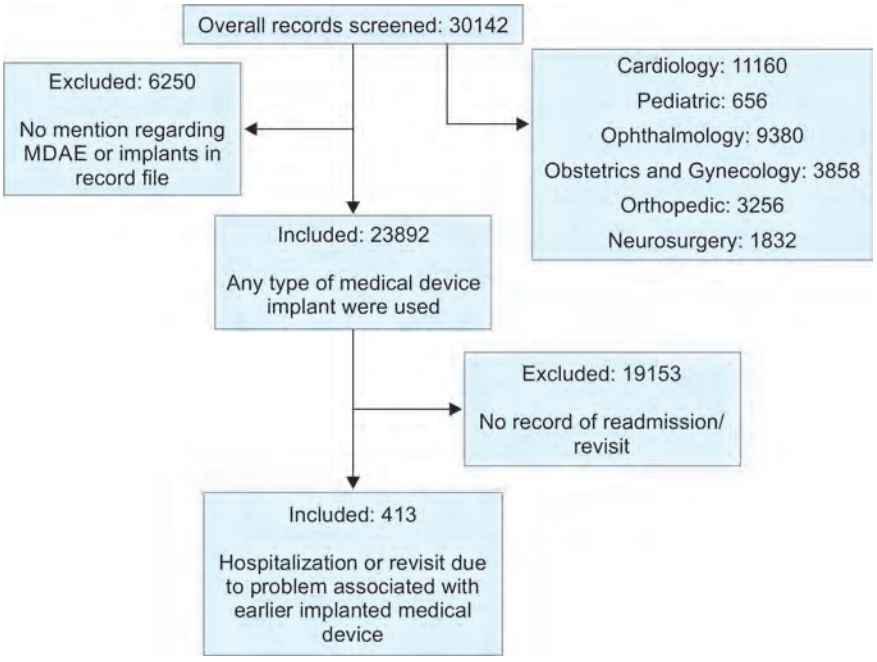

Fig. 1: A depiction of retrospective data screening

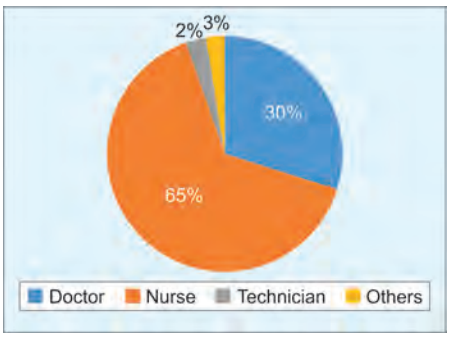

Fig. 2: Healthcare professionals reported MDAE

F: 179, 43%) studies (M: 100, 52%, F: 92, 48%). Demography was not recorded for near-miss events. To understand the age-wise distribution of MDAE, all patients were divided into nine age groups (Fig. 3). The incidence of MDAE was highest among the age group of 21–30 years in both retrospective (n = 96, 23.2%) and prospective studies (n = 43, 19.1%). The mean age of the patients was 41.8 years in the retrospective and 33.7 years in the PS. About 5% (n = 19) of MDAEs were observed in children (age <12 years) in the RS compared to 15% (n = 29) in the PS. Further, in the PS, it was observed that infants (0–1 year) were also prone to MDAE, as 7.5% (n = 17) cases were reported among these cohorts. Nearly 6.9% (n = 15) of elderly people (age >65) were affected with MDAE. The youngest patient was 3 days old, and the eldest was 84 years old.

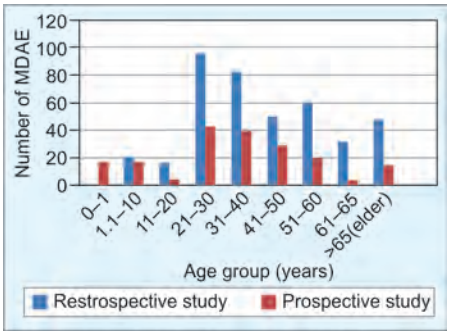

Fig. 3: Age-wise distribution of patients with MDAE in a retrospective and PS

Medical Devices (MDs) Frequently Associated with MDAE

Personal protective equipment (PPE) (n = 58, 25.8%) accounted for a quarter of AE, followed by Kojak syringe (n = 36, 16%) and Infusion/syringe pumps (n = 33, 14.7%) (Fig. 4). We also analyzed whether the MDs involved in AE relied on any software support for their intended functioning and found that 29.46% (n = 66) of MDs were software-enabled. In terms of near-miss events, 14% (n = 32) of the instances were classified as near-missed events in the PS. Further, regarding the invasive status of MDs, most AEs were associated with noninvasive (n = 200, 89.3%) and single-use (n = 160, 71.7%) devices (Table 1).

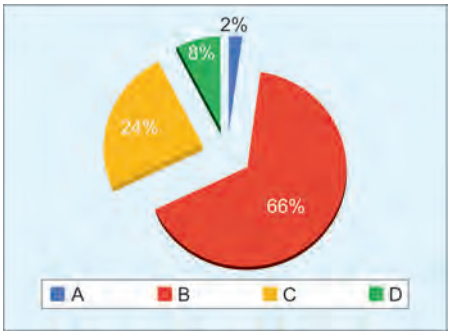

Fig. 5: Medical device (MD) risk class and distribution of MDAE in the PS (A, low-risk; B, low-to-moderate risk; C, moderate-to-high risk; D, high-risk)

Different Classes of MDs and Frequency of MDAE

In the PS, two-thirds of the AE were caused by low to moderate-risk devices (class B: n = 147, 66%), while the remaining one-third of AE was caused by moderate- to high-risk devices. (class C: n = 55, 24% and class D: n = 17, 8%) (Fig. 5). However, in the RS, no adverse events were reported with low- to moderate-risk devices (classes A and B), whereas high-risk devices (class C: n = 210, 51% and class D: n = 203, 49%) were responsible for all MDAEs. A brief description of the adverse events caused by different classes of MDs is given in Table 1.

Notification Status of MDs and Incidence of MDAE

Overall, a slightly higher incidence of MDAE was reported among notified (n = 119, 53%) MDs in the PS. When it comes to SAE, nonnotified MDs were responsible for more than half of the SAE (n = 35, 60%) (Table 1). However, no significant relation between SAE and

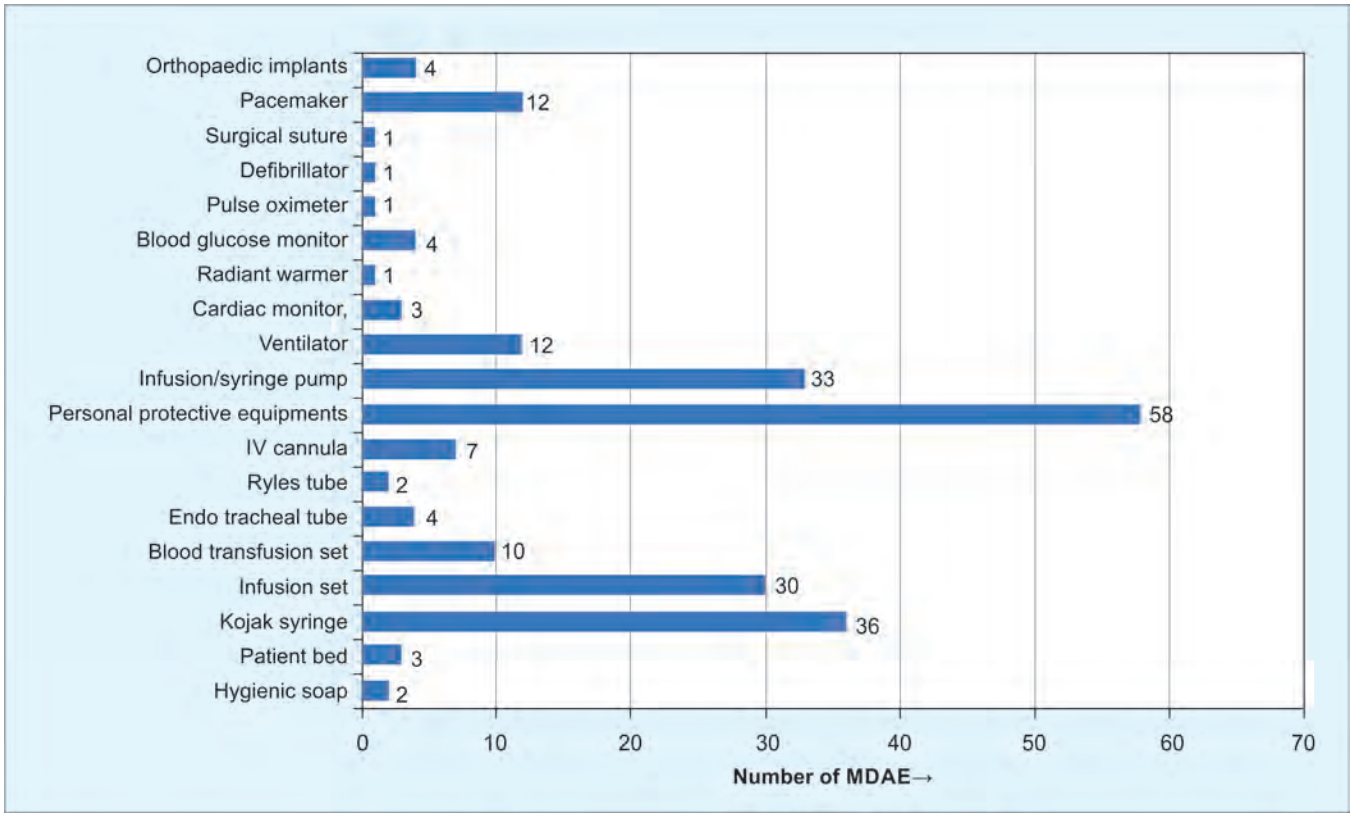

Fig. 4: Medical devices (MDs) associated with adverse events in the PS

Table 1: Brief description of adverse events caused by different classes of MDs

Device risk class	*MD*	*Number of MDAE*	*Notification status of MD*	*Invasive status of MD*	*Usage practice*	*Software/ program-enabled device*	*Adverse event*	*Severity of AE*
Class A (low-risk)	Hygienic soap	2 (PS = 2 and RS = 0)	Notified	Noninvasive	Single-use	No	Hypersensitivity	Nonserious = 2; SAE = 0
	Electronic bed	3 (PS = 3 and RS = 0)	Notified	Noninvasive	Reusable	No	Exacerbation of breathing difficulty, Malfunction	Nonserious = 3; SAE = 0
Class B (low-to-moderate risk)	Kojak syringe	36 (PS = 36 and RS = 0	Notified	Noninvasive	Single-use	No	Problems with diluting and titration for small doses, waste of medicine due to plunger breaking while loading medicine, leak, broken syringe, quality defect, difficulty in withdrawing samples.	Nonserious = 36; SAE = 0
	Infusion set	30 (PS = 30 and RS = 0)	Notified	Noninvasive	Single-use	No	Material quality, kinking, twisting, decreased flow rate	Nonserious = 30; SAE = 0
	Blood transfusion set	10 (PS = 10 and RS = 0)	Notified	Noninvasive	Single-use	No	Leakage of chamber	Nonserious = 9; SAE = 1
	Endotracheal tube	4 (PS = 4 and RS = 0)	Notified	Invasive	Single-use	No	Injury to the oropharynx due to high hardness. Failed cuff inflation.	Nonserious = 4; SAE = 0
	Ryles tube	2 (PS = 2 and RS = 0)	Notified	Invasive	Single-use	No	Leakage	Nonserious = 2; SAE = 0
	Intravenous cannula	7 (PS = 7 and RS = 0)	Notified	Invasive	Single-use	No	Thrombophlebitis, leakage	Nonserious = 6; SAE = 1
	PPE (N-95 mask, gown, cap, face shield)	58 (PS = 58 and RS = 0)	Non Notified	Noninvasive	Single-use	No	Quality defect, suffocation, tear, profuse sweating, syncope, allergy, skin mark, hyperpigmentation, fogging, pus formation over nasal bridge, injury to eyelid by metal rod on nose clip of mask, exacerbation of acne	Nonserious = 39; SAE = 17
Class C (moderate-to-high risk)	Infusion and syringe pump	33 (PS = 33 and RS = 0)	Nonnotified	Noninvasive	Reusable	Yes	Battery backup failure, delayed completion of infusion, bolus infusion when programmed over 1 hour, false alarm	Nonserious = 25; SAE = 8
	Ventilator	12 (PS = 12 and RS = 0)	Nonnotified	Noninvasive	Reusable	Yes	Ventilator-associated pneumonia, sudden halt of working, Humidifier malfunction, Overdelivery and underdelivery of programmed FiO_2	Nonserious = 4; SAE = 8
	Cardiac monitor	3 (PS = 3 and RS = 0)	Notified	Noninvasive	Reusable	Yes	Battery backup failure, improper ECG waves	Nonserious = 3; SAE = 0
	Radiant warmer	1 (PS = 1 and RS = 0)	Nonnotified	Noninvasive	Reusable	Yes	Overheating	Nonserious = 0; SAE = 1
	Blood glucose monitor	4 (PS = 4 and RS = 0)	Notified	Noninvasive	Reusable	Yes	Wrong reading (cross-checked)	Nonserious = 3; SAE = 1
	Pulse oximeter	1 (PS = 1 and RS = 0)	Nonnotified	Noninvasive	Reusable	Yes	Wrong reading (cross-checked)	Nonserious = 0; SAE = 1
	Defibrillator	1 (PS = 1 and RS = 0)	Notified	Noninvasive	Reusable	Yes	Backup failure during operation	Nonserious = 0; SAE = 1
	Copper T	116 (PS = 0 and RS = 116)	Notified	Invasive	Single-use	No	Pain, bleeding, infection, thread missing, Failure	Nonserious = 0; SAE = 116

Contd…

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Device risk class	*MD*	*Number of MDAE*	*Notification status of MD*	*Invasive status of MD*	*Usage practice*	*Software/ program-enabled device*	*Adverse event*	*Severity of AE*
Class D (high-risk devices)	Absorbable surgical suture	1 (PS = 1 and RS = 0)	Notified	Invasive	Single-use	No	Break of suture material during suturing	Nonserious = 0; SAE = 1
	Pacemaker	12 (PS = 12 and RS = 0)	Notified	Invasive	Single-use	Yes	Pacemaker site infection, endocarditis, battery failure, lead infection	Nonserious = 0; SAE = 12
	Orthopedic implants	207 (PS = 4 and RS = 203)	Notified	Invasive	Single-use	No	Broken implant, pain and restriction flexion movement, implant site infection, malunion, implant fatigue, nonunion, loosening	Nonserious = 0; SAE = 207
	IOL	94 (PS = 0 and RS = 94)	Notified	Invasive	Single-use	No	Lens drop, subluxated IOL, dislocated IOL, decentered IOL, emulsified IOL	Nonserious = 0; SAE = 94
	Coronary stent	2 (PS = 2 and RS = 0)	Notified	Invasive	Single-use	No	Stent thrombosis and death, chronic dissection flap proximal to coronary stent	Nonserious = 0; SAE = 2

MD, medical device; MDAE, medical device adverse event; PS, prospective study; RS, retrospective study

non-notified MDs was found at a *p*-value of <0.05, as the calculated *p*-value was 0.699806. In the RS, all devices which caused MDAE belonged to the list of notified devices.

Severity of MDAE

In the PS, a quarter of AEs were reported as SAE (*n* = 58, 26%). Among SAE, life-threatening AE has happened in 32% (*n* = 18) cases, prolongation of hospitalization was reported in 34% (*n* = 19) cases, intervention to prevent further complications was needed in 34% (*n* = 19) cases, and a few (4%) adverse events resulted in deaths (*n* = 2). Concerning the risk class of devices and SAE, class B caused 33% (*n* = 19) SAE, class C caused 34% (*n* = 20) SAE, and class D devices caused 33% (*n* = 22) SAE. The incidence of SAE among notified MDs was 39.6% (*n* = 23), whereas among nonnotified devices, it was 60.4% (*n* = 35) (Table 1). Software-supported devices accounted for 36.84% of all SAEs. In the RS, all MDAEs were reported as SAE since they needed hospitalization.

Discussion

The present study is the first of its kind to evaluate the pattern of MDAEs according to GHTF risk classification, which is followed in India and to identify the notification status of causative MDs.

We received 224 MDAEs in the PS and identified 413 MDAEs in the RS. Since the retrospective analysis was performed for a 3-year (2017–2019) period and the PS was performed for a 1-year (2019) period, the discrepancy in cumulative counts might have occurred. However, none of the MDAEs that happened during the RS period were reported to the same hospital's functional MvPI centre. The number of MDAE in our PS was lower than a previous study by Samore et al., who detected 552 MDAE over 9 months.[20] However, their study was based on computer-flag-based surveillance, while our study was based on a spontaneous reporting approach.

In this study, nurses reported the majority of adverse effects (65%), followed by doctors, a few by OT technicians, and negligible reporting from biomedical engineers. A study by Kavanagh et al. also found nurses report MDAE 2.77 times more often than doctors directly to the United States FDA-manufacturer and user facility device experience (MAUDE).[21] Another study by Shamim et al. was also of the same opinion, where the reporting of AE was found to be significantly more among nurses ($p = 0.006$).[22] However, a study conducted by Alsohime et al. among intensive care unit nurses in Saudi Arabia found that even though 66% of nurses experienced MD adverse events, only 2% of nurses reported it correctly to the existing national reporting system.[23] Therefore, there is a possibility that the adverse events reported in this study might be an iceberg of the total MDAEs that originally occurred.

All the patients who have been exposed to MDs, regardless of age or gender, are at risk for MDAE since we found the incidence of MDAE in adults (85%), including the elderly population (6.9%) and children (15%) including infants (7.5%). The age group of 21–30 years has the highest prevalence of MDAE in both retrospective (23.2%) and prospective studies (19.1%). Male patients outnumbered females in both studies. (RS: M = 52%, F = 48%. PS: M = 57%, F = 43%). However, this finding is contradictory to the findings of Peterson et al., who reported female patients are more likely than men to have procedure-related adverse events in the hospital.[24] The male sex predominance in our study may be attributed to the fact that the majority of admitted patients were male. The mean age of the patient population in the RS was 41.8 years, while the mean age in the PS was 33.7 years.

In the PS, the devices associated with frequent MDAE were PPE kits (25.89%), followed by Kojak syringes (16.07%) and infusion pumps (14.73%). Since the PS was conducted during the COVID-19 pandemic, there is an increased reporting of AE associated with PPE. Furthermore, AEs related to PPE have a direct impact on the health of healthcare professionals, and their experience of monitoring and reporting MDAE may have contributed to increased reporting of AE with PPE. This coincidental result indicates that improved recognition of MDAE by users would aid in the early detection and reporting of MDAE. A study by Kavanagh et al. found patients and their relatives were the most frequent submitters of reports directly to the US FDA MAUDE database.[21] So, Indian regulatory agencies should extend postmarketing monitoring to recipients (patients) rather than limiting it to healthcare professionals. Another study by Samore et al. found Foley catheters (57%) and arterial catheters were the devices most commonly associated with MDAE in their study.[20] However, in the present study, no cases with these devices were reported. However, a study by Gagliardi et al. showed that infusion pumps are the most common device associated with priority 1 recall in Canada.[25] Conversely to the PS, in the RS, it was found that orthopedic implants were responsible for almost half (49.1%) of the adverse events, followed by copper T (28%) and intraocular lenses (22.9%). However, no adverse events associated with these devices were reported during the PS period. Since adverse events associated with these devices are primarily detected by treating clinicians, especially by surgeons, there is an urgent need to promote MDAE reporting behavior among surgeons in our country. Also, the pattern of MDAE will be influenced by which professional category reports more MDAE.

We identified low- to moderate-risk devices (class B) as being responsible for the majority (66%) of adverse events, followed by moderate- to high-risk (class C, 24%) and high-risk (class D, 8%) devices in a PS, But, in our RS, it was found that classes C and D devices were associated with all the adverse events. The disparity may be due to the adverse event by class B devices, which are not commonly recorded in patients' case files, and nurses reported most of MDAE in the PS.

We found that the majority (74%) of MDAEs were nonserious, while a quarter (26%) resulted in serious consequences, including death. However, these findings were inconsistent with the MvPI study, which indicates that the majority (66.1%) of reported cases to MvPI were SAEs. This may be due to stakeholders' preference to report merely SAEs to MvPI. Further, the incidences of SAEs were equally prevalent among class B (33%), C (34%), and D (33%) devices and higher in nonnotified (60.4%) MDs. So, we recommend bringing all the devices under the purview of the notified list, irrespective of risk class, as early as possible.

The overall incidence of near-miss adverse events was 14%. Near-miss adverse events mean a patient is exposed to a potentially dangerous scenario but is spared from injury due to chance or early identification by the reporter. Further, most of the adverse events were reported among noninvasive devices (89%). So, the regulators need to ensure the quality and safety of noninvasive material as well.

The present study also identified that more than one-third of (36.84%) SAEs were caused by software-supported MDs. A previous study by Gagliardi et al. reported that software-supported MD (Laboratory software, diagnostic software, patient management software) caused recalls, including priority-1.[25] Therefore, a separate surveillance system for software used in the healthcare field is a need of the hour.

Conclusion

Identifying the pattern of adverse events caused by MDs is essential for prevention. MDs are prone to cause adverse events irrespective

of their risk class classification, notification status, or demographic characteristics of the patient population. So stringent regulatory control in terms of notification of all MDs available in the Indian market is needed to ensure patient safety. Accelerated participation by all the cadres of healthcare professionals, including treating clinicians, is recommended to safeguard the health of the Indians. We found that reporting the culture of a particular category of healthcare professionals may alter the overall result of the pattern identification study, which can be disposed of by future researchers. This study warrants the development of possible intervention strategies to reduce the public burden of MDAEs by forming a separate discipline to assess the economic impact of MDAEs, namely materioeconomics similar to pharmacoeconomics.

Limitation of the Study

Overall, the present study was limited to bedside MDs and not focused on *in vitro* diagnostic devices. The root cause analysis of reported adverse events was not performed widely.

Declaration

Ethics Approval and Consent to Participate

The present study was approved by the IEC of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, vide order no INT/IFC/2020/SPL-407/2020. Collecting and reporting of MDAE were performed as per Indian Council for Medical Research (ICMR) guidelines for biomedical research in October 2017 and good clinical practice established by CDSCO under the Drug and Cosmetic Act 1940. As per the MvPI, healthcare workers need to report MDAEs voluntarily, and informed consent from patients is not mandatory to report MDAEs as it does not collect the names of patients and does not disclose the identity of the patients. So, informed consent was not obtained from the patients. The IEC of the PGIMER, Chandigarh, approved this study after the declaration of the author that the confidentiality of each patient will be maintained. Before the commencement of the study, we educated healthcare workers regarding MvPI and their responsibility of voluntarily reporting MDAEs. Further, healthcare workers were informed that the data provided by them would be utilized for basic studies to strengthen MvPI, which is a secondary objective of MvPI.

Consent for Publication

The author gives their full approval for publication.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contribution Statement

Saifuddin PK, Ajay Prakash, and Bikash Medhi formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript. Saifuddin PK collected data with the contribution and guidance from Ram Samujh, SK Gupta, Vanita Suri, Rohit Manoj Kumar and Siddhartha Sharma. Saifuddin PK, Ajay Prakash, and Bikash Medhi analyzed data and wrote the manuscript. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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Authors Declaration

Supplementary tables are available with corresponding author and can be provided whenever required.

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ORIGINAL ARTICLE

Declining Trend in Antimicrobial Sensitivity in Respiratory Tract Bacterial Pathogens against Commonly Used Drugs at a Tertiary Care Hospital

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Abstract

Objectives: Antimicrobial resistance (AMR) is a major health issue. To determine trends in bacterial organisms in respiratory tract infections (RTIs) and their antibiotic sensitivity at a tertiary care center in India, we performed this study.

Methods: Successive samples received from January 2017 to December 2021 from the respiratory tract (sputum, endotracheal secretion, and bronchoalveolar lavage) from intensive care units and medical inpatients were processed for bacterial growth. The identification of isolates and antibiotic sensitivity patterns was performed using an automated VITEK-2 system. Descriptive statistics are reported.

Results: We received 7,204 respiratory samples. Significant bacterial growth was in 3,000 (41.6%), and 2,992 (41.5%) were gram-negative. *Klebsiella pneumoniae* was the most prevalent, followed by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, and *Enterobacter aerogenes*. Increasing secular trends were observed for *Klebsiella* and *Pseudomonas* and declining trends for *Acinetobacter* and *Escherichia* ($p < 0.05$). Antimicrobial sensitivity patterns showed that *Klebsiella, Pseudomonas*, *Acinetobacter*, *E. coli*, and *Enterobacter* had a high sensitivity with colistin and polymyxin (99–100%). Moderate sensitivity was observed with carbapenems (*Acinetobacter:* 47.5%, *Enterobacter:* 62.0%, *Escherichia:* 76.5%, *Klebsiella:* 72.3%, *Pseudomonas:* 66.7%) and tigecycline (*Acinetobacter:* 50.4%, *Enterobacter:* 68.0%, *Escherichia:* 81.1%, *Klebsiella:* 66.6%, *Pseudomonas:* 0%). Aminoglycosides had <50% sensitivity for various organisms, and <25% sensitivity was observed with third-generation cephalosporins and quinolones. Trend analysis showed persistent sensitivity of various pathogenic bacteria to colistin and polymyxin and declining pharmacological sensitivity in *Acinetobacter* (carbapenems and tigecycline), *Escherichia* (carbapenems, quinolones, and tigecycline), *Klebsiella* (carbapenems, quinolones, aminoglycosides, and tigecycline), and *Pseudomonas* (carbapenems and aminoglycosides) species ($p < 0.05$).

Conclusion: Common respiratory tract gram-negative bacterial pathogens at a tertiary care hospital are *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *E. coli*. All these bacteria demonstrate high sensitivity only with colistin and polymyxin. Significant AMR is observed to carbapenems, tigecycline, aminoglycosides, and third-generation cephalosporins. Secular trends show declining antimicrobial sensitivity among various bacterial pathogens.

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Introduction

Declining sensitivity and increasing antimicrobial resistance (AMR) in bacteria is a major threat to global health.[1,2] According to the World Health Organization (WHO), mutations in microorganisms that result in AMR render commonly used drugs ineffective and lead to persistent infections and increased risk to patients.[3] There are many reasons for the development of AMR, ranging from microbial-related factors, physician factors (overuse and over-prescription of antimicrobials), human behavioral factors, agricultural factors, and commercial application of antimicrobials in the animal sector.[2,4] Our ability to treat common pathogens becomes challenging because of AMR, as it leads to increased duration of illness, costs, number of complications, and deaths.[1]

Respiratory tract infections (RTIs) are one of the most common causes of infections and are a major cause of global deaths and lead to significant loss of working hours in affected individuals.[5] RTIs are also the leading cause of hospital admissions and consume huge amounts of health resources, especially in developing countries.[6,7] Many newer antibiotics have been introduced to treat these infections, whose sensitivity pattern is still not clearly understood due to the paucity of published data and may not be available in developing countries.[8–11] AMR is widespread in India,[1,2] but there are limited recent studies that have evaluated its prevalence and antimicrobial sensitivity.[12–25] We performed a retrospective study to analyze types of bacteria in patients with RTIs and to study their antibiotic sensitivity pattern over a 5-year period from 2017 to 2021.

Methods

The study protocol has been approved by the Ethics Committee of Eternal Heart Care Centre and Research Institute, Jaipur, India (Government of India registration, CDSCO No. ECR/615/Inst/RJ/2014/RR-20). Specific consent was obtained for the use of anonymized data, and individual patient-level consent was waived by the ethics committee. This retrospective study of patients with lower RTIs includes sputum, endotracheal secretions, and bronchoalveolar lavage specimens that were received at the microbiology laboratory at our hospital.

Sampling

Patients with symptoms suggestive of RTI underwent sampling from sputum, endotracheal or bronchial alveolar lavage. These respiratory samples were collected from patients of all ages and both sexes from hospital intensive care units (ICUs) and specialty wards. The inclusion criteria comprised clinical and radiological imaging evidence of RTI among inpatients of the hospital. We did not classify the patients based on community-acquired or hospital-acquired infections. The samples received from January 2017 to December 2021 have been included. During this period, 7,204 respiratory secretion samples were received,

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of which 3,000 (41.6%) samples were found positive for significant bacterial growth. Samples that were negative for bacterial growth were excluded.

Laboratory Assessment

The samples were immediately transferred to the microbiology laboratory in sterile containers and stored at 4°C till analyses were performed. In the Microbiology Department, calibrated wire loops were used to inoculate the sample in blood agar and MacConkey agar, which provides the growth of most organisms. MacConkey culture medium specialized for the isolation of gram-negative bacteria was used. The culture media were incubated at 35 ± 2°C for 24 hours. The culture was considered positive if isolated organism growth was present without contaminants and normal flora. Identification of isolates and antibiotic sensitivity patterns was conducted by the automated VITEK-2 machine.

Statistical Analyses

All the data were transferred to customized MS Excel spreadsheets. Descriptive statistics are reported. The values are provided in numbers and percent. Trends were evaluated using X^2 for trend using the SPSS statistical package. All *p*-values <0.05 are considered significant.

Results

Out of the 7,204 respiratory samples received for culture and sensitivity, 3,000 (41.6%) led to significant bacterial growth and 2,992 (41.5%) samples had growth of gram-negative organisms. Gram-positive bacteria were in eight (0.1%) patients. Additionally, we isolated 1,368 (18.9%) benign gram-positive organisms, the most common being normal throat flora (*Streptococcus viridans*, coagulase-negative *Staphylococci*, etc.). The rest of the samples, 2,836 (39.3%), had no growth on culture. Among the gram-negative organisms (2,992), *Klebsiella pneumoniae* (2,236, 74.7%) constituted the most prevalent organism, followed by *Pseudomonas aeruginosa* (289, 9.6%), *Acinetobacter baumannii* (242, 8.0%), *Escherichia coli* (175, 5.8%), and *Enterobacter aerogenes* (50, 1.6%). The annual trends from 2017 to 2021 in various bacterial isolates are shown in Figure 1. Significant increases and declines are observed in *K. pneumoniae* (P_{trend} of 0.686) and an increase in *P. aeruginosa* (P_{trend} of 0.004) with declining trends in *A. baumannii* (P_{trend} < 0.001) and *E. coli* (P_{trend} of 0.009).

All these gram-negative bacterial species (*A. baumannii*, *E. aerogenes*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*) showed a universal sensitivity to colistin and polymyxin (Table 1). The sensitivity for third-generation cephalosporins was <20%. A sensitivity of <20% was also observed for quinolones except against *Pseudomonas* (24.2%). Low sensitivity was observed for aminoglycosides (*Acinetobacter*: 4.1%, *Enterobacter*: 32.0%, *Escherichia*: 45.7%, *Klebsiella*: 37.9%, and Pseudomonas: 34.2%). Higher sensitivity was observed with carbapenems (*Acinetobacter*: 47.5%, *Enterobacter*: 62.0%, *Escherichia*: 76.5%, *Klebsiella*: 72.3%, *Pseudomonas*: 66.7%). Tigecycline sensitivity was also variable (*Acinetobacter*: 50.4%, *Enterobacter*: 68.0%, *Escherichia*: 81.1%, *Klebsiella*: 66.6%, *Pseudomonas*: 0%).

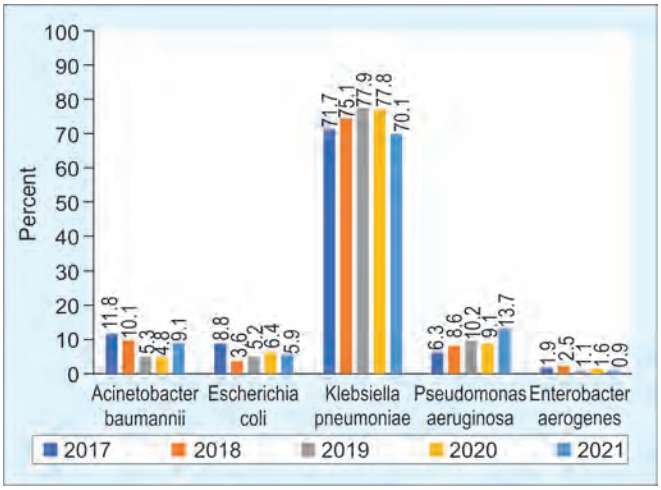

Fig. 1: Annual trends in organisms isolated from respiratory tract specimens (%) (2017–2021)

Trends in antimicrobial sensitivity are shown in Figure 2. There is a persistent sensitivity to colistin and polymyxin and declining sensitivity to other pharmacological agents in various bacterial organisms. Declining trends are observed among *A. baumannii* for carbapenems and tigecycline; *E. coli* for carbapenems, quinolones, and tigecycline; *K. pneumoniae* for aminoglycosides, carbapenems, quinolones, and tigecycline); and *P. aeruginosa* for aminoglycosides and carbapenems ($p < 0.05$).

Discussion

This study shows that gram-negative bacteria are the most prevalent respiratory pathogens at a tertiary care hospital in India and were *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *E. coli*. All these bacteria demonstrated high sensitivity only with colistin and polymyxin, and significant AMR was observed in carbapenems, tigecycline, aminoglycosides, and third-generation cephalosporins. The secular trends showed a declining antimicrobial sensitivity to all these antibiotics.

The Antimicrobial Resistance Surveillance Network of the Indian Council of Medical Research reported that in the year 2020, the most commonly isolated bacterial pathogen from all samples received at nationwide microbiological laboratories was *E. coli* (25%) followed by *K. pneumoniae* (18%), *P. aeruginosa* (12%), *A. baumannii* (10%), and *Staphylococcus aureus* (10%).[24] Among these isolates, *E. coli* was the most predominant isolate from urine (51%), *K. pneumoniae*, and *A. baumannii* from the lower respiratory tract (28%) and *S. aureus* from skin to soft-tissue (21.5%). Higher isolation of *Klebsiella* and *Acinetobacter* from respiratory specimens is similar to our study, where *Klebsiella* constituted the most prevalent organism (Fig. 1). Older studies from India highlighted a high prevalence of *Streptococcus pneumoniae* and other gram-positive bacteria in respiratory specimens from community hospitals,[26,27] but at our tertiary care referral hospital we could find them in <1%. Veeraraghavan et al. obtained 2,731 isolates of gram-negative bacilli to evaluate drug sensitivity patterns.[27] The most common organism was *E. coli*, followed by *K. pneumoniae*. These are different from the present study, which also included urinary tract specimens. In a previous study from Jaipur, it was reported that *Escherichia* was the most common organism.[28] Findings of the present study are similar to reports from other Indian tertiary care hospitals.[14,16,18,19,21,26]

Antibiotic resistance is an emerging problem in critically ill patients and affects the prognosis and survival of these patients.[1–3] It also results in a prolonged stay in the hospital, increasing the cost of treatment.[2,4] High levels of resistance to third-generation cephalosporins show predominant extended-spectrum β-lactamase producing organisms. These findings are also similar to recent reports of emerging AMR in India.[27,29–31] Drug

Table 1: Trends in the antimicrobial sensitivity of various bacterial species from 2017 to 2021

Bacteria	*Year*	*Numbers*	*Antimicrobial agents*						
			Third-generation cephalosporins	*Quinolones*	*Aminoglycosides*	*Carbapenems*	*Tigecycline*	*Colistin*	*Polymyxin*
A. baumannii	Total	242 (8.0)	0 (0)	0 (0)	10 (4.1)	115 (47.5)	143 (50.4)	242 (100)	242 (100)
	2017	58 (11.8)	0 (0)	0 (0)	5 (8.6)	36 (62)	40 (68)	58 (100)	58 (100)
	2018	71 (10)	0 (0)	0 (0)	0 (0)	38 (53.5)	42 (59.1)	71 (100)	71 (100)
	2019	39 (5.3)	0 (0)	0 (0)	1 (3)	22 (56)	24 (62)	39 (100.0)	39 (100)
	2020	23 (4.8)	0 (0)	0 (0)	3 (13)	10 (43)	10 (43)	23 (100)	23 (100)
	2021	51 (9.1)	0 (0)	0 (0)	1 (2)	9 (17.6)	6 (12)	51 (100)	51 (100)
	P_{trend} value	–	–	–	0.036	<0.001	0.002	1.00	1.00
E. coli	Total	175 (5.8)	33 (18.8)	37 (21.1)	84 (48)	134 (76.5)	142 (81.1)	175 (100)	175 (100)
	2017	46 (8.8)	8 (17.3)	18 (39.1)	24 (54)	37 (80.4)	41 (89.1)	46 (100)	46 (100)
	2018	26 (3.6)	7 (26.9)	8 (30.7)	11 (42.3)	22 (84.6)	23 (88.4)	26 (100)	26 (100)
	2019	38 (5.2)	8 (21)	3 (37)	18 (47)	31 (82)	34 (89)	38 (100)	38 (100)
	2020	31 (6.2)	6 (19)	4 (13)	16 (52)	22 (71)	23 (74)	31 (100)	31 (100)
	2021	34 (6.0)	4 (12)	4 (12)	15 (44)	22 (64)	21 (62)	34 (100)	34 (100)
	P_{trend} value		0.800	0.026	0.985	0.952	0.820	1.00	1.00
K. pneumoniae	Total	2236 (74.7)	370 (16.5)	405 (18.1)	849 (37.9)	1617 (72.3)	1490 (66.6)	2236 (100)	2236 (100)
	2017	373 (71.7)	54 (14.4)	83 (22.2)	158 (42.3)	294 (78.8)	330 (88.4)	373 (100)	373 (100)
	2018	531 (75.1)	80 (15)	96 (18)	195 (36.7)	419 (78.9)	467 (87.9)	531 (100)	531 (100)
	2019	565 (78.0)	98 (17)	110 (19)	178 (32)	423 (75)	352 (62)	565 (100)	565 (100)
	2020	373 (77.8)	87 (23)	68 (18)	178 (48)	253 (68)	164 (44)	373 (100)	373 (100)
	2021	394 (70.1)	51 (13)	48 (12)	140 (36)	228 (58)	109 (28)	394 (100)	394 (100)
	P_{trend} value	–	0.012	0.037	0.011	0.025	<0.001	1.00	1.00
P. aeruginosa	Total	289 (9.6)	0 (0)	70 (24.2)	99 (34.2)	193 (66.7)	0 (0)	289 (100)	289 (100)
	2017	33 (6.3)	0 (0)	11 (33.3)	11 (36)	28 (84.8)	0 (0)	33 (100)	33 (100)
	2018	61 (8.6)	0 (0)	22 (36)	20 (32.7)	52 (85.2)	0 (0)	61 (100)	61 (100)
	2019	74 (10.2)	0 (0)	15 (20)	20 (27)	52 (70)	0 (0)	74 (100)	74 (100)
	2020	44 (9.1)	0 (0)	12 (27)	23 (52)	29 (66)	0 (0)	44 (100)	44 (100)
	2021	77 (13.7)	0 (0)	10 (13)	25 (32)	32 (42)	0 (0)	77 (100)	77 (100)
	P_{trend} value	–	1.00	0.111	0.445	0.096	–	1.00	1.00
E. aerogenes	Total	50 (1.6)	6 (12)	8 (16)	16 (32)	31 (62)	34 (68)	50 (100)	50 (100)
	2017	10 (1.9)	1 (10)	2 (20)	3 (30)	7 (70)	8 (80)	10 (100)	10 (100)
	2018	18 (2.5)	3 (16.6)	4 (22.2)	5 (27.7)	12 (66.6)	15 (83.3)	18 (100)	18 (100)
	2019	8 (1.1)	1 (13)	1 (13)	2 (25)	4 (50)	6 (75)	8 (100)	8 (100)
	2020	8 (1.6)	1 (12)	1 (12)	4 (50)	6 (75)	4 (50)	8 (100)	8 (100)
	2021	6 (1.1)	0 (0)	0 (0)	2 (33)	2 (33)	1 (17)	6 (100)	6 (100)
	P_{trend} value	–	0.473	0.947	0.918	0.603	1.00	1.00	1.00

Numbers in parentheses are in percent

sensitivity patterns of the bacterial specimens in the present study are similar to national and international data. Antimicrobial Resistance Collaborators have reported a high prevalence of third-generation cephalosporin resistance in *Acinetobacter*, *Escherichia*, and *Klebsiella*, which are similar to the present study.[1] The high prevalence of carbapenem resistance is also similar to recent reports. Studies from India have reported antimicrobial sensitivity to *Acinetobacter* in <20%, and although in our report, >62% of specimens were sensitive to carbapenems in 2017, this has now declined to <20% (Fig. 2). Carbapenem sensitivity has declined to <60% in recent years for all other bacteria evaluated in the present study, which is similar to the data from Antimicrobial Resistance Collaborators.[1] Persistent sensitivity of various bacteria to colistin and polymyxin is commensurate with the low use of these drugs in India. A recent report has highlighted a very low resistance to these drugs (1.28% of 533 *Klebsiella* specimens),[32] but this scenario could change given the paucity of other alternatives in the country combined with indiscriminate use of these compounds.[30]

According to WHO,[3] India has one of the highest multidrug resistance bacteria in the world, and Antimicrobial Resistance Collaborators and others have projected a dire scenario ahead.[1,4,30] The Government of India[24,33,34] and other agencies have suggested multiple ways to control drug overuse in humans and animals to prevent AMR.[2,4,7,35–37] Important factors in high antibiotic use in India are poor prescription practices, self-medication, over-the-counter sale of antibiotics, and poor awareness.[34] Strict antibiotic stewardship practices are recommended to curb antibiotic misuse.[33–36] Other strategies include the development of region-wide, state-level, and hospital-based antibiotic clinical guidelines; focused undergraduate, postgraduate, and general practitioner medical education; development of disease-based treatment guidelines and state-wide infection control policy;

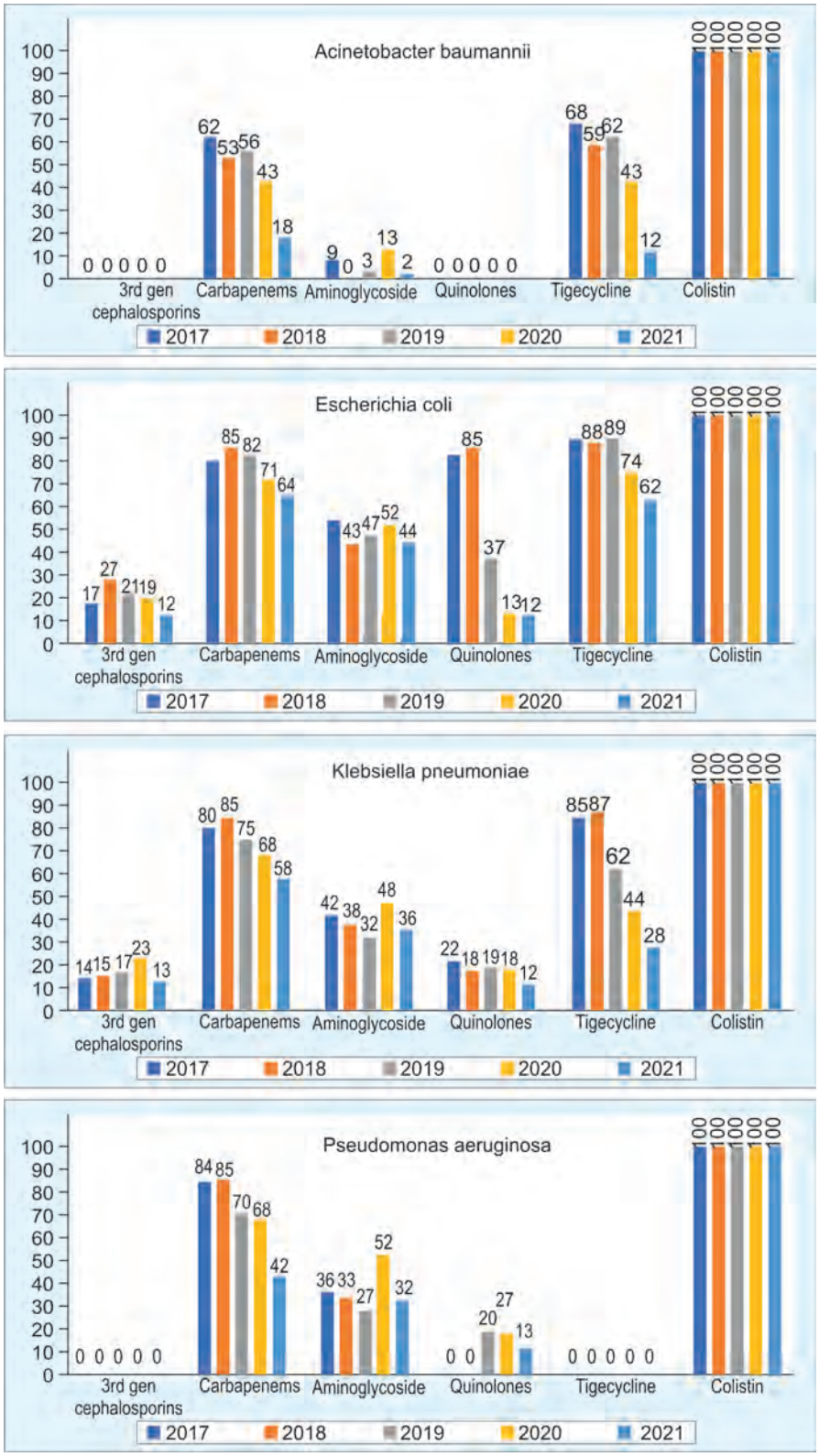

Fig. 2: Trend of antimicrobial sensitivity pattern (%) of selected gram-negative bacteria (2017–2021)

and rescheduling.[37] Strict rules regarding the availability of third-generation at primary and secondary care levels should be implemented.[30,33] Focusing on research on the development of new antimicrobials is important, and such efforts should be supported not only by the pharma industry but also by national research agencies.[36,37] Animals are a major source of antibiotic resistance.[38] Indiscriminate veterinary use of antibiotics and harmful farming practices must be eliminated.[2]

An important limitation of the study is that we have restricted samples to inpatients in the hospital. There is no segregation of samples according to admission status (community-dwelling, interhospital-transferees or prolonged-hospital stay) or according to patients from general wards or ICUs. In an earlier study, we reported differences in bacterial isolates among community-based patients vs patients referred from other health facilities and also among ward-dwelling or ICU-based patients.[19] In this study, we reported significant differences in the type of bacterial isolates and antibiotic sensitivity patterns in various groups of patients, similar to studies from other centers in the country.[12–23] Other limitations of the study are that the data is limited to a single site and that the tertiary care hospital has an antibiotic sensitivity pattern that may not reflect the exact situation in the country. However, our data are similar to studies performed in other tertiary care hospitals in the country and reflect the emergence of a serious medical problem that needs urgent solutions. We have focused on gram-negative bacteria only, which is similar to data from India and other South Asian countries. On the other hand, in more developed countries, gram-positive bacteria such as methicillin-resistant *S. aureus* and vancomycin-resistant Enterobacteriaceae are important problems, a pattern different from this region.[1] On the other hand, this is one of the larger single-center studies from the country, and we have focused on respiratory tract pathogens, one of the largest causes of disease burden in India.[5,6]

In conclusion, our study shows that gram-negative organisms are the most important cause of respiratory infection in a tertiary care hospital setting. Major pathogens identified include *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *E. coli*. All these bacteria demonstrate significant and increasing AMR to third-generation cephalosporins, aminoglycosides, and carbapenems. There is a need to develop and implement national and state-level antibiotic stewardship practices and other measures highlighted above. However, the major focus must be on upstream determinants of infections and antibiotic overuse, including sanitation, environmental hygiene, agricultural policies, veterinary practices, and healthcare financing and restricted use of third-generation antibiotics along with physician and public education to prevent inappropriate antibiotic use in our country.

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REVIEW ARTICLE

An Indian Expert Group Review of Acanthosis Nigricans with Recommendations for Early Detection and Timely Management

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Abstract

Introduction: Acanthosis nigricans (AN) is a visible cutaneous manifestation of several underlying systemic conditions, such as prediabetes, diabetes mellitus (DM), polycystic ovarian syndrome (PCOS), metabolic syndrome (MS), and malignancy. AN is commonly seen in obese individuals and is a proven skin marker of insulin resistance (IR). Its typical clinical presentation and location, especially on the nape of the neck, allows for easy visual identification. Obesity, IR, and other noncommunicable diseases (NCD) are on the rise in India, with many cases being undiagnosed or missed. Every sixth diabetic in the world is Indian. AN can thus play a vital role in screening, early identification, and reduction of morbidity, especially of IR-related disorders. Currently, there are no national or international multidisciplinary guidelines or recommendations for AN.

Objective: To review published current literature and evidence on AN, its associations, and management. To recommend an approach to clinical identification of AN, associated/underlying disorders, investigations, and management, including lifestyle modifications. To sensitize and familiarize clinicians and healthcare workers across India with AN presentations. This will enable early detection of conditions such as IR, prediabetes, DM, PCOS, malignancy, etc., in practice and in the community.

Materials and methods: The PCOS Society of India constituted a multispecialty Expert Working Group with representation from various national societies to review all published scientific evidence. Expert group meetings were conducted to provide recommendations.

Conclusion: Acanthosis nigricans is a simple, non-invasive, cost-effective screening tool for early identification of IR. It is important to integrate and disseminate information and training on AN across medical specialties. The government of India has launched several National Health Programmes to help address the rising burden of NCD in the population. AN would provide a simple screening tool to pick up undiagnosed or missed cases.

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Introduction

Acanthosis nigricans (AN) is characterized by dark, thickened skin with a velvety texture in a symmetrical distribution on the neck, axillae, antecubital and popliteal fossae, and groins [international classification of diseases-10 (ICD-10), L.83; ICD-11 ED51.0].[1] AN has multiple causes (Table 1); however, benign AN is typically related to high concentrations of insulin, which binds to insulin-like growth factor receptors, leading to epidermal skin cell proliferation.[2] Thus, AN is often a visible cutaneous sign of insulin resistance (IR) (Table 2).

The global prevalence of AN varies from 7 to 74%. The prevalence of AN varies among different ethnic groups. AN appears to be especially prevalent among Asians and individuals of mixed ancestry. A possible genetic predisposition or increased sensitivity of the skin to hyperinsulinemia among certain populations is reported.[3,4] It continues to rise due to an increase in noncommunicable diseases (NCDs) including polycystic ovarian syndrome (PCOS), diabetes mellitus (DM), and metabolic syndrome (MS) in the general population.[6] It is known that IR precedes diabetes by approximately 10–15 years.[7] The presence of AN on physical examination is a reliable marker of IR.[8] Hence, it has been proposed as a simple, noninvasive, cost-effective tool for screening and diagnosis of underlying chronic metabolic disorders such as prediabetes, DM, and MS.[6]

Given the association of AN with DM and obesity, the American Diabetes Association (ADA) has included AN as an indicator of DM risk in overweight youth entering puberty.[9]

Recognizing the higher risk for NCDs specifically in Indians, early detection of AN as a marker of IR is of immense importance.[10,11] Currently, it is an underutilized practical tool. The goal for managing AN is to treat its primary cause, bring about cosmetic resolution of AN lesions, reduce morbidity with timely treatment, and improve the quality of life. Thus, the management of AN needs an interdisciplinary, structured, and systematic approach. Currently, there are no international or national guidelines that address a multidisciplinary approach for AN. We present an evidence-based review and propose expert recommendations for early detection, treatment, and preventive management in the Indian setting.

Materials and Methods

The PCOS Society of India identified AN as a priority area and constituted a multidisciplinary Expert Working Group (Table 3) for review and recommendations.

A detailed review of the literature was performed using PubMed and Google Scholar using the main keywords such as "acanthosis nigricans," "insulin resistance," and "PCOS." Publications available in the English language were included in the final review. The references were classified as per the available evidence as level 1–5, with level 1 being the highest evidence (randomized controlled trial/meta-analysis) and level 5 being the lowest (case report). Expert group meetings were conducted to deliberate on the recommendations for early detection of AN, prevention, and management of AN-associated disorders in the Indian context.

Clinical Features and Diagnosis

Clinical Features of Acanthosis Nigricans

The typical clinical appearance of AN allows for easy diagnosis.[12] AN can sometimes be

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Table 1: Acanthosis nigricans and causes[2]

Causes	*Forms of AN*
Metabolic disorders	Obesity-associated AN
	• Most common form of AN, associated with IR • Severity of lesions related to the amount of weight excess
	Syndromic type A and B
	• Type A (HAIR-AN): AN with IR, hyperandrogenemia • Type B: AN, DM, ovarian hyperandrogenemia
Genetic disorders	Unilateral AN
	• Linear, unilateral variant, similar to classical AN • Manifests during childhood or later
	Familial AN
	• Rare autosomal dominant disease in early childhood • Self-limited, stabilizes or recedes postpuberty
	Benign genetic AN
	• Develops from birth or early childhood as a rare autosomal dominant form
Autoimmune	AN associated with autoimmune disease
	• Anti-IR antibodies in autoimmune diseases (e.g., SLE)
	AN only with autoantibodies
Paraneoplastic AN	AN associated with neoplasia
	• Rapid onset, sudden and intensely pruritic lesions • Usually associated with adenocarcinomas of abdominal organs and genitourinary cancers • Precedes, accompanies, or follows diagnosis of internal cancer
Iatrogenic AN	• Adverse effect of certain drugs, for example, insulin, niacinamide, oral corticosteroids, oral contraceptives, aripiprazole, somatotropin, diethylstilbestrol, testosterone, pituitary extract of β-MSH, triazinate, amprenavir, palifermin, fusidic acid • Lesions usually reversible on discontinuation of drug
Idiopathic AN	• Acral AN
	• Limited to dorsal surfaces of hands and feet (less to elbows, knees, knuckles)
Mixed type AN	• AN lesions with any two forms of AN from above

Table 2: What is IR?[5]

- IR is an impaired biologic response to insulin stimulation of target tissues (liver, muscle, and adipose tissue)
- IR impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia
- Till date the clinical definition of IR remains elusive
- Clinically, IR is recognized by the metabolic consequences associated with it, namely MS and IR Syndrome

Table 3: Acanthosis nigricans Expert Working Group

- PCOS Society of India in collaboration with the following:
  - Association of Physicians of India (API)
  - Endocrine Society of India
  - Experts from Sports/Fitness medicine
  - Indian Academy of Pediatrics (IAP)
  - Indian Association of Dermatologists Venereologists and Leprologists (IADVL)
  - Indian College of Obstetricians &Gynaecologists (ICOG)
  - ICMR-National Institute for Research in Reproductive and Child Health (ICMR-NIRRCH)
  - Indian Dietetics Association
  - Indian Society of Medical and Pediatric Oncology (ISMPO)
  - Medical Research Centre-Kasturba Health Society
  - Mumbai Obstetrics and Gynecological Society (MOGS)
  - Sir Vithaldas Thackersey College of Home Science (Autonomous), SNDT Women's University
  - Tata Institute of Social Sciences (TISS)

pruritic, associated with skin tags, or present at atypical sites including the face, knuckles, etc. (Fig. 1). Burke et al. have developed a validated, quantitative scale (Table 4) to measure the severity of AN lesions appearing on various body parts.[13]

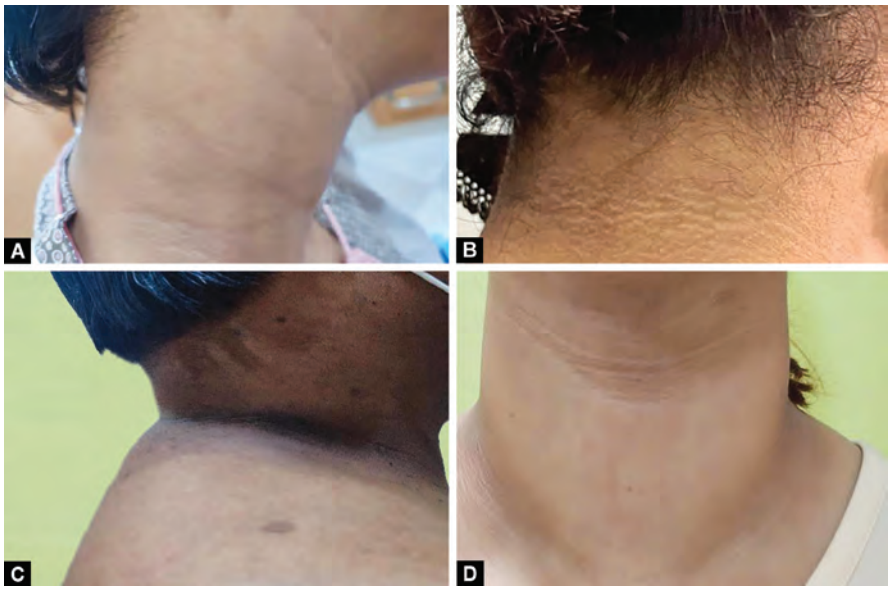
Recommendation 1: Acanthosis nigricans can be suspected from general skin examination due to its classical clinical appearance on typical sites.

Diagnosis of Acanthosis Nigricans

Clinical examination is usually sufficient to diagnose AN as the clinical picture is quite characteristic. Clinicians can rule out dermatitis neglecta (accumulation of dirt on the skin) by wiping the skin with an alcohol swab. For other differentials, a dermatologist can be consulted. Rarely, a skin biopsy may be required.

Dermoscopy

It is a skin magnification test done using a dermatoscope, not commonly performed in



Figs 1A to D: Clinical grades of AN (Burke's scale); Courtesy: Dr Gulrez Tyebkhan, Saifee Hospital, Mumbai; Grade 1: Present; Grade 2: Mild; Grade 3: Moderate; and Grade 4: Severe

clinical practice and requires special training. Features are detailed in Figure 2.[14]

Acanthosis Nigricans, Insulin Resistance and Associated Conditions

Prevalence

Insulin resistance syndrome (IRS) is a manifestation of excess insulin and variable resistance to its action. Features include hyperglycemia, hypertension, dyslipidemia, visceral adiposity, and hyperuricemia. Elevation of inflammatory markers, endothelial dysfunction, and a prothrombotic state are also observed. Table 5 provides the reported prevalence of AN with the associated conditions in adults and children.

Prospective analysis of plasma insulin levels in healthy normoglycemic male (19–73 years) and female (19–55 years) volunteers are reported. Reference range for insulin in a

Table 4: Burke's scale for AN[13]

Location and score	*Description*
Neck severity	
0	Absent: Not detectable on close inspection
1	Present: Clearly present on close visual inspection, not visible to the casual observer, extent not measurable
2	Mild: Limited to the base of the skull, does not extend to the lateral margins of the neck (usually 3 inches in breadth)
3	Moderate: Extending to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually 3–6 inches) should not be visible when the participant is viewed from the front
4	Severe: Extending anteriorly (6 inches), visible when the participant is viewed from the front
Axilla	
0	Absent: Not detectable on close inspection
1	Present: Clearly present on close visual inspection, not visible to the casual observer, extent not measurable
2	Mild: Localized to the central portion of the axilla, may have gone unnoticed by the participant
3	Moderate: Involving the entire axillary fossa, but not visible when the arm is against the participant's side
4	Severe: Visible from the front or back in the unclothed participant when the arm is against the participant's side
Neck texture	
0	Smooth to touch: No differentiation from normal skin to palpation
1	Rough to touch: Clearly differentiated from normal skin
2	Coarseness can be observed visually, with portions of the skin clearly raised above other areas
3	Extremely coarse: "Hills and valleys" observable on visual examination
Knuckles	Present
	Absent
Elbows	Present
	Absent
Knees	Present
	Absent

normoglycemic Indian cohort was derived as 2.7–17 IU/mL, and 17 IU/mL is proposed as the cutoff for diagnosing hyperinsulinemia in healthy Indians.

Recommendation 2: AN is a cutaneous marker of IR and related conditions such as prediabetes, DM, PCOS, and MS. Its presence should raise an index of suspicion for further investigations.[23]

Obesity, diabetes, hypertension, low physical activity, and a family history of DM and/or hypertension are known risk factors for AN. As weight and body mass index (BMI) increase, the prevalence of AN increases.[24,25] Progression of untreated IR leads to type 2 DM, nonalcoholic fatty liver disease (NAFLD), and MS. A variety of dermatologic manifestations have been linked with DM, AN being one of them. Such skin changes offer insight into patients' glycemic control and could be the first sign of metabolic disturbances in undiagnosed patients.[26,27] Reportedly, 30% of type 1, and 70% of type 2 DM have skin manifestations.[28,29] Prediabetes is a reversible condition; early detection is extremely crucial to prevent further progression.[29,30]

Acanthosis Nigricans and Other Endocrine Disorders

Polycystic ovary syndrome is often associated with AN. Obesity, IR, and hyperandrogenism are seen in patients with PCOS.[31] PCOS patients with a family history of DM and obesity, with a BMI of >30 kg/m^2 and a waist circumference of ≥90 cm are more likely to develop AN, as reported in an Indian study.[32] Hirsutism and AN are the most reliable cutaneous markers of PCOS and warrant further evaluation for metabolic comorbidities.[32,33] Patients with rare conditions such as Cushing syndrome and acromegaly can present with AN.[34,35]

Drug-induced Acanthosis Nigricans

Drug-induced AN is associated with certain medications, and the condition reverses once the medication is stopped. A systematic review has identified 13 drugs responsible for drug-induced AN, of which nicotinic acid was the most common (refer Table 1).[36]

Recommendation 3: All possible causes responsible for AN must be considered to provide appropriate treatment. For suspected drug-induced AN, before stopping the causative medication, a risk–benefit analysis and an available alternative must be evaluated.

Acanthosis Nigricans and Malignancy

Generalized involvement, sudden and rapid onset, location in atypical sites such as palms or mucous membranes, intense pruritus, or thickened velvety palmar folds (tripe palms) are highly suggestive of internal malignancy. Paraneoplastic AN is usually associated with adenocarcinomas of abdominal organs and genitourinary cancers. Regression of AN lesions occurs with the treatment of the underlying tumor, and recurrence of the lesions may precede relapse of the malignancy.

Recommendation 4: The clinician must be aware of the red flags in the presentation of AN suggesting underlying malignancy.

Evaluation of Acanthosis Nigricans and Its Associations

Depending upon the findings of clinical evaluation (Flowchart 1), blood tests, imaging, and other tests may be required to rule out underlying IR, DM, PCOS, MS, or even malignancy. The age of the patient, weight, and family history decide the type of investigations needed (Refer to Tables 6 and 7). The mental status examination may also be considered as required.

Although AN is a reliable cutaneous marker of IR in children as well as adults, documentation of IR can be done by estimating fasting insulin levels only if required; else, it is not recommended. Overweight/obese female adolescents with AN, clinical signs of hyperandrogenism, and irregular menses require work-up for PCOS.

Recommendation 5: To undertake a detailed medical evaluation, including family history and relevant investigations, to rule out the underlying/associated conditions.

Management of Acanthosis Nigricans

Treating underlying/associated conditions and recommending lifestyle changes is the cornerstone of management.

Skin lesions are treated using topical, systemic, and procedural modalities. Complete resolution is difficult to achieve.[12] Psychological stress is very common, hence, counseling should be part of the therapy. A multidisciplinary approach (Flowchart 2) is required for better clinical outcomes.[42] Table 8 briefly describes currently available topical, systemic, and procedural therapies.[43]

Lifestyle Modification

General health factors such as diet control with appropriate nutrition, increased physical activity, normalizing sleep patterns, and reducing stress levels improve metabolic health and help in the resolution of AN. Weight reduction is the most scientific and practical management strategy in the treatment of AN.[12]

Fig. 2: Dermoscopy of AN (10× magnification); red circle—furrows; black circle—dark structureless areas; blue circle—hyperpigmented areas; Courtesy: Department of Dermatology, MGM Institute of Health Sciences, Kamothe, Navi Mumbai

Table 5: Reported prevalence of AN in associated conditions[11,15–22](evidence level 2)

Associated conditions	*Reported prevalence of AN*
Patients with IR	31.3–59.6%
Patients with type 2 DM	35–72%
Women with PCOS	5.2–77.7%
Patients with MS	68.4%
Obese women with MS	60%
PCOS women with MS	70–82%
Patients with type 1 DM and MS	13%
Obese children and adolescents	86%
Obese adults	74%
Obese PCOS women	39.9%
Lean PCOS women	12–50%
Healthy pregnant women	2.9–49.1%
PCOS women with gestational DM	17.5–62%
Pregnant PCOS with preeclampsia or hypertension	77.7%

Diet

Obesity is an important contributor to IR, PCOS, DM, MS, and other endocrinological disorders.[51–53] A diet comprising 60% of energy from carbohydrates, 15% from protein, 25% from fats, and limiting animal products to a single portion a day, has been shown to increase insulin sensitivity, decrease visceral and subcutaneous fat, significantly decrease inflammation and improve leptin levels.[54] Limiting the consumption of processed foods, refined grains, sugars and foods high in sodium, and trans fats would help in weight loss.[55] Table 9 provides general diet recommendations for Indians.[56]

Exercise

Exercise is a crucial lifestyle management tool for weight loss and weight maintenance.[57] It leads to significant fat loss including visceral fat loss.[57] It also improves IR among prediabetes, DM, obese patients, and overweight children and adolescents.[58–61] It improves insulin sensitivity regardless of the type of exercise program[62] and prompts the release of endorphins bringing in the feeling of well-being. A strong association between physical activity and AN is well-known and established in many studies globally and in India.[63] Recommended activities include walking, jogging, cycling, swimming, playing an outdoor sport, aerobic exercise, resistance training, high-intensity interval training (HIIT), etc.

However, currently, there are no published guidelines that recommend specific exercise regimes to treat AN. In any case, the exercise regime requires customization based on the patient profile, general fitness, accompanying comorbidities, and current fitness literacy. As a general guideline, we can consider a combination of exercises from the American College of Sports Medicine (ACSM) recommendations (Table 10). Increasing physical activity throughout the day by minimizing sedentary time is essential.

Sleep

Poor sleep is known to increase IR and elevates DM risk through multiple pathways. Distortion of metabolic pathways alters glucose metabolism resulting in IR, obesity as well as DM.[64] Poor sleep results in mood swings, irritability as well as elevated blood pressure.[65] Short sleep duration (≤ 6 hours) is known to increase weight ≥5 kg whereas a sleep duration of 9 hours is associated with a reduced risk of weight gain.[66]

Recommendation 6: It is important to advise patients about healthy eating practices, a nutritionally diverse and balanced diet, physical activity, and good sleep habits.

Mental and Psychological Health

Low self-esteem scores have been reported in adolescent obese girls with AN, especially with high insulin and testosterone levels.[67] These may lead to social anxiety and depression. Family involvement is the key to success, especially when AN and IR occur at an early age. Behavioral approaches in terms of diet changes, sleeping habits, engaging in physical activities, and reducing stress yield positive outcomes. Yoga, meditation, and mindfulness practices help toward mental and psychological well-being. Medication for depression may be necessary. Counseling

Table 6: Acanthosis nigricans—basic approach to evaluation

A	History • Onset and progression of AN • Associated symptoms • Medication history • Family history
B	Complete physical examination • Measurement of BMI (normal range for Indians 18.5–22.9 WHO criteria)[37] • Waist circumference: Indian cut-off male >90 cm; Indian cut-off female >80 cm • Waist-to-hip ratio; men ≥0.89; women ≥0.81[38] • Abdominal examination (fatty liver and tumor) • Blood pressure (BP) Evaluation for the presence of hyperandrogenism (hirsutism, acne, female pattern hair loss), genetic disorders, etc.
C	Clinical examination • Morphology of AN for typical skin lesions, location, and distribution

Flowchart 1: Acanthosis nigricans—approach to clinical evaluation

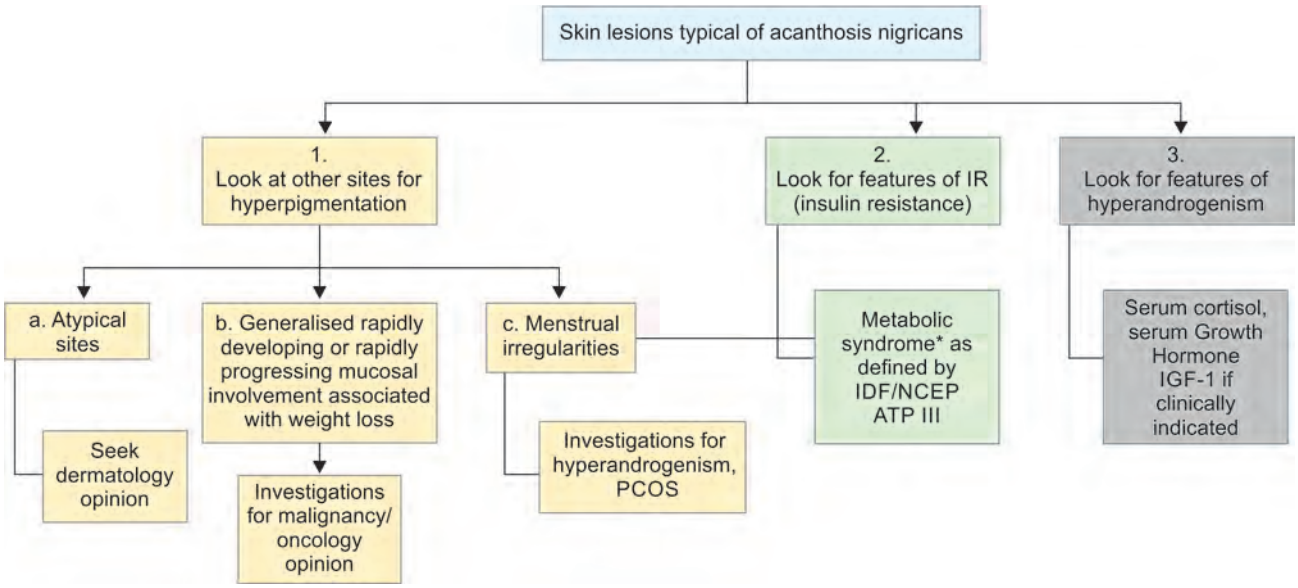


Table 7: Acanthosis nigricans—recommended investigations for associations

Association	*Investigations*
IR	• Fasting insulin level to confirm or exclude IR (insulin value inappropriately high for glucose level)* • Glucose/insulin ratio (<4.5 denotes IR)[39] (level 2) • Homeostasis model assessment-IR (HOMA-IR) (research tool)
Prediabetes	• Fasting glucose: ≥100 mg/dL but <126 mg/dL • Hemoglobin A1c: 5.7 to <6.5% • 2 hours oral glucose tolerance test (OGTT) with 75 gm sugar ≥140 mg/dL and ≤199 mg/dL Should follow ADA recommendations[40] (level 1)
Diabetes	Diagnosis of diabetes is established if any of the following criteria is present and verified on repeat testing as per ADA guidelines[40] (level 1) • HbA1C ≥6.5% • Fasting glucose ≥126 mg/dL • Random plasma glucose ≥200 mg/dL with classic symptoms of hyperglycemia or hyperglycemic crisis
PCOS	• OGTT (as per ADA guidelines)[40] (level 1) • TSH • Prolactin • Total/free testosterone (days 2–5 of menstrual cycle) • 17-hydroxyprogesterone • DHEAS • USG pelvis and abdomen
Lipid abnormality	Classification of results from lipoprotein profile (mg/dL)[41] (NCEP criteria) LDL cholesterol (primary target of therapy) • Optimal: <100 • Near-optimal: 100–129 • Borderline high: 130–159 • High: 160–189 • Very high: ≥190 Total cholesterol • Desirable: <200 • Borderline high: 200–239 • High: ≥240 HDL cholesterol • Low: <40 (risk factor) • High: ≥60 (desirable) Triglycerides • Normal: <150 • Borderline high: 150–199 • High: 200–499 • Very high: ≥500
Liver enzymes (transaminase levels)	To look for NAFLD
Thyroid abnormalities	Thyroid profile: TSH
Sudden onset of AN or rapidly progressive AN	Evaluation for underlying malignancy • Complete blood count • Stool test for occult blood • Chest and abdominal X-ray/CT/MRI • Abdominal and pelvic ultrasonography • Gastrointestinal endoscopy

*, Generally, not recommended; at the discretion of the treating clinician and/or for research purposes

Flowchart 2: Management of AN and associated conditions

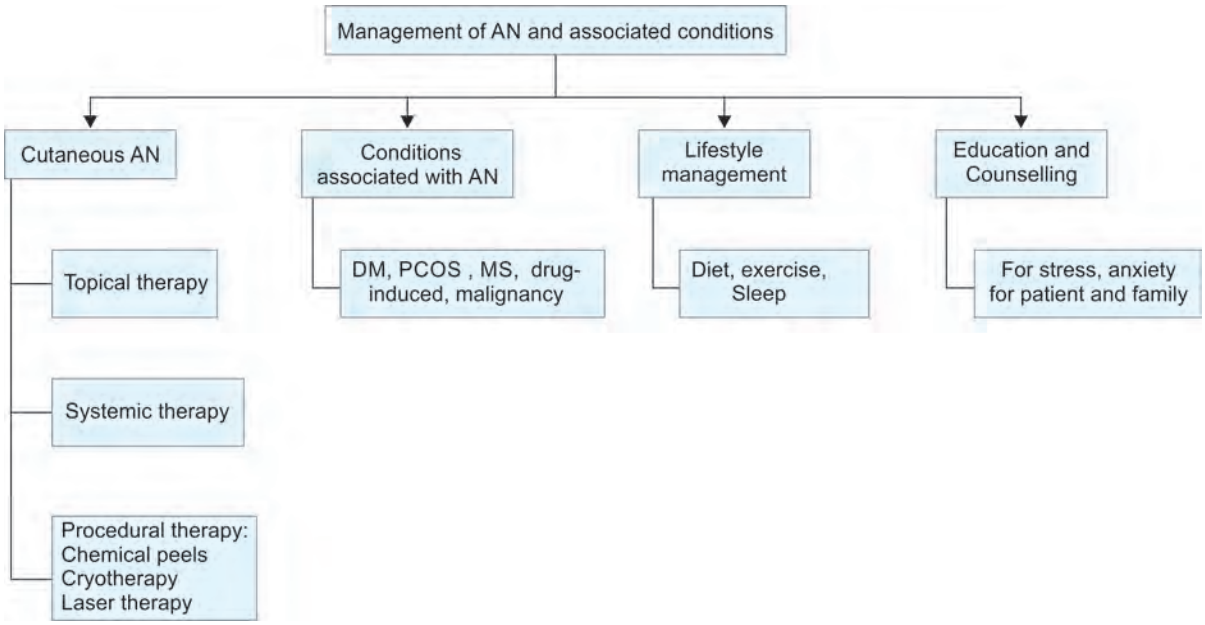


Table 8: Acanthosis nigricans—treatment modalities

Classification	*Therapy*	*Details in brief*	*Reference number and level of evidence*
Topical therapy			
Retinoids	Tretinoin, (0.025, 0.05%) and adapalene (0.1%)	• Alters epidermal turnover and epidermal keratinization • Treatment duration 4–14 weeks • Risk of relapse on stopping treatment	44; level 2
Topical vitamin D analogs	Calcipotriol (0.005%)	• Inhibits keratinocyte proliferation • Promotes differentiation by increasing keratinocyte intracellular calcium and cyclic GMP levels. Treatment duration 3 months	42; level 2
Other topical treatment	Urea (10 and 20%), glycolic acid (GA) (20–70%), lactic acid (ammonium lactate 12%) and salicylic acid–mandelic acid chemical peel combinations; TCA peel (15 and 20%)	• Acts by keratinolysis • Safe and effective	42; level 2 45; level 3
Systemic therapy			
Oral Hypoglycemic agents*	Metformin (dosage range 500–1500 mg per day)	• Improves insulin sensitivity • Reduces hyperinsulinemia, body weight, fat mass • Can be combined with other OHAs/insulin	2; Level 2 1; level 2 46; level 1 47; level 5
Antioxidants	α-lipoic acid (ALA) (400 mg per day)	• Potent biological antioxidant • Enhances insulin sensitivity, improves the signs of AN	48; level 1
Oral retinoids	Isotretinoin, acitretin (3 mg/kg/day)	• Acts by normalizing epithelial growth and differentiation. • Not recommended for young women with AN due to teratogenic effects • Duration: 2 months	1; level 2 42; level 2
Procedural treatment			
Chemical peels	Trichloroacetic acid (TCA) peels 15%	• Acts by precipitation of proteins in epidermal cells • Causes necrosis and destruction of the epidermis leading to reepithelialization • Safe, easy accessibility, inexpensive	49; level 2 42; level 2
Cryotherapy	Liquid nitrogen/cryogen	• Acts by tissue damage due to freezing • Efficacy depends on depth and extent of lesions, duration and number of freezing cycles	43; level 4
Laser therapy	Alexandrite, fractional CO_2 550-nm erbium fiber laser	• Destroys AN lesion without damaging the surrounding tissues • Available laser treatment protocols • Alexandrite—every 3 weeks for five sessions • Fractional CO_2—every 4–6 weeks for maximum four sessions • 550-nm erbium fiber—every 4 weeks for maximum three sessions	50; level 1

*, Beneficial effects of sitagliptin and pioglitazone in treatment of AN are reported[42]

of the patient and family can be done by the clinician or by seeking professional help from a psychologist or psychiatrist. Please refer to Flowchart 3 for recommended steps for the prevention and management of AN in children.

Table 11 provides the summary of all recommendations suggested in this manuscript.

Recommendation 7: Physical and mental well-being should receive equal emphasis. Education and counseling are crucial for initiating and sustaining lifestyle changes.

Table 9: Steps toward a healthy and nutritious diet: dos and donts

Do's

- Diverse food plate with different food Groups (NIN, ICMR, My Plate for the day 2020. https://www.nin.res.in/)
- Daily diet to include plant proteins (pulses, dals, peas, beans, nuts, and oilseeds)
- Cereal pulse combination (roti usal or dal; dal chawal) along with curd or milk
- Include a diet with high omega 3 and MUFA (black chana, cow pea (chawli), urad dal, rajmah, soyabean, nuts, seeds, cereals green leafy vegetables)
- Limit the quantity of cooking oil (approximately 500 gm/adult/month); use of MUFA rich oil (rice bran, til, groundnut), omega 3 rich oil (soyabean, mustard), or a blended oil
- Use prebiotic foods high in dietary fiber and resistant starch (raw banana, chick pea, whole moong, bajra flour, etc). Enhance the prebiotic effect by soaking, steaming, cooling, and roasting with limited oil
- Regularly consume probiotic food items such as curds, etc.

Dont's

- Avoid salt intake above one level teaspoon (5 gm) per day.
- Minimize added sugars in foods and beverages
- Avoid refined flour, saturated fats, and trans fats foods like khari, pav, maida roti, doughnuts, pastries, cakes, biscuits, etc.
- Minimize the use of packaged and processed food

Table 10: Exercise recommendations for AN (adapted from the ACSM's guidelines for exercise prescription for overweight and diabetes conditions)

	Aerobic	*Resistance*	*Flexibility*
Frequency	>3 days/week	2–3 days/week. Nonconsecutive days	>2–3 days/week
Intensity	Moderate (40–59% of HRR or VO_2R) to vigorous (>60% HRR or VO_2R) intensity as per fitness levels. May have to start with low intensity initially but goal should be to progress	Moderate (50–69% of 1RM) to vigorous (70–85% of 1RM)	Stretch to the point of tightness or slight discomfort
Time	30 minutes/day (150 minutes/week) progressing to 60 minutes/day (250–300 minutes/week)	2–4 sets of 8–12 repetitions of 8–10 exercises involving major muscle groups	Static stretches for major muscle groups to be held up to 30 seconds and to be done 2–4 times
Type	Prolonged, rhythmic activities using large muscle groups (e.g., walking, jogging, cycling, swimming)	Resistance machines, free weights, resistance bands or body weight	Combination of static and dynamic

1RM, 1 repetition maximum; HRR, heart rate reserve; VO_2R, VO_2 reserve (maximal oxygen uptake); intensity of exercise is calculated using the following methods—HRR method: target HR = $[(HR_{max} - HR_{rest}) \times \%$ intensity desired$] + HR_{rest}$; VO_2R method: target $VO_2R = [(VO_{2max} - VO_{2rest}) \times \%$ intensity desired $+ VO_{2rest}$; 1RM: the maximum weight that can be lifted for a single repetition

Flowchart 3: Approach to AN in pediatric age-group

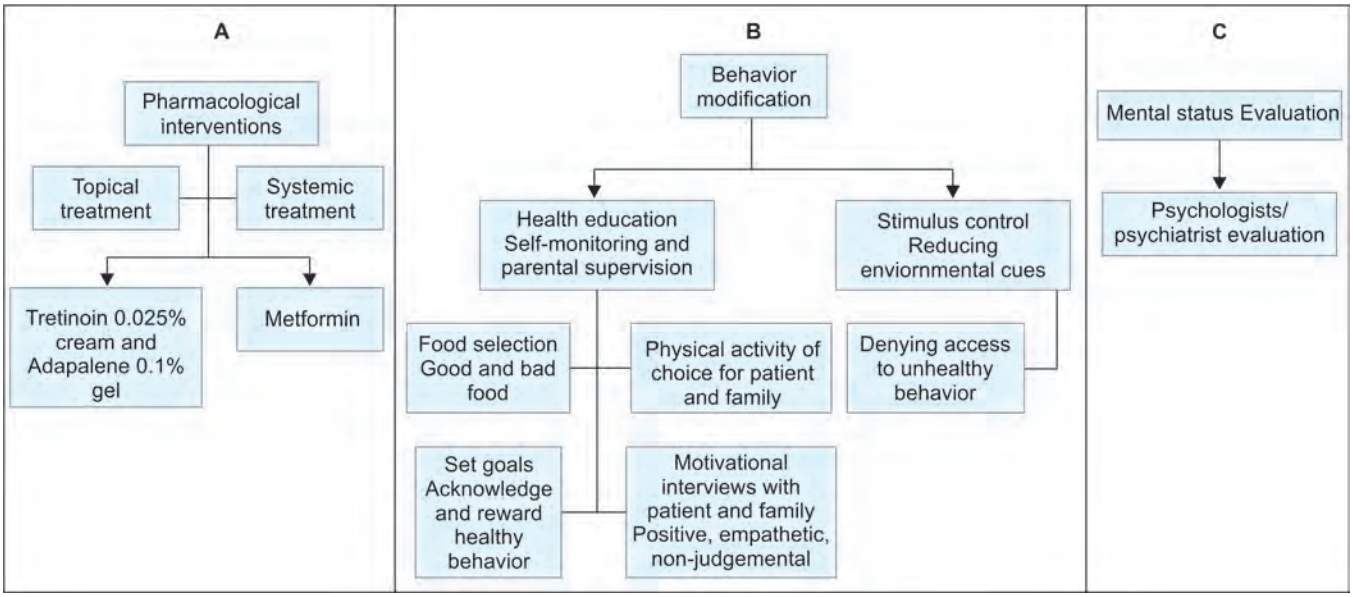


Table 11: Summary table of recommendations

Recommendations	*Expected outcomes*
Recommendation 1: AN can be suspected from general skin examination due to its classical clinical appearance on typical sites	Early detection of IR cases
Recommendation 2: AN is a cutaneous marker of IR and related conditions such as prediabetes, DM, PCOS, and MS. Its presence should raise an index of suspicion for further investigations	An appropriate investigational plan can help detect the root cause of AN
Recommendation 3: All possible causes responsible for AN must be considered to provide appropriate treatment. For suspected drug-induced AN, before stopping the causative medication, risk–benefit analysis and an available alternative must be evaluated	Clinicians can be made aware of drug-induced AN and can advise the patient accordingly
Recommendation 4: The clinician must be aware of the red flags in the presentation of AN suggesting underlying malignancy	Atypical AN due to underlying malignancy can be detected early for better prognosis
Recommendation 5: To undertake a detailed medical evaluation, including, family history, and relevant investigations to rule out the underlying/associated conditions	Early diagnosis helps in timely management and reducing morbidity
Recommendation 6: It is important to advise patients about healthy eating practices, a nutritionally diverse and balanced diet, physical activity, and good sleep habits	Lifestyle changes shall help attain good metabolic health
Recommendation 7: Physical and mental well-being should receive equal emphasis. Education and counselling are crucial for initiating and sustaining lifestyle changes	Motivation and self-esteem improve emotional health and contribute to good quality of life
Recommendation 8: It would be appropriate and timely to integrate AN as a simple, visible, screening sign for early detection of IR in National Health Programmes	Allows diagnosis of previously undetected or missed cases of prediabetes, DM, and MS in the community

Challenges and Call for Action

The Government of India, recognizing the need to control the rise of NCDs, proactively launched the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS) in 2010. The main focus of this program is health promotion, early diagnosis, management, and referrals for positive health outcomes. The NCD program currently focuses only on adults aged 30 years and above. They have a well-defined risk score to identify NCD cases for referral. AN would be a highly useful addition to the risk score.

The National Diabetes Control Programme focuses on the early detection and management of prediabetes and DM. However, India still has 69.2 million people with DM and 36.5 million with prediabetes. The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, conducted in all 30 states/union territories of India between 2008 and 2020, has reported a 150% increase in DM cases, with the young population between the ages of 25–34 years being affected. Unfortunately, every sixth diabetic person in the world is Indian.[68]

The Ministry of Health and Family Welfare has also launched a health program for adolescents (age-group of 10–19 years), namely Rashtriya Kishor Swasthya Karyakram (RKSK), which addresses issues such as nutrition, reproductive health, NCDs, mental health, and substance abuse.

India has a huge experience with its trained workforce to reach the local population at the remotest of places through National Health Mission programs. Grassroots healthcare workers, namely auxiliary nurse midwife (ANM), accredited social health activist (ASHA), anganwadi worker (AWW), who are directly in contact with Indian households in every urban and rural area could be trained to detect AN and report to the primary healthcare center (PHC). The PHC can then undertake certain tests and provide counseling for lifestyle changes and further management. School health programs could incorporate this sign as one of the components of school health checkups. Adequate linkage to NCD program needs to be ensured such that the child is followed up to assess further risks.

It is reported that approximately 57% of individuals continue to remain undiagnosed for diabetes in India.[69] The inclusion of AN in National Health Programmes can help to detect these currently missed cases.

Recommendation 8: It would be appropriate and timely to integrate AN as a simple, visible, screening sign for early detection of IR in National Health Programmes.

Conclusion

Acanthosis nigricans is a reliable and easy-to-detect marker of IR. It should be an integral part of the routine general examination by clinicians and healthcare workers (HCWs). India has a huge burden of NCDs such as DM, MS, and PCOS. Hence, early detection of IR and its appropriate management is crucial. AN must receive its due attention and incorporation into the national health mission programs. Training modules for the detection of AN need to be disseminated to all clinicians and healthcare workers.

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POINT OF VIEW

Chronic Obstructive Pulmonary Disease and Oxygen Therapy: A Double-edged Sword

Yash Sanjay Kedia[1*], Vidushi Rathi[2], Pranav Ish[3], Nitesh Gupta[4], Rohit Kumar[5]

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Abstract

Oxygen, like all medicines, is a drug which needs moderation. Hypoxia, as well as excess oxygen supplementation, can be harmful in a patient with chronic obstructive pulmonary disease (COPD). Both the European and the British guidelines recommend a target oxygen saturation of 88–92% in patients with COPD. Hypoxia can result in symptoms, such as restlessness, anxiety, agitation, and headache, while excess oxygen can lead to altered sensorium due to the retention of carbon dioxide (CO_2) in patients with COPD. We often come across patients who come with breathlessness and have hypoxia, and the knee–jerk reaction is to start the patient on oxygen support to maintain an oxygen saturation of >95%, and this may result in hypercapnia and type II respiratory failure. Here, we present a descriptive review of the proper application of oxygen therapy in a patient presenting with acute exacerbation of COPD, the rationale behind the target oxygen saturations, and the mechanisms of type II respiratory failure due to hyperoxygenation.

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A 60-year-old man with COPD was brought to the casualty by his wife and son with increased shortness of breath, cough with expectoration, and undocumented fever for the previous 5 days. The patient was a current smoker for 20 years, with a smoking index of 250. His body mass index was 23.05 kg/m^2, and he did not have any history suggestive of obstructive sleep apnea. He did not have any comorbidities like diabetes mellitus, hypertension, or coronary artery disease. He was diagnosed with COPD 2 years before his current presentation. The patient had previous spirometry available with him (Figs 1 and 2) done 6 months prior with forced expiratory volume at first second/forced vital capacity (FEV1/FVC) ratio of 41.26 and FEV1 being 0.78 L (27.18% of predicted) signifying severe obstruction. After 15 minutes of giving four puffs of metered dose inhaler (MDI) salbutamol 100 mcg, his spirometry was repeated, which revealed a FEV1/FVC ratio of 43.73 and FEV1 0.82 (28.73% of predicted).

Despite regularly using dual bronchodilator inhaler therapy, he had a history of one hospitalization, requiring noninvasive ventilation (NIV) and oxygen supplementation in the previous 1 year.

In the casualty, his pulse rate was 128/minute, respiratory rate was 26/minute, blood pressure was 140/96 mm Hg, and room air saturation (SpO_2) was 72%. There was no use of accessory muscles for respiration. His Glasgow Coma Scale (GCS) was E4V4M5. He had pedal edema and visible jugular venous pulsation with raised jugular pressure. Chest radiograph was suggestive of hyperinflation without obvious consolidation (Fig. 3) and computed tomography (CT) chest was suggestive of barrel-shaped chest and extensive air trapping (Fig. 4). An arterial blood gas (ABG) was drawn i/v/o hypoxemia, which was suggestive of pH—7.29, partial pressure of carbon dioxide (pCO_2)—65.4, partial pressure of oxygen (pO_2)—38.5, bicarbonate (HCO_3)—30.9, and SpO_2—74.8%.

Question 1

What are the causes of worsening dyspnea in a case of COPD?

A: Exacerbation with or without pneumonia.

B: Pleural effusion and pneumothorax.

C: Pulmonary thromboembolism.

D: All of these.

Answer 1: (D) All of these.

Chronic obstructive pulmonary disease patients can have worsening of their breathlessness due to multiple etiologies and sometimes even nonpulmonary etiologies. According to GOLD guidelines[1] 2024, COPD exacerbation (ECOPD) is defined as worsening dyspnea and/or cough in <14 days, which may be associated with tachypnea and/or tachycardia.

Other confounders/contributors to be considered in patients presenting with suspected ECOPD include pneumonia, pulmonary embolism, heart failure, pneumothorax, pleural effusion, myocardial infarction, and cardiac arrhythmia.

In view of hypoxemia, oxygen supplementation was initiated *via* nasal cannula at 6 L/minute. His SpO_2 quickly improved to 99%. He was also nebulized with bronchodilators using a jet nebulization chamber and face mask driven by oxygen from the wall port at a flow rate of 15 L/minute. This provided the patient with initial relief from dyspnea. An ABG sample drawn after 30 minutes revealed pH—7.24, pCO_2—87.4, pO_2—298, HCO_3—31.5, and SpO_2—99.9%. The patient's sensorium worsened (GCS-E1V2M1). He underwent emergency endotracheal intubation and was put on invasive volume-controlled ventilation.

Question 2

What are the appropriate treatment strategies in a case of COPD on invasive mechanical ventilation (MV)?

A: Bronchodilation and parenteral steroids.

B: Ventilatory settings to correct acute hypercapnia and hypoxemia.

C: Both A and B.

D: Chronic obstructive pulmonary disease (COPD) patients do not recover from ventilation.

Answer 2: (C) Both A and B.

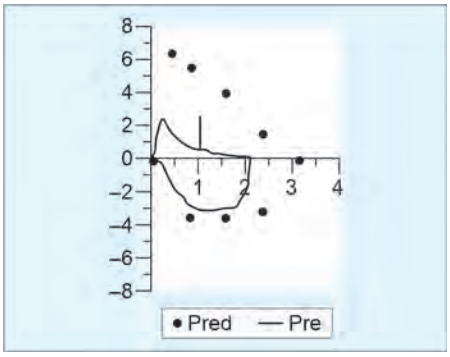

Fig. 1: Flow volume curve showing obstruction

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Forced vital capacity:

	Predicted	Pre-observed	% Pred	Post-observed	% Pred	% change	LLN	Z-score
FVC (L)	3.59	1.90	52.79	1.87	52.09	–1.33	3.08	–5.54
FEV1 (L)	2.88	0.78	27.18	0.82	28.43	4.58	2.44	–6.96
FEV 3s (L)	2.76	1.30	47.00	1.33	48.21	2.57	2.03	–3.24
FEV1/FVC (%)	80.06	41.26	51.53	43.72	54.62	5.99	70.89	–5.28
PEF (L/S)	7.61	2.77	36.45	2.74	35.99	–1.26	5.62	–4.03
MEF25 (L/S)	1.40	0.20	13.91	0.18	13.10	–5.82	0.12	–1.57
MEF50 (L/S)	4.01	0.34	8.47	0.36	9.03	6.57	1.84	–2.76
MEF75 (L/S)	6.67	0.61	9.16	0.78	11.62	26.87	3.86	–3.45
MEF (L/S)	2.67	0.31	11.51	0.32	12.15	5.50	1.53	–4.41
FIV1 (L)	0.00	1.94	—	1.82	—	–5.81	—	—

Fig. 2: Forced expiratory maneuvers results

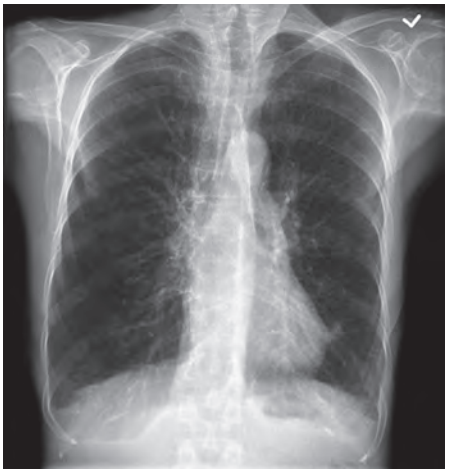

Fig. 3: Chest X-ray suggestive of bilateral hyperinflated lungs

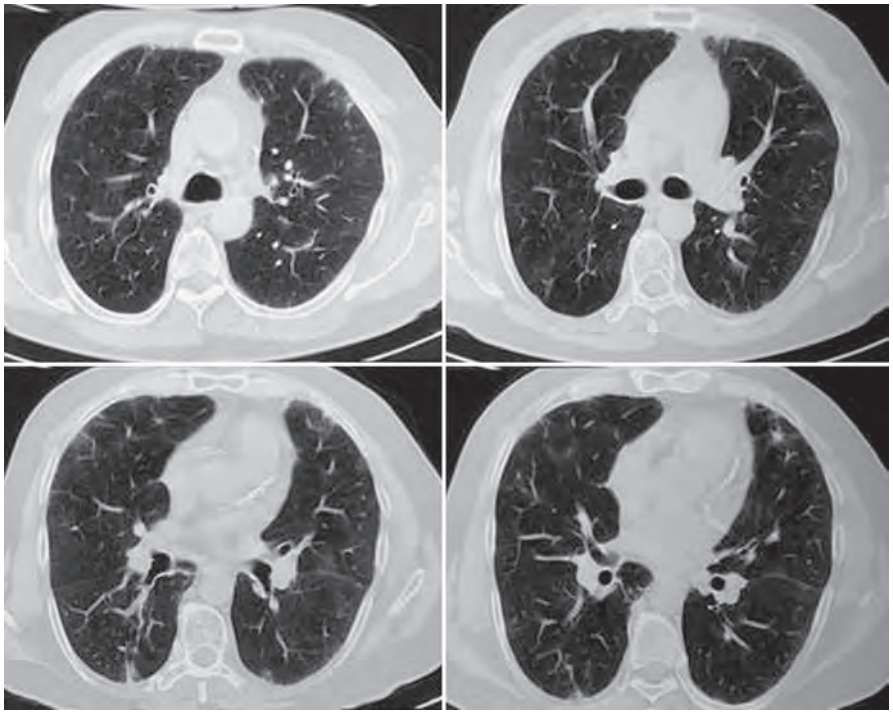

Fig. 4: Computed tomography chest suggestive of extensive air trapping and barrel-shaped chest

GOLD 2024 guidelines[1] for the management of COPD recommends:

Short-acting inhaled β-2 agonists, with or without short-acting anticholinergics, are the initial choice of bronchodilators in ECOPD.

Systemic steroids can improve FEV1 oxygenation and reduce recovery time and hospitalization duration.

Noninvasive ventilation is the first choice of ventilation to be used in COPD patients with acute respiratory failure, as it improves gas exchange, reduces work of breathing, and the need for intubation.

When invasive MV is used, settings should be adjusted in a way that minimizes hyperinflation while providing reasonable gas exchange, respiratory muscle rest, and proper patient-ventilator interaction. The most important goal while ventilating patients with COPD is to allow higher exhalation time for CO_2 to washout and pH to normalize. This can be achieved by setting a slower respiratory rate and higher peak inspiratory flow rate to maintain an I:E ratio of 1:3 to 1:5. At the same time; it is important to maintain a plateau pressure <30 cm H_2O to avoid barotrauma in these mechanically ventilated patients.[2]

The patient was treated with a tidal volume of 8 mL/kg, positive end-expiratory pressure (PEEP) of 6 cm H_2O, inspiratory/expiratory ratio of 1:3 and respiratory rate of 14 breaths/minute with FiO_2 set at 30% to maintain SpO_2 between 88 and 92%. The peak and plateau pressures at these ventilator settings were 46 and 32 mm Hg, respectively, with an autoPEEP of 12 mm Hg. Simultaneously, he was treated with nebulized bronchodilators, intravenous steroids, and antibiotics.

Critical care lung sonography revealed lung sliding with A-profile bilaterally. Critical care echocardiography did not show regional wall motion abnormality. The left ventricular ejection fraction was 55%, the right atrium and ventricle were dilated, and the right ventricular systolic pressure was 44 mm Hg. Laboratory testing showed mild leukocytosis (TLC 12300/mm^3), differential leukocyte count—polymorphonuclear neutrophils 82%, lymphocytes 13%, eosinophils 1%; hemoglobin 16.5 gm/dL, and hematocrit 56.2%. Liver and kidney function tests were within normal limits.

After 2 hours, his peak and plateau pressures reduced to 30 and 22 mm Hg. ABG revealed pH—7.50, pCO_2—41.6, pO_2—70.2, HCO_3—36.5, and SpO_2—92.1%. The patient improved over the next 48 hours, became afebrile, and sensorium regained. He was extubated to NIV with PEEP of 6 cm H_2O and pressure support of 16 cm H_2O

Question 3

What was the possible reason for the need for invasive MV in this patient?

A: Worsening respiratory failure due to infective exacerbation.

B: Oxygen therapy-induced hypercapnia.

C: Both A and B.

D: All COPD exacerbations eventually require ventilatory support.

Answer 3: (C) Both A and B.

Various studies have shown that uncontrolled oxygen administration to patients with acute exacerbation of very severe COPD can induce hypercapnia. Various mechanisms have been proposed for the same:

Oxygen-induced hypoventilation: Uncontrolled oxygen administration leads to an early initial decrease in minute ventilation with an elevation of partial pressure of CO_2 ($PaCO_2$). Minute ventilation recovers from the initial decrease and is only marginally reduced in comparison with the baseline. However, $PaCO_2$ increases further despite the recovery of the minute ventilation.[3]

Hyperoxygenation causing ventilation-perfusion mismatch: Hypoxia causes pulmonary vasoconstriction. Reduced ventilation due to bronchospasm (thus O_2 tension) in the alveolus leads to reduced perfusion because of the hypoxic pulmonary vasoconstriction mechanism. However, high oxygen tension in alveoli will prevent this hypoxic pulmonary vasoconstriction mechanism and increase V/Q mismatch.[4]

Haldane effect: The ability of deoxygenated hemoglobin to bind to CO_2 is much higher than that of oxygenated hemoglobin. When the FiO_2 is increased, oxygen displaces CO_2 from hemoglobin, causing an increase in oxygenated hemoglobin and shifting the CO_2 dissociation to the right, thus releasing more CO_2 into the blood and causing an increase in $PaCO_2$.[5]

Question 4

What measure could have prevented the need for invasive MV in this patient?

A: Noninvasive ventilatory (NIV) support.

B: Oxygen therapy using Venturi or high flow nasal cannula (HFNC).

C: Nebulise with nebulizers and not oxygen in COPD, especially in hypercapnia.

D: All of the above.

Answer 4: (D) All of the above.

Noninvasive ventilation (NIV) has been recommended as the first choice of ventilatory device to support patients with COPD exacerbation. Several randomized controlled trials have proven its efficacy and ability to reduce the need for invasive MV.[1]

HFNC has also been shown to reduce breathing work, and trials have shown that there was no difference in the risk of intubation with HFNC compared to NIV.

Oxygen-driven nebulization may lead to the delivery of excess oxygen over and above the SpO_2 target of 88–92%, which can cause oxygen therapy-induced hypercapnia.

Over a period of 3 days, the patient was weaned off NIV support. He required oxygen supplementation at 1 L/minute delivered *via* nasal cannula, maintaining a SpO_2 of 92%. His ABG on room air at the time of discharge was suggestive of pH—7.37, pCO_2—46.2, pO_2—58.2, HCO_3—26.6, SpO_2—89.1%, and the patient was discharged on home oxygen therapy 1 L/minute for at least 15 hours daily.

There are many iatrogenic mechanisms which eventually lead to invasive MV in patients with COPD. They are preventable, and underlying physiology needs to be emphasized by all pulmonologists, emergency medicine physicians, and intensivists. This case, thus, highlights the issues of oxygen toxicity, which still prevail in India, even in tertiary care centers, due to a lack of awareness.

Discussion

Hypoxemic respiratory failure in acute ECOPD (AECOPD) is treated with oxygen supplementation titrated to a target SpO_2 of 88–92%. This target corresponds to a PaO_2 level of 55–60 mm Hg. In an observational study, this SpO_2 target was found to be associated with the lowest inhospital mortality in AECOPD.[6] Oxygen supplementation can be delivered by either variable (low flow) or constant (high flow) FiO_2 devices. The nasal cannula is a variable FiO_2 device commonly used for oxygen supplementation. The most appropriate case for a nasal cannula is when the FiO_2 requirement is between 25 and 38%, translating to 1–4 L/minute of oxygen flow, and the inspiratory flow demand of the patient is low. In such a scenario, a nasal cannula delivers sufficient oxygen while also being comfortable and unobtrusive.

However, AECOPD with hypoxemic respiratory failure is often associated with severe bronchoconstriction, which leads to high inspiratory flow demand. When a nasal cannula is used in such a patient, the excess inspiratory flow causes entrainment of ambient air along with oxygen from the cannula. This leads to a substantially lower FiO_2 received by the patient compared to the FiO_2 being delivered by the nasal cannula. Consequently, the oxygen saturation picks up less than what would be expected for the delivered FiO_2. It becomes tempting to increase the delivered FiO2 to values greater than the 4 L/minute mark further to achieve the target SpO_2 of 88–92%. Meanwhile, inhaled bronchodilator therapy is also instituted for the individual. With successful bronchodilation, there is an improvement in respiratory distress and, therefore, the demand for inspiratory flow. This, in turn, decreases the required FiO_2. As a result, the SpO_2 now picks up beyond 92% with the same FiO_2 that was required earlier. If SpO_2 and respiratory rate are left unmonitored, as might happen in a busy emergency room, such a patient quickly transitions to oxygen therapy-induced hypercapnia.

Constant flow oxygen devices and NIV accomplish two advantages by addressing both the high inspiratory flow rate demand of severe bronchoconstriction and the FiO_2 requirement. Firstly, the individual's work of breathing improves. Secondly, the FiO_2 received by the patient is matched to the FiO_2 being delivered by the supplementation device.

A Venturi device attached to a face mask can deliver constant target FiO_2 at high flow rates. It is appropriate for FiO_2 requirements between 25 and 60%. The Venturi mask uses the Bernoulli principle to deliver a predetermined and fixed concentration of oxygen to the patient. This is achieved in spite of the patient's respiratory pattern by providing a higher gas flow than the peak inspiratory flow rate. Thus, Venturi devices are very effective in delivering fixed FiO_2 and reduce the risk of hyperoxygenation, even if the flow rate is increased.[5]

Another device, high flow oxygen therapy (HFOT), delivered by specialized nasal cannula, also addresses both high FiO_2 requirements and inspiratory flow demand. The high flow delivered by HFOT devices provides a washout effect of the upper airway dead space, which reduces hypercapnia. Additionally, it also provides end-expiratory positive pressure of 3–6 cm of water and reduces airway resistance and, consequently, the work of breathing. The nasal interface of HFOT is more comfortable than the Venturi's face mask. In a prospective observational study by Yuste et al., HFOT was found to be effective for moderate hypercapnic respiratory failure, as it helps normalize clinical and gas exchange levels with an acceptable rate of nonresponders who require ventilatory support.[7]

The utility of NIV in the setting of AECOPD without respiratory acidemia lies in its ability to reduce the work of breathing and prevent respiratory muscle fatigue. The Indian Society of Critical Care Medicine recommends that NIV should be used in the management of AECOPD in patients with acute or acute-on-chronic respiratory acidosis (pH = 7.25–7.35) and NIV should be attempted in patients with acute exacerbation of COPD (pH < 7.25 and $PaCO_2$ ≥ 45) before initiating invasive MV except in patients requiring immediate intubation. They also highlight that the lower the pH,

the higher the chance of failure of NIV.[8] By using appropriate inspiratory and expiratory pressures in the pressure support mode of NIV, high inspiratory flow rates can be delivered with each breath. The inspiratory pressure should be set to achieve a tidal volume of at least 6–8 mL/kg, and the expiratory pressures should be set to reduce the use of accessory muscles. Additionally, a constant FiO_2 can also be guaranteed. However, the obtrusive and uncomfortable nature of the interface makes NIV less than optimal for hypoxemic nonrespiratory acidemic AECOPD compared to HFOT or Venturi devices.

Pisani et al. systematically reviewed the evidence behind using HFOT, the Venturi device, and NIV in AECOPD.[9] This review found HFOT to be superior to the Venturi device and, like NIV, in reducing breathing work. The Venturi device was, in fact, associated with an increase in work of breathing. Further, there was no difference in the risk of intubation with HFOT compared to NIV. However, it should be noted that the success of NIV depends on minimizing air leaks. Ensuring this often means excessive tightening of face mask straps. The helmet interface addresses this problem. However, it is even more uncomfortable than face masks. The interface problems reduce patient compliance with NIV and contribute to the failure of therapy.

HFOT is an appropriate device for delivering oxygen therapy in individuals with AECOPD without respiratory acidemia and rarely in acidemia, especially if NIV cannot be used.[10] In its absence, a Venturi device can easily be used. However, when respiratory fatigue is an imminent danger, either HFOT or NIV should be used, while Venturi devices are avoided altogether. During and after administration of bronchodilators, careful monitoring of respiratory distress, respiratory rate, and SpO_2 is necessary. Reducing the delivered FiO_2 and targeting SpO_2 of 88–92% is crucial to avoid oxygen therapy-induced hypercapnia. Once the individual can maintain this target with ambient air inhalation, supplemental oxygen should be promptly withdrawn.

As seen in this case, with the initiation of MV, with sudden washout of CO_2, the patient developed metabolic alkalosis, also known as "posthypercapnic metabolic alkalosis." This occurs as the CO_2 washes out quickly; compensation by the kidney to reduce the HCO_3 levels to return the pH to normal takes time, and the patient develops metabolic alkalosis. Metabolic alkalosis in itself can lead to certain complications. It attenuates respiratory central drive performance by reducing the stimulatory effects of hypercapnia, and this can lead to longer dependence on the ventilator, longer intensive care unit stay and increased morbidity and mortality. Alkalosis also impairs oxygenation mainly due to a shift to the left of the dissociation curve of oxyhemoglobin, and it may also worsen cardiac output and favor cardiac arrhythmias due to electrolyte imbalances.[11]

Inhaled bronchodilators can be delivered by using dry powder inhalers, MDIs, or nebulizers. Individuals with severe AECOPD commonly have high respiratory rates and an inability to generate a long, deep breath followed by an inspiratory hold. This makes nebulizers the most commonly used modality in emergency cases. The aerosol generation in commercially available jet nebulizers can be driven by either ambient air or oxygen. While the former requires a dedicated nebulizer device, oxygen-driven nebulization can be easily delivered using an oxygen port, a flow meter, and a nebulization mask. However, oxygen-driven nebulization may lead to delivery of excess oxygen over and above the SpO_2 target of 88–92%.[12] This is associated with oxygen therapy-induced hypercapnia. In a randomized controlled trial in 90 AECOPD individuals, oxygen-driven nebulization was associated with a significantly greater $PaCO_2$ compared to ambient air-driven devices.[13] It is therefore advisable to use these jet nebulizers instead of oxygen-driven ones.

Conclusion

Despite clear pathophysiology and ample evidence, oxygen continues to be delivered by low-flow variable FiO_2 devices for COPD exacerbation along with oxygen-driven nebulization. Oxygen therapy in COPD is a double-edged sword-hypoxia kills, but hyperoxygenation can also be harmful in these patients. Titrated oxygen therapy has been shown to reduce the risk of death in patients with hypercapnic respiratory failure.[12] The selection of a proper high-flow oxygen delivery device is of vital significance in helping these patients achieve oxygenation goals. In low-resource settings like India, a Venturi device can be used as a good initial choice to avoid the risk of hyperoxygenation.

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CASE REPORT

Primary Aortoenteric Fistula Due to *Salmonella typhi*-related Mycotic Aneurysm

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Abstract

Primary aortoenteric fistulas (AEF) are rare. The majority of these are due to atherosclerotic aortic aneurysms. Mycotic aortic aneurysms leading to primary AEF are exceedingly uncommon. Here we report a rare case of primary AEF secondary to *Salmonella*-related mycotic aneurysm and discuss the diagnostic and therapeutic issues.

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Introduction

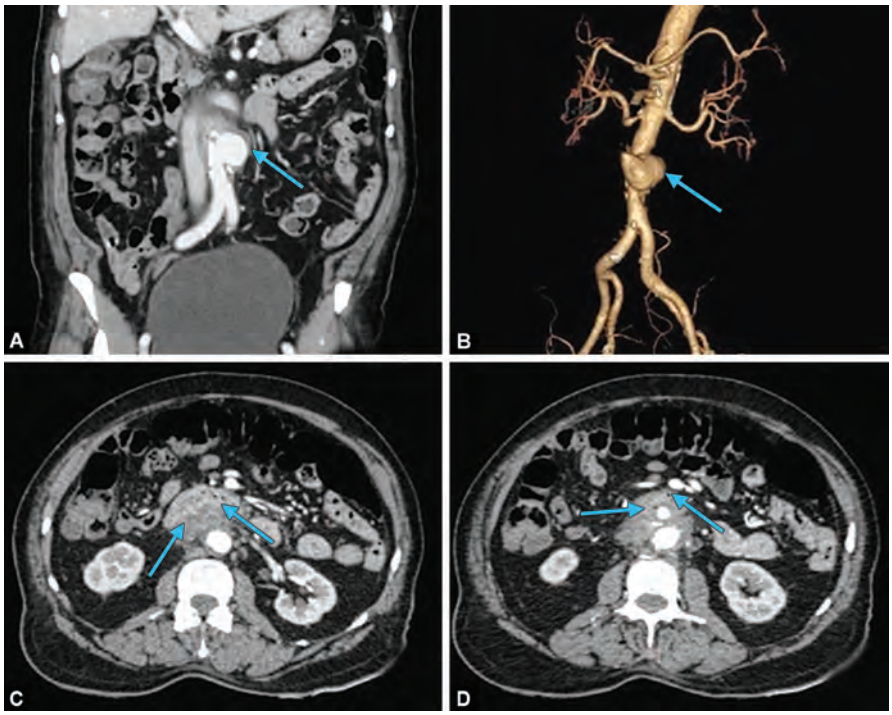
Aortoenteric fistulas (AEF) can be primary or secondary. Primary AEF are those occurring in patients without any prior aortic surgeries; secondary ones occur following aortic repair by prosthesis or grafts.[1] Primary AEF are very rare and account for <1% of all AEF.[2] A recent report suggests that in the last century, only about 300 cases have been reported.[3] Although multiple causes have been reported for primary AEF, >90% are due to atherosclerosis. Infective causes, malignancies, and radiotherapy are among the other causes reported.[3] Overall, infective causes account for <5% of cases of primary AEF.[3] Mycobacteria species (spp.),[4–8] *Salmonella* spp.,[1,9–12] and *Streptococcus* spp.[1] are among the infective causes reported. Here, we report a case of primary AEF caused by *Salmonella enterica* subspecies *typhi*. To the best of our knowledge, this is the first reported case from India.

Case Description

A 71-year-old male presented to our institute with a history of four episodes of hematemesis of about 300–400 mL each and three episodes of melena. He reported a few episodes of melena 3 days ago as well. He was symptomatic for hypovolemia with giddiness and had postural hypotension. He was afebrile and had heart rate and supine blood pressure of 86 beats per minute and 120/70 mm Hg. He did not have any significant past medical history. He was a nonsmoker and a reformed alcoholic. He denied any form of substance abuse or sexual exposures.

After initial stabilization, he underwent upper and lower gastrointestinal endoscopies, both of which were normal. A computed tomography (CT) scan with angiography showed a saccular aneurysm with a wide neck arising from the anterior and left lateral wall of the infrarenal part of the aorta. The anterior part of the aneurysm measured 20 × 16 mm, and the lateral part measured 21 × 12 mm. An intramural hematoma was noted in the anterior part of the aneurysm. The hematoma extended up to the posterior wall of the third part of the duodenum, and a few air foci were seen within the hematoma in the vicinity of the duodenum, strongly suggesting erosion of the duodenal wall and formation of an aortoduodenal fistula (Fig. 1). He underwent exploration and repair of the aneurysm. Operative findings confirmed the suspicion raised by the CT scan findings. Postoperatively, he developed accelerated hypertension, which was managed with nitroglycerin infusion. By the 3rd postoperative day, he was ambulatory and was tolerating a liquid diet.

Histopathology of the excised specimen was consistent with aortic aneurysm with an AEF. Culture from the aortic thrombus grew *Salmonella typhi*, which was sensitive to cotrimoxazole, chloramphenicol, ampicillin, nalidixic acid, ciprofloxacin, and ceftriaxone. Blood cultures were repeated thrice and all were negative. On subsequent questioning, he revealed a weeklong febrile episode around 3 months ago. He had received some antibiotics from a local physician with resolution of the fever. In view of aortic thrombus growing *S. typhi*, he received intravenous ceftriaxone and



Figs 1A to D: Showing the (A) aneurysm; (B) reconstruction; (C) loss of fat planes with the intestinal wall; and (D) air pockets within hematoma/aneurysm wall

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Table 1: *Salmonella* species-related primary AEF cases

First author	*Year*	*Age*	*Gender*	*Preoperative suspicion*	*Operated*	*Antibiotics**	*Duration of antibiotics*	*Long-term outcome*	*Ref number*
Daugherty	1979	52	Female	No	Yes	?	2 months	Alive at 6 years	13
McIntyre	1982				Details not available; full text not found				12
Morrow	1987	32	Female	No	Yes	Genta, Chloram, Nafcillin	2 weeks	Alive at 3.5 years	11
Morrow	1987	67	Male	No	Yes	Ampicillin	4 weeks	Alive at 6 months	11
Pagni	1999	67	Female	Yes	Yes	?	6 weeks	Alive at 6 months	10
Tozzi	2001	65	Female	Yes	Yes	–	–	Died postoperatively	1
Skourtis	2010	51	Male	No	Yes	Amoxy + Clav, Cipro	3 months	Alive at 10 months	9
Kritpracha	2011	60	Male	Yes	No (Endo-vascular prosthesis)	–	–	Died on postoperatively day 1	14
Current case	2015	71	Male	Yes	Yes	Ceftriaxone, Cipro, Azi	12 weeks	Alive at 6 months	–

*Abbreviations: ?, Not known; Amoxy + Clav, Amoxycillin + Clavulanate; Azi, Azithromycin; Chloram, Chloramphenicol; Cipro, Ciprofloxacin; Genta, Gentamicin

oral azithromycin for 4 weeks followed by a combination of oral ciprofloxacin and azithromycin for 8 weeks. His subsequent course has been uneventful. He is doing well at 6 months follow-up.

Discussion

Enteric fever is common in India and in many other countries of the world. In spite of *Salmonella* infections being common, primary AEF due to *Salmonella* is extremely rare. Using the search term "aortoenteric fistula," "aortoduodenal fistula," and "*Salmonella*" in PubMed, and checking the references of the obtained articles, we could find out only eight previously reported cases of *Salmonella*-related primary AEF.[1,9–14] The details of these cases are summarized in Table 1. The species of *Salmonella* identified in these cases include one with *S. typhi* (this case), two with *Salmonella* type C,[10,11] one case with *Salmonella enteritidis* group B,[11] one case with *Salmonella* nontyphimurium (group not mentioned),[1] one case with *S. enterica* subspecies *arizonae* (formerly known as *Arizona hinshawii*),[12] and three cases with unknown species.[9,13,14]

In all the above cases, the site of AEF was duodenal. One study found >80% of all AEF are aortoduodenal.[15] Etiologically, among the primary aortoduodenal fistulas, atherosclerosis was the most common accounting for about 73% cases. Infectious and traumatic causes combined accounted for about 26% of cases of primary aortoduodenal fistula.[15,16] The most common organisms responsible for infectious causes of primary AEF have been reported to be *Salmonella* and *Klebsiella*.[16] Other reported organisms include mycobacteria (tuberculous and nontuberculous),[4–8] staphylococcus and streptococcus.[16]

The precise pathogenesis of AEF remains unclear. It has been found that, in abdominal aortic aneurysms, there is increased expression of matrix metalloproteinase-9 (MMP-9) and other degradative enzymes.[17] This in combination with the anatomic fixity of the duodenum likely plays a role in the development of AEF. What factors precisely predispose only a small fraction of patients with mycotic aneurysms to develop AEF is unknown.

The characteristic clinical triad of AEF (primary or secondary) is upper gastrointestinal bleeding, abdominal pain, and the presence of a pulsatile abdominal mass.[3] Among these three, bleeding is the most common and occurs in >90% of patients.[3] However, all the three features are present in only 6–12% of the patients.[1] In the majority of the cases, the diagnosis is not suspected preoperatively and is confirmed only at laparotomy. It is quite likely that there are many cases going undiagnosed. At least a fraction of patients with gastrointestinal bleeding related to enteric fever may be having an AEF. Hence, it is essential to have a high index of suspicion for this uncommon complication in all patients with enteric fever who develop gastrointestinal bleeding or perforation, particularly if the patient is having hemodynamic compromise.

Presence of air within the hematoma or the wall of the aneurysm on imaging should make one suspect the development of a fistula. Other radiological signs of AEF include visualization of intravenous contrast in the bowel loops and loss of fat planes between the aneurysm and the bowel wall.[3] These should be carefully looked for in the CT scan. In our case, as well in the case reported by Tozzi, air foci were noted within the hematoma.

Surgery and appropriate antibiotic therapy are essential in the treatment of primary AEF. Surgery is the mainstay of therapy and without surgery, the mortality is essentially 100%.[2] The optimal choices of antibiotic as well as the optimal duration of antibiotic therapy after surgery are unclear. The choice of antibiotic should probably be based on the local antibiotic susceptibility patterns. Regarding duration of therapy, in cases with long-term survival, antibiotics have been given for 2–8 weeks. Our patient received a 12-week course of antibiotics after successful surgery.

The prognosis of primary AEF remains poor. Even with appropriate surgery, the mortality has been reported to be 60–100% in various studies. A part of this is also due to the operative mortality. However, as stated above, the vast majority of the cases of primary AEF are due to atherosclerosis. It is likely that these patients have an older age and accompanying comorbid conditions. In contrast, the outcome of *Salmonella*-related primary AEF seems to be more favorable. Of the previously published and this case

combined, six out of eight (75%) patients have had long-term survival (data not available for one case).

In conclusion, primary AEF is a rare complication of *Salmonella* infection. It is essential to remain vigilant for this complication and to carefully evaluate for the radiological signs of this condition. Aggressive surgery and appropriate antibiotic therapy are essential. Early diagnosis and aggressive intervention may possibly contribute to a more favorable outcome of this otherwise catastrophic complication.

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Erratum

In the April 2024 Issue of JAPI, the article entitled "Fortifying Micronutrient Supplementation in India: Expert Consensus by American College of Physicians (India Chapter)" on Page No. 81 should be read as "Fortifying Micronutrient Supplementation in India: Indian Experts Consensus".

CASE REPORT

Postdengue Acute Disseminated Encephalomyelitis

Sudipto Chakraborty[1*], Akash Narayan[2], Debabrata Chakraborty[3], Bhaskar Ukil[4], Satya Narayan Singh[5]

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Abstract

A 38-year-old gentleman, following an uncomplicated dengue fever 2 weeks back, developed acute onset bilateral lower limb weakness and numbness for 5 days, associated with bladder and bowel incontinence and a band-like sensation in T4 dermatome. On examination, he had paraparesis with normal cranial nerves except for left upper motor neuron-type 7th cranial nerve palsy and normal higher mental function. Magnetic resonance imaging (MRI) of the brain and spine detected multiple demyelinating lesions. A diagnosis of postdengue acute disseminated encephalomyelitis (ADEM) was made as part of postinfective inflammatory process after the fever had subsided. Cerebrospinal fluid study ruled out active infection. He was treated with intravenous steroids and is currently recovering. An interesting point in our case was that the patient had significant imaging findings in MRI of the brain with no symptoms or signs suggestive of intracranial involvement—ADEM without evidence of encephalitis.

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Introduction

Dengue fever is a ribonucleic acid arboviral infection, endemic to tropical countries. It has four serotypes: DENV (dengue virus)-1, DENV-2, DENV-3, and DENV-4. It is transmitted to humans through bites of female *Aedes aegypti* mosquito. Dengue fever clinical spectrum may range from mild uncomplicated cases to severe hemorrhagic fever and shock syndrome.[1]

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the central nervous system, which involves widespread demyelination of the brain and spinal cord, predominantly affecting the white matter. It usually occurs after a viral infection or vaccination.[2]

Case Description

A 38-year-old gentleman, with no previous comorbidities, presented to the emergency with complaints of both lower limb weakness for 5 days.

The limb weakness was insidious in onset, gradually progressive, and during presentation, he could not walk on his own. He had bladder and bowel incontinence for 1 week before presentation. On further inquiry, he had a band-like sensation just below the nipple area and had decreased sensation in both lower limbs compared to the upper limbs. On further inquiry, he had an episode of uncomplicated dengue fever 2 weeks back. There was no history of vaccination or toxin exposure in the recent past.

His general examination was insignificant. On neurological examination, higher mental function was normal. The left nasolabial fold was less prominent with weakness of left-sided facial muscles suggestive of upper motor 7th nerve palsy. Other cranial nerve examination was within normal limits. Tone in both upper limbs was normal but reduced in both lower limbs. Power in both upper limbs was 4+/5, and in both lower limbs, it was 3/5 [Medical Research Council (MRC) grading]. Deep tendon reflexes were all present. Planters were bilateral extensor. On sensory examination, he had decreased sensation in both lower limbs compared to the upper limbs. He had a band-like sensation in T4 dermatome. Other systemic examination was within normal limits.

He underwent all the relevant investigations. Blood investigations revealed hemoglobin 14.6, total leukocyte count (TLC) 10,100 N84L9, platelet count 1.26 lakh, creatinine 0.8, sodium 134, potassium 4.8, calcium 9.2, albumin 3.8, serum glutamic oxaloacetic transaminase (SGOT) 60, serum glutamic pyruvic transaminase (SGPT) 115, alkaline phosphatase (ALP) 91, and the triple serology was negative. He underwent magnetic resonance imaging (MRI) of the brain with gadolinium contrast (Figs 1 to 3) and MRI of the spine (Fig. 4), which detected multiple demyelinating lesions suggestive of ADEM.

Further blood tests revealed negative antinuclear antibody (ANA) and ANA panel, negative anti-NMO (neuromyelitis optica) antibody and anti-MOG (myelin oligodendrocyte glycoprotein) antibody. Cerebrospinal fluid (CSF) study was done—cell count 10 with 100% lymphocytes, CSF glucose 91, CSF protein 56, CSF adenosine deaminase (ADA) 0.4, CSF *Mycobacterium tuberculosis* (MTB) GeneXpert negative, CSF Gram stain and culture negative, CSF fungal stain negative, CSF comprehensive infection panel negative (ruled out active infection). Visual evoked potential of both eyes showed normal P100 latencies.

He was started with pulse dose of intravenous (IV) methylprednisolone 1 gm once daily for 5 days and other supportive measures including Foley's catheter and daily physiotherapy. He has improved with the treatment. Currently, he is on an oral tapering dose of steroids and is being able to walk with minimal support.

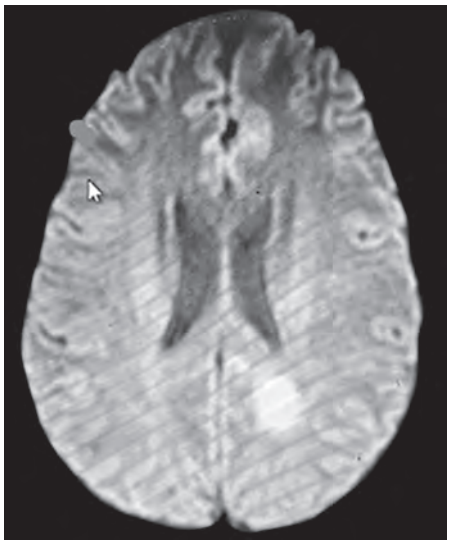

Fig. 1: Magnetic resonance imaging of the brain with gadolinium contrast showed altered signal intensity involving the bilateral middle cerebellar peduncles, the splenium of the corpus callosum, and the left parietal periventricular white matter, suggestive of demyelination and ADEM

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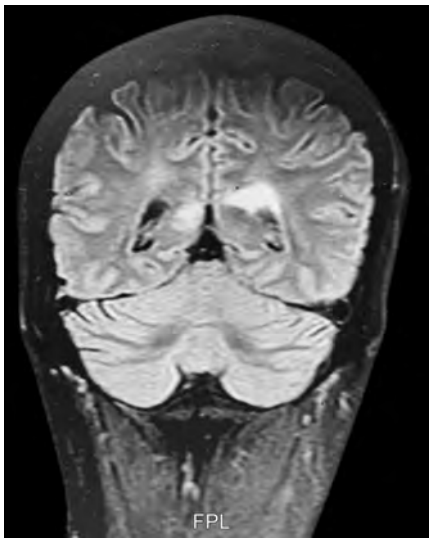

Fig. 2: Magnetic resonance imaging of the brain with gadolinium contrast showed altered signal intensity involving the bilateral middle cerebellar peduncles, the splenium of the corpus callosum, and the left parietal periventricular white matter, suggestive of demyelination and ADEM

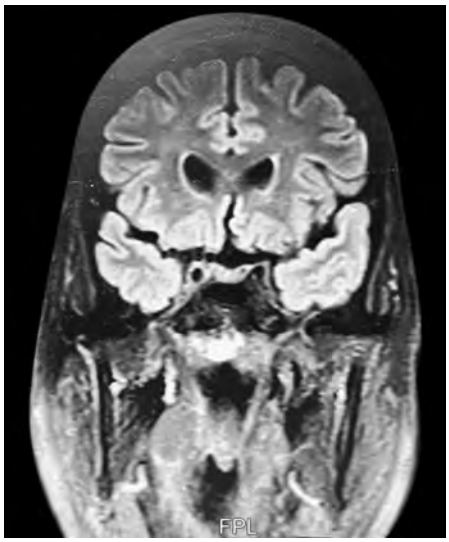

Fig. 3: Magnetic resonance imaging of the brain with gadolinium contrast showed altered signal intensity involving the bilateral middle cerebellar peduncles, the splenium of the corpus callosum, and the left parietal periventricular white matter, suggestive of demyelination and ADEM

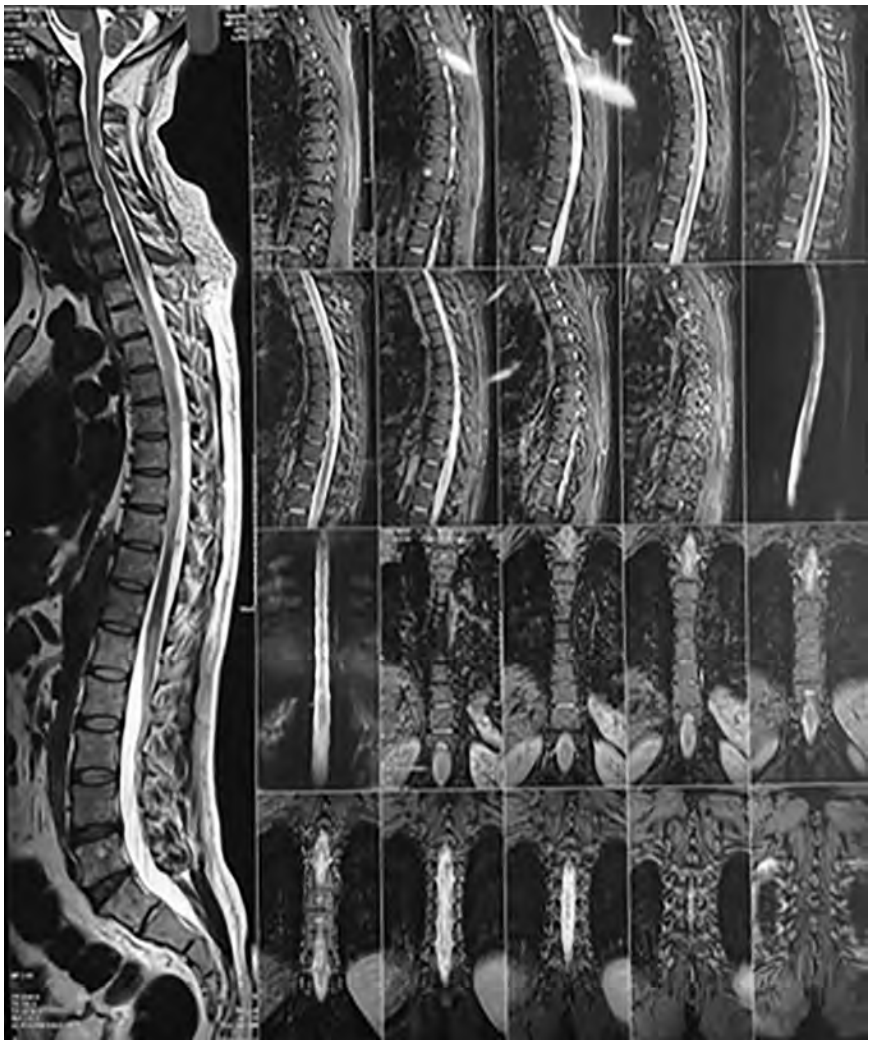

Fig. 4: Magnetic resonance imaging of the spine showed T2-weighted intramedullary hyperintensity at C4 level and from C6 to T10, suggestive of myelitis

Discussion

Dengue fever in most patients is uncomplicated, and only requires symptomatic treatment. But sometimes they can cause complications for the patient to get admitted. The most common complications are falling in blood pressure, rise in hematocrit by >20% above baseline, dehydration, fall of platelet count, and bleeding resulting in dengue hemorrhagic fever and dengue shock syndrome, which is part of capillary leak syndrome. These patients require hospitalization and intensive treatment. There are also severe complications which are not because of the capillary leak syndrome. These include fulminant hepatitis, myocarditis, arrhythmias, rhabdomyolysis, optic neuritis, retinal vasculopathy, hemophagocytic syndrome, and so on.[3]

Neurological complications of dengue fever have a wide spectrum and can be fatal if not identified and treated at the right time. DENV is a neurotropic virus and can infect the supporting cells of the central nervous system. Acute phase complications occur due to direct neuroinvasion or antigen–antibody reaction. Delayed phase complications occur because of immunological mechanisms for molecular mimicry. The manifestations include ischemic or hemorrhagic strokes, isolated cranial nerve palsy, maculopathy, posterior reversible encephalopathy syndrome (PRES), ADEM, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), and so on.[4] In a study by Vyas et al.[5] in northern India, in patients with dengue fever having neurological complications, MRI was done. A total of 36 patients were included in the study, out of which 11 had normal MRI. A total of 12 had encephalitis pattern, 4 had encephalopathic pattern, 3 had features suggestive of ADEM, and 6 had isolated micro- or macrohemorrhages.[5]

In ADEM, there is usually involvement of cerebral white matter and gray nuclei typically. Dengue encephalitis and postdengue ADEM are very difficult to distinguish. Dengue encephalitis is usually in the acute phase, whereas ADEM occurs after recovery of the primary illness.[6] In one meta-analysis, the development of postdengue ADEM is from 3 to 19 days from onset of dengue fever.[7] ADEM following dengue infection requires early recognition and immunosuppressive treatment with corticosteroids, or it can be fatal.[8] There have been multiple case reports in the literature of ADEM following dengue infection.[9,10]

In our patient, diagnosis of ADEM was made over dengue encephalitis as the patient developed symptoms 2 weeks after onset of illness after fever had subsided

via immunological mechanism. He had no features of encephalitis during the clinical course. All the clinical symptoms in the patient could be explained by the demyelinating lesions of the spinal cord. But despite having such widespread demyelinating lesions in the brain, he only had upper motor 7th nerve palsy. He had no other features of brain lesion despite the MRI detecting them. Even though he had ADEM, there was no evidence of encephalitis. This discrepancy of the radiological and clinical findings in ADEM could not be explained despite extensive review of literature search and needs further research.

Conclusion

Hence, we report a rare case of ADEM following an episode of uncomplicated dengue fever in a gentleman who was treated with a pulse dose of IV methylprednisolone and is recovering.

Patient Consent

The authors have obtained written informed consent from the patient for publication of the case report details and related images.

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CASE REPORT

Surgical Management in a Medical Emergency: Disseminated Extensive Tissue Damage Due to Snake Envenomation

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Abstract

Many snakebite deaths in India may remain unreported as these patients still seek treatment from traditional healers or quacks. Though local and systemic toxicity due to snake envenomation is quite common, the clinical presentation as disseminated extensive tissue damage and ulceration is not seen. We present a lady who presented with extensive skin erosions with tissue necrosis in all four limbs and the trunk. The case was successfully managed with antisnake venom, wound debridement, and split skin grafting. Early antisnake venom halts the progression of tissue damage effects of snake venom. The future treatment of these extensive ulcerations may be the use of drugs that can inhibit the hydrolyzing enzymes of snake venom. The case also stresses the need for excellent wound care after the management of systemic envenomation with antivenom treatment.

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Introduction

The World Health Organization (WHO) added snakebite envenoming to its priority list of neglected tropical diseases (NTDs) in June 2017. Though the Million Death study noted 45,900 annual snakebite deaths in India, many snakebite deaths remain unreported as these patients seek treatment from nonmedical sources. Many people have either no access to antivenom in rural areas or cannot afford to pay. Antisnake venoms (ASVs) are included in the WHO Essential Medicine List and should be part of any primary health care package where snakebites occur.[1] Though local and systemic toxicity due to snake envenomation are well known, the clinical presentation as disseminated extensive tissue damage and ulceration is rarely seen. In this case report, we present a lady who presented with altered sensorium and extensive skin peeling off with tissue necrosis in all four limbs and the trunk.

Case Description

A 55-year-old woman, with no prior comorbidities, was admitted with an alleged history of snakebite on the left hand 36 hours earlier while working on the farm. Immediately after the bite, while running for help, she fell unconscious on the ground. She was initially taken to the primary health center after 12 hours of the bite when she started developing blisters over all four limbs, back, and left gluteal region. She was managed for 24 hours with intravenous (IV) antibiotics; however, no ASV was administered. She was shifted to our center after 36 hours of the bite. There was no history of gum bleeding, epistaxis, hematemesis, hemoptysis, melena, vaginal bleeding, breathing difficulty, focal neurological deficit, or blurring of vision. She had gross hematuria on presentation. On examination, she was drowsy, confused but arousable. She was hemodynamically stable with a pulse rate of 84 beats per minute, blood pressure of 128/76 mm Hg, and respiratory rate of 20 per minute. Fang marks were present over the dorsal aspect of the base of the left thumb. Systemic examination was unremarkable. Dermatological examination showed multiple well-defined erosions of varying sizes with a clear erythematous base over the medial aspect of the right leg, medial aspect of the right forearm, right arm, left arm, left gluteal region, and the largest one measuring 30 cm by 10 cm, extending from 2 cm below the right knee joint up to 1 cm above the right ankle. A single, well-defined, bulla of size 3 cm present over the lateral aspect of upper one-third of left arm was filled with serosanguineous fluid (Fig. 1). Investigations revealed: Hemoglobin 8.4 g/dL, total leukocyte count—8.3×10^3/mm^3 with differential count of 74% neutrophils, 17% lymphocytes, 1% eosinophils, 8% monocytes, platelet count 105×10^3/mm^3, 20-minute whole blood clotting test (20WBCT)—more than 20 minutes, prothrombin time—16 (test) and 11.5 (control) with international normalized ratio of 1.53, activated partial thromboplastin time—38 (test) and 25 (control), blood urea nitrogen—16 mg/dL, creatinine—0.6 mg/dL, sodium—139 mEq/L, potassium—3.6 mEq/L, chloride—102 mEq/L, calcium—9.4 mg/dL, uric acid—2.42 mg/dL, protein—6.2 g/dL, albumin—3.45 g/dL, bilirubin—0.7 mg/dL, aspartate aminotransferase—38 U/L, alanine aminotransferase—22 IU/L, random blood sugar—125 mg/dL, creatine phosphokinase—849 U/L, and lactate dehydrogenase—798 IU/L. Urine examination showed albumin 3+, sugar nil, pus cells 10–15 per high power field, numerous red blood cells, sterile urine culture/blood culture, and procalcitonin was 0.05 ng/mL. Viral serology for human immunodeficiency virus, hepatitis C, and hepatitis B were negative. Electrocardiogram and two-dimensional (2D) echocardiography were normal. A noncontrast computed tomography (CT) scan of the head showed small vessel ischemic changes. The patient was diagnosed with snake envenomation, rhabdomyolysis, and skin lesions due to a viper bite. She was treated with polyvalent ASV injection manufactured by the VINS Bioproducts Limited (Telangana, India), which neutralizes the venom of the four most common venomous species in India. It was administered as an IV infusion over 3 hours after reconstituting 10 vials of lyophilized ASV in 100 mL of 0.9% isotonic saline. Adverse reaction occurred in the form of anaphylactic shock when her blood pressure dropped to 54/34 mm Hg and oxygen saturation dropped to 70% in room air. Anaphylaxis was managed as per institution protocol and ASV was restarted after 10-minute intervals. Thereafter, her blood pressure rose to 90/66 mm Hg on injection noradrenaline infusion and ASV was continued and completed over 3 hours. The coagulation abnormality was corrected as observed by a repeat 20WBCT done at 6 hours. A total of 30 vials of lyophilized ASV were used. Her sensorium improved over the next 24 hours and noradrenaline was tapered off. She underwent repeated wound debridement followed by negative pressure wound therapy. The wound healing was slow with underlying devitalized tissue requiring intensive wound care. Repeated wound swab cultures were

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Fig. 1: Multiple well-defined erosions of varying sizes with clear erythematous base over limbs and trunk; Also showing a solitary well-defined bulla with serosanguineous fluid (extreme right lower row)

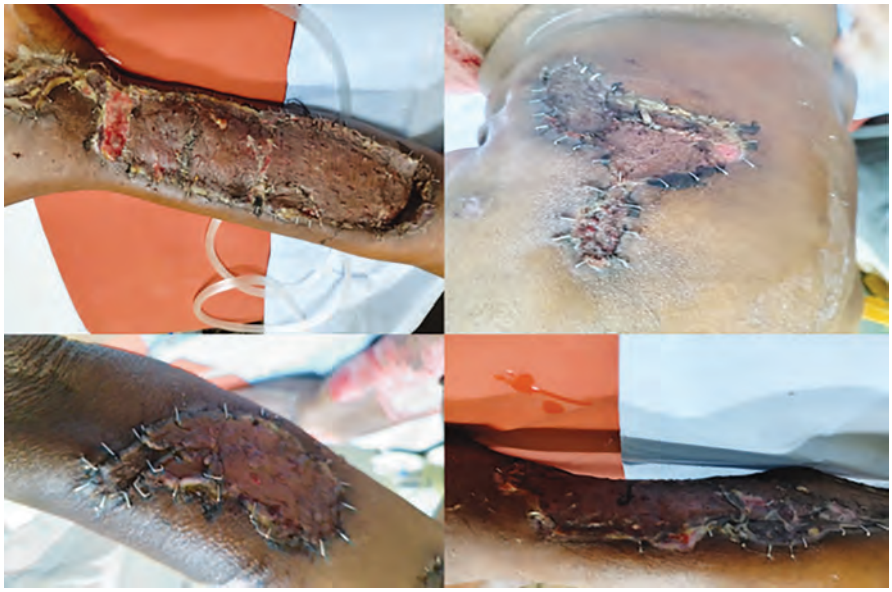

Fig. 2: After split skin grafting; The graft was taken from both thigh and upper arm

sterile. Split skin grafting was done once these wounds became healthy after harvesting grafts from both thigh and upper arm. The graft uptake was good, and the patient was discharged after 8 weeks of hospitalization (Fig. 2).

Discussion

It is well-known that local tissue damage caused by snake venom, either cytotoxic or necrotic, can continue even after the systemic crisis has expired. Tissue necrosis with or without local infection often needs debridement, wound lavage, amputation, and skin graft.[2] In a study from South India, there was only 0.1% (n = 10) of local wounds that required surgical intervention.[3,4] As a late manifestation, due to systemic envenomation, there may be skin blisters with infections, loss of sensation, and lymphangitis. In this patient too, the patient developed new skin erosions with an erythematous base progressively after a few hours of systemic envenomation, but it was disseminated and not localized. These inflammatory effects on the skin are due to the widespread toxic components of the venom. Improperly treated snakebite wounds may also be complicated with chronic ulcerations, osteomyelitis, joint contractures, and osteomyelitis. Surgical management will be needed when there is severe envenomation resulting in extensive tissue damages, particularly if it remains untreated in the absence of ASV. Like in this case, surgical intervention is required only when the patient has been stabilized and has a normal coagulation profile. The extent of tissue damage may be more than what it appears. In the index case too, it took multiple rounds of wound debridement to remove necrotic tissue and make the wound healthy. The localized swelling may also give a false impression of compartment syndrome, and fasciotomy in these cases does not reduce envenomation.[5,6]

Early ASV protocol curbs the local tissue damage effects of snake venom. Excisional treatment was used in the management of a few snakebite wounds on the assumption that most of the snake venom will remain in the area of the bite, and the removal of these tissues will reduce both local and systemic toxicity.[7] The rapid development of extensive tissue damage in this case and the limited efficacy of ASV on the spread of these ulcerations might be due to its late administration and widespread hydrolyzing enzymes such as metalloprotein phospholipase A2 and hyaluronidase in venom. The future management of these extensive ulcerations may be the development of drugs that can inhibit these hydrolyzing enzymes.

Conclusion

Disseminated skin lesions with extensive ulcerations may be late manifestations of snake envenomation if ASV administration is delayed. Timely ASV administration may prevent widespread skin damage and its associated complications. The role of hydrolyzing enzymes inhibitor needs to be investigated in these cases. This case also stresses the need for proper wound management after the control of systemic envenomation to limit complications.

Patient Consent

Informed written consent from the patient was taken.

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CASE REPORT

Neuroparacoccidioidomycosis

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Abstract

Paracoccidioidomycosis (PCM) is caused by a dimorphic fungus Paracoccidioides Brasiliensis and is endemic to subtropical areas of Central and South America. CNS involvement of PCM is extremely variable. NeuroPCM is found in 9.65% to 27.18% of PCM cases .Most neuro PCM patients presents with simultaneous involvement of other organ but isolated or initial CNS involvement may be a feature in 21%. Here we report a case of CNS PCM and this appears to be first reported case of PCM and CNS PCM in India.

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Case Description

A 14-year-old boy resident of Maharashtra presented to the emergency department at a tertiary care hospital, Ruby Hall Clinic, located in Pune city of Maharashtra, with a history of 7 days of fever. The patient's mother reported two episodes of generalized tonic-clonic seizures that had occurred 3 days earlier, followed by drowsiness over a period of time. On examination, he was afebrile, hemodynamics stable, drowsy but conscious, obeying orders with a Glasgow Coma Scale 12/15. He had neck rigidity but no focal signs.

On laboratory evaluation, hemogram of hemoglobin: 14.1 gm%, white blood cell (WBC): 7000 mm3, platelets: 3.6 lakhs. Cerebrospinal fluid (CSF) analysis showed WBC: 3200, neutrophils 80%, proteins 66 gm%, and sugar 90 mg%. His serum electrolytes, renal and hepatic functions, chest X-ray, and electrocardiogram were normal. Human immunodeficiency virus (HIV) and hepatitis B surface antigen were negative.

Computed tomography (CT) of the brain done at an outside hospital showed a left frontal mass lesion with perilesional edema.

Magnetic resonance imaging (MRI) done in our hospital showed increased meningeal enhancement consistent with meningitis and an area of abnormal signal intensity with evidence of patchy rim enhancement in the left frontal region (Fig. 1). Imaging differential to be considered include hemorrhagic meningoencephalitis or hemorrhagic demyelination, but it was felt unlikely to be neoplasm.

However, clinically, the opinion was that he required decompression given the midline shift and the possibility of abscess.

The patient was started on injections—vancomycin, ceftriaxone, mannitol, steroids, and antiepileptics. However, the same night he became drowsier and more convulsed in ICU and became unconscious. At that time, he was intubated and ventilated, and decompression craniotomy was done as a life-saving procedure, and the sample was sent for examination. Unusual thick yellow exudates were noted in the brain. The patient deteriorated rapidly postsurgery, and he succumbed to his disease, and the diagnosis was given as? Brain abscess? Fungal abscess (Fig. 2).

Biopsy specimen send for examination:

- Gram stain: Few pus cells. No organisms were seen.
- Acid-fast bacteria (AFB) stain (zinc stain): Negative for AFB.
- Fungal stain [potassium hydroxide (KOH)]: Fungal element detected.
- Direct microscopy: KOH mount (10% KOH) multiple budding yeasts (blastoconidia 2.30 µ in diameter) were seen, which was considered diagnostic for paracoccidioidomycosis (PCM). The typical pathogenic feature is thick-walled spherical yeast cells, and with Gomori's methenamine silver stain showed slender hyphae. With characteristic large thick-walled spherical yeast (2–30 µ size) and those hyphae, the histological opinion was PCM.

Discussion

Fungal infections of the central nervous system (FI-CNS) have increased in the last 2 decades. Invasion of CNS depends on the immune status of the host and the virulence of the fungal strain.

FI-CNS can have various presentations, such as meningitis, encephalitis, hydrocephalus, mass lesions, abscesses, and stroke syndromes.

The neuroinfectious fungi are yeasts, molds, mucormyecetes, dimorphic fungi, and dematiaceous fungi. A common route of transmission is inhalation of spores or inoculation from trauma or neurosurgery. There are limited drugs available in our armamentarium as they need the property of CNS penetration. It is estimated that 300 species show virulence to humans, and only 10–15% could influence CNS.

The FIs in CNS are common in patients of HIV, transplant recipients, long-term steroids, and renal failure patients, but few fungi, such as *Cryptococcus*, *Coccidiodes*, and *Histoplasma*, can cause infections in immunocompetent patients.

The systemic fungus illness[1] known as PCM, which is native to South and Central America, is present in Brazil. In some areas, it is the most prevalent systemic fungal infection. PCM *brasiliensis* and *P. Lutzi*[2] are two varieties of thermal dimorphic fungi that are responsible for PCM. These fungi develop as mycelium in surroundings with temperatures between 18 and 23°C, but when they are present in human tissue or are grown at a temperature of 37°C, they change into yeast.

The predominant source of infection is the lungs, where mycelium or conidia, the infectious forms, are often inhaled.[3] The fungus changes into yeast cells inside alveolar macrophages after being breathed. This change sets off a generalized inflammatory response, which at this stage typically controls the disease. As a result, the majority of immunocompetent patients experience an asymptomatic infection that goes away on its own.

However, the fungus can spread *via* the lymphatic and venous systems in some circumstances, typically after a period of

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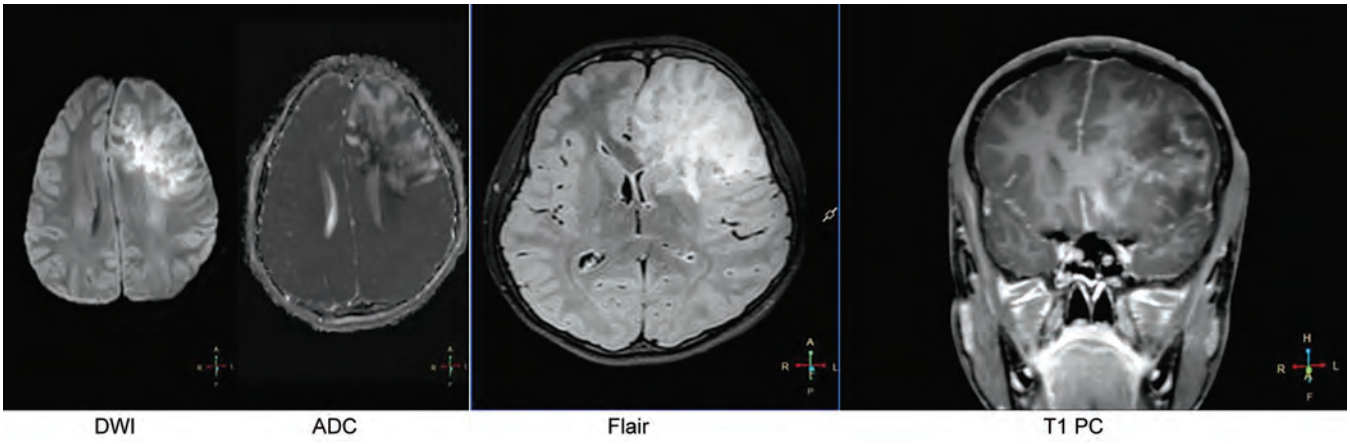

Fig. 1: MRI Brain ADC map showing restriction

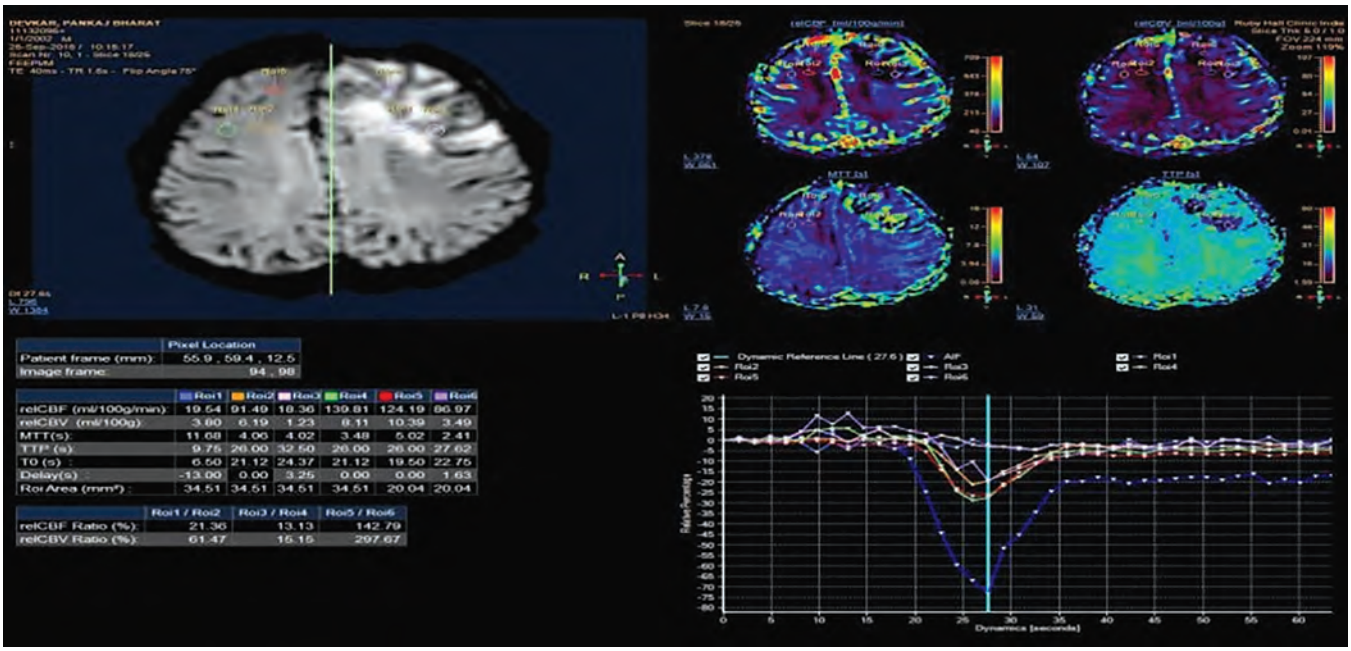

Fig. 2: PERFUSION SCAN – showing slightly reduced rCBV

weeks to decades, causing granulomatous illness in a variety of tissues.

Juvenile PCM

Acute or subacute PCM, which primarily affects children and adolescents, manifests in around 15% of clinical cases of PCM. Following a recent exposure, this disease's course is quick. It predominantly affects the reticuloendothelial system, which can result in more serious symptoms, including hepatosplenomegaly (enlarged liver and spleen) and persistent lymphadenopathy (enlarged lymph nodes). Other typical signs include fever, malaise, and weight loss.

The condition manifests as swelling of the lymph nodes, which causes suppuration (the production of pus), as well as the formation of sinus tracts. Additionally, there are numerous skin lesions and mucous membrane involvement. When PCM takes this form, and respiratory symptoms are unusual. Additionally, this specific disease presentation frequently appears in HIV-positive patients.

Adult PCM

Only 80–90% of PCM infections are the adult (chronic) kind, which is an illness that recurs years after the original exposure to the fungus. Although our patient did not have such a history, people frequently report having visited South and Central America in cases that occur elsewhere.

The disease can manifest as unifocal, affecting just one organ (most frequently the lungs), or multifocal, affecting several organs, including the lungs, skin, and lymph nodes. Adult males are more likely to develop this type of disease.

Primary lung infection is a common finding, and it is characterized by symptoms like weight loss, dyspnea, malaise, fever, and productive or nonproductive coughing. In 5% of patients, pulmonary hypertension and cor pulmonale can be caused by persistent pulmonary problems like lung fibrosis, bullae, and emphysematous alterations.[4]

In 50% of patients with acute pulmonary infection, mucous membrane involvement might appear as laryngeal and pharyngeal lesions, leading to symptoms like dysphagia, dysphonia, stridor, and perioral granulomatous. Aguiar-Pupo stomatitis, nasal and pharyngeal ulcers, and enlargement of the mandibular or cervical lymph nodes can all be symptoms of oral diseases.

In 25% of patients, cutaneous lesions brought on by hematologic spread from the lungs are seen. There is often lymphadenopathy, most frequently in the cervical area. Other sites of involvement can be long bones (including the ribs, humeri, and clavicles), mesenteric lymph nodes, which can result in bowel obstruction, and the adrenal glands, which have a 48% incidence rate and may cause adrenal insufficiency in 15% of patients.

The CNS might be involved and result in symptoms like headaches. While solitary meningitis or spinal cord lesions are uncommon occurrences, meningoencephalitis happens in 10–25% of individuals as a component of a disseminated illness.

Sex-related Demographics[5]

The juvenile acute/subacute type of PCM affects both sexes equally. However, men are more frequently affected than women when it comes to the chronic adult version of the condition, with a reported ratio ranging from 6:1 to 15:1.

The fungus that causes the sickness, *Paracoccidioides*, has receptors that selectively bind estrogen. The change of the mycelium into the yeast phase, which is required for the invasion of tissues, is prevented by estrogen binding. It's important to note that patients under 14 and over 45 don't exhibit any gender differences. However, there is a noticeable male preponderance in all cases in the age period between 14 and 45 due to a substantial sex ratio of about 33:1.

CNS Involvement [Neuro-PCM (NPCM)]

When the CNS is affected, the majority of patients have a broadly distributed illness that is noticeable. However, the CNS may be the only afflicted site or the first site to be impacted in 21–27% of instances.

In various datasets, the prevalence of CNS involvement in PCM ranges from 9.65 to 25.45%. The majority of young guys (with a mean age of 44 years) and rural laborers are often thought to be affected by PCM.

The following categories might be used to group PCM's CNS manifestations:

- A modest to moderate increase in the number of cells in the cerebrospinal fluid characterizes this kind of meningitis, which usually affects the base of the skull. Cell counts can occasionally surpass 700, with lymphocytes being the most often seen cell type.
- Granulomatous form: This is the most common kind of CNS involvement and is distinguished by significant ring enhancements, typically in one hemisphere of the brain (over 50% of cases). It is less frequently noticed in the posterior fossa (cerebellum and brain stem) and uncommon (4% of instances) in the spinal cord. These granulomas can occur alone (65% of the time) or in clusters (35% of the time).
- Meningitis linked with granuloma: This condition combines meningitis with the presence of granulomas in the CNS. The most frequent signs of CNS involvement are seizures, which occur in 33% of cases, hemiparesis (side-to-side weakness), cerebellar signs (related to coordination and balance), headaches, which occur in 25% of cases, and hydrocephalus (fluid buildup in the brain), which occurs in 21% of cases. Other less frequent signs and symptoms include confusion (13% of cases), paresthesias (13% of cases), and bulbar signals (associated with the brainstem) (8% of cases).

Initially, the illness may be misdiagnosed as a space-occupying lesion, such as a malignant glioma or a metastatic tumor. It may also be mistaken for bacterial, parasitic, or tuberculous abscesses.

Neurococcidioidomycosis (NPCM) in the spinal cord is rare. The first documented case of his NPCM in the spinal cord was reported by Canelas et al. report. Since then, 13 cases have been announced, all documented in Brazil. Among these cases, the thoracic spinal cord level was most commonly involved (58% of cases). On CT or MRI images, granulomatous lesions usually appear as large annular lesions with nodular enhancement and secondary edema.

Several factors should be considered when diagnosing systemic PCM disease. This includes visualizing *Paracoccidioides brasiliensis (P. brasiliensis)* by light microscopy, isolating the fungus by culture from sputum or biopsy specimens, and performing immunological tests on serum B. Double immunodiffusion or enzyme-linked immunosorbent assay (ELISA) using specific antigens. These diagnostic methods are useful in diagnosing systemic PCM disease.

Microbiology

Around >90% of patients have big, many budding yeasts (blastoconidia)[6,7] present when sputum or lesional material is examined using a KOH preparation. Large, spherical yeast cells with thick walls and many peripheral buds around the center cell, like a pilot's wheel or mariner's wheel,[6] are the pathognomonic feature. This distinctive shape aids in distinguishing *Paracoccidioides* from yeasts such as *Blastomyces dermatitidis* and other kinds.

A granulomatous response with epithelioid and large cells, as well as a significant inflammatory infiltration, are shown by a histologic investigation. Within gigantic cells or widely dispersed throughout the inflammatory infiltrate, the yeast cells with the distinctive pilot's wheel structure may be discovered. Caseous necrosis may be seen in lymph nodes. Diffuse tissue reactions are typical in juvenile patients. Using Gomori's methamine silver stain, it is possible to identify thin hyphae together with the distinctively big, thick-walled, spherical yeast cells as a diagnostic discovery (Figs 3 to 5).

Even in situations of meningitis, CSF analysis has little usefulness as a diagnostic tool, and mycological tests on CSF typically provide negative results.[8] The identification of the 43 kDa glycoprotein known as gp43, which is present in *P. brasiliensis*, is crucial

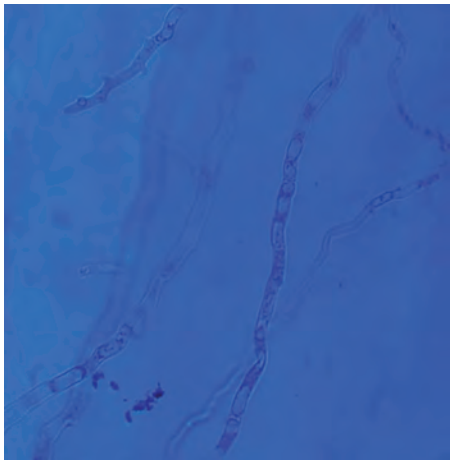

Fig. 3: Lactophenol cotton blue mount

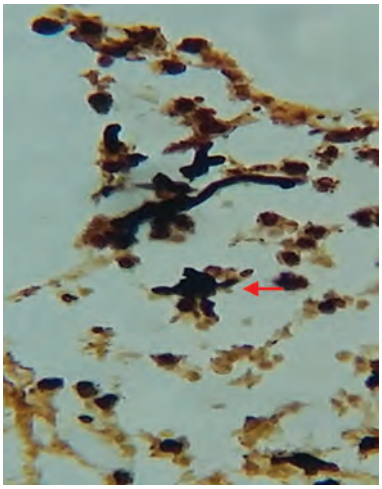

Fig. 4: Grocott`s silver methenamine stain (multiple budding yeast cells Mariner's wheel form)

Fig. 5: Potassium hydroxide (KOH) wet mount

for the diagnosis. It is the primary diagnostic antigen for PCM and is released during the infective yeast phase. In 89% of CSF samples from these individuals, the ELISA anti-gp43 test is positive, with high sensitivity (89%) and specificity (100%). Additionally, gp43 antigen might be seen in PCM patients' urine.

Mortality

The severity of the infection, the organs affected, the patient's age and sex, the existence of other underlying medical disorders, and the patient's immunological status all have an impact on the fatality rate in PCM. For instance, patients with HIV often experience greater death rates than patients without HIV.

In Brazil, where PCM is the ninth most common cause of death, the research found a mean mortality rate of 1.45 fatalities/1 million people. On a national level, the mortality rate related to particular geographic regions was estimated to be 3.73 fatalities/10000 km^2. In general, males had a greater death rate than females.

The reported death rate for children with acute PCM ranges from 7 to 10%.[9]

Treatment

The main treatment for PCM is systemic antifungal therapy. Triazoles like itraconazole, voriconazole, and posaconazole are effective antifungal medications for treating this illness. It is also possible to use other drugs like ketoconazole and sulfonamides [such as trimethoprim (TMP)/sulfamethoxazole (SMX), which includes sulfadiazine]. Sulfonamides, ketoconazole, or itraconazole are possible therapy choices for non-CNS PCM.[10,11]

When PCM affects the CNS, oral TMP-SMX in conjunction with fluconazole or voriconazole is the best course of therapy. Typically, therapy lasts between 12 and 84 months. Systemic diseases without CNS involvement are often the only conditions in which itraconazole or ketoconazole are used because of their restricted penetration into the CNS. Amphotericin may be used in extreme circumstances.

When a granuloma creates compression-related symptoms and indications that offer a life-threatening risk owing to mass effect, neurosurgical treatments may be required in some circumstances.

Conclusion

Our patient presented with a hemorrhagic mass lesion with subfalcine herniation. The diagnosis was made from a biopsy taken after decompression. Craniotomy revealed the diagnosis of PCM. The GP-43 antigen and ELISA anti-GP43 antibody test could not be done. As of today, there is no case detected of PCM, turn unclear. It should be considered as a differential diagnosis of a ring-enhancing lesion in brain parenchyma.

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CASE REPORT

Adult Partial Anomalous Pulmonary Venous Connection: Case Reports (Including a Case of Scimitar Syndrome)

Rekha Gupta[1], Pranav K Udupi[2*], Ankita Sharma[3], Lipi Uppal[4]

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Abstract

Partial anomalous pulmonary venous connection (PAPVC) is a congenital heart defect in which one or more pulmonary veins drain abnormally into the systemic venous circulation, leading to the development of pulmonary arterial hypertension. It can be supracardiac type, draining into the superior vena cava or right atrium (also called cardiac type) and infracardiac type with drainage into the inferior vena cava (IVC). We present two cases—supracardiac and infracardiac types of PAPVC in this case report.

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Introduction

Anomalous partial pulmonary venous communication is abnormal communication of the pulmonary veins with the systemic circulation.[1,2] Supracardiac partial anomalous pulmonary venous connection (PAPVC) is the most common type, in which the pulmonary veins drain into the superior vena cava, right atrium, or coronary sinus. It can be an infantile form or an adult form. While in the infracardiac type of PAPVC, the anomalous vein is seen draining into the inferior vena cava (IVC). Adults with PAPVC are typically asymptomatic but may present with symptoms of cyanosis, shortness of breath, or heart failure.[3] Echocardiography can visualize the pulmonary veins and determine their abnormal drainage pattern.[4] Cardiac catheterization may be used to confirm the diagnosis and to assess the severity of the defect. However, cross-sectional imaging can also be used to identify the anomalous connection in doubtful cases. Cross-sectional imaging can also identify the complications of PAPVC, like pulmonary hypertension and is useful for preoperative planning.[5,6] Treatment is surgical redirection of the pulmonary veins to the left atrium.

Case Report 1: Supracardiac PAPVC

A 36-year-old female presented with complaints of palpitations for 2 months. No past history of pulmonary tuberculosis (TB), community-acquired pneumonia, or orthopnea. The patient had no significant medical or family history. On examination had mild tachycardia and was maintaining normal oxygen saturation levels. Chest auscultation was normal, and cardiovascular examination revealed normal S1 and S2.

Electrocardiography (ECG) was normal, and routine biochemistry parameters were noncontributory. Chest X-ray was grossly normal. Two-dimensional (2D) echocardiography showed situs solitus, dextroposition with normal left ventricular (LV) systolic function, and no evidence of aortic regurgitation or mitral regurgitation. The right atrium and right ventricle were dilated; however, they showed normal function. Mild tricuspid regurgitation was seen. Ostium secundum atrial septal defect (ASD) was seen (12 and 4 mm: two jets were seen). Further, cross-sectional imaging was requested to identify the location of communication.

Multiphasic computed tomography angiography (CTA) chest with prospective ECG gating was done. It showed situs solitus, normal ventricular loop, and normal atrioventricular position. Anomalous drainage of the right superior pulmonary vein into the superior vena cava just proximal to the right atrial opening was seen. In addition, communication was seen between the right atrium and left atrium at the level of opening of the superior vena cava, indicating sinus venous type of ASD. Another communication was noted between the right atrium and left atrium in the expected location of septum secundum, suggesting ostium secundum ASD. The main pulmonary artery was dilated, measuring up to 31 mm with mosaic attenuation in the bilateral lung fields, suggesting the development of early features of pulmonary arterial hypertension in the patient (Figs 1 and 2).

Case Report 2: Scimitar Syndrome with Infracardiac PAPVC

A 20-year-old male presented with complaints of shortness of breath, cough with expectoration and fever for 3–4 days. He reported a history of similar episodes since childhood. No history of pulmonary TB, community-acquired pneumonia, posterior nasal drip or orthopnea. The patient was a nonalcoholic, nonsmoker, had no significant medical or family history, and had no complaints suggestive of infertility. On examination, he had mild tachycardia. On chest auscultation, bilateral basal crepts were heard, and cardiovascular examination revealed normal S1 and S2.

Chest X-ray was suggestive of dextrocardia and demonstrated an anomalous vein paralleling the right heart border, extending to the diaphragmatic surface in the right lung. ECG was normal, routine biochemistry and arterial blood gas was noncontributory. The hemogram showed evidence of mild leukocytosis—mainly raised neutrophil sputum examination for acid-fast bacilli was also negative. Serum immunoglobulin G levels were found to be 1285 mg/dL (normal: 800–1800 mg/dL), and serum IgA were found to be 185.5 mg/dL (normal: 110–410 mg/dL). X-ray paranasal sinuses was normal. 2D echocardiography showed situs solitus, dextroposition with normal LV systolic function, and no evidence of aortic regurgitation, mitral regurgitation or tricuspid regurgitation.

Multiphasic computed tomography angiography (CTA) chest revealed volume loss of the right lung field with ipsilateral mediastinal shift and cardiac dextroposition, raised right dome of the diaphragm, and hypoplastic right pulmonary artery (RPA).

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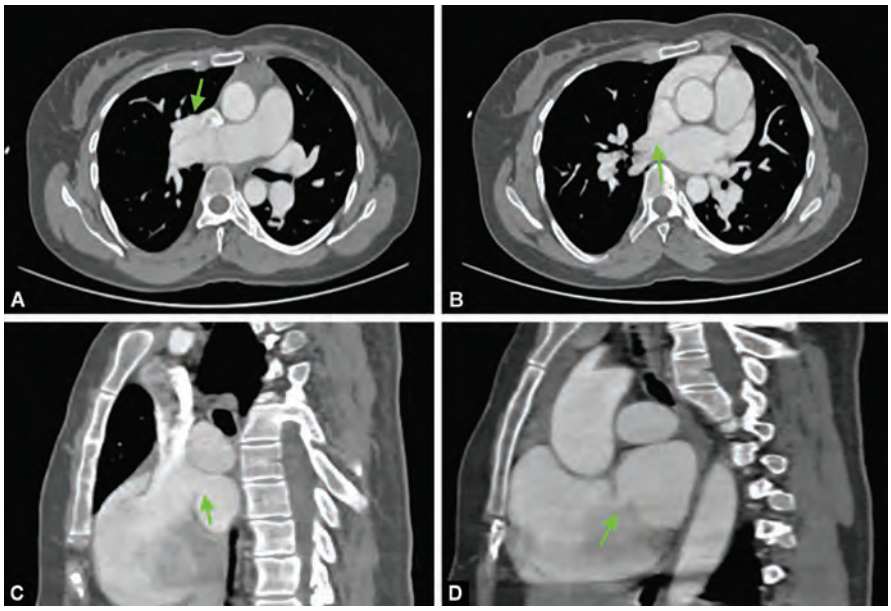
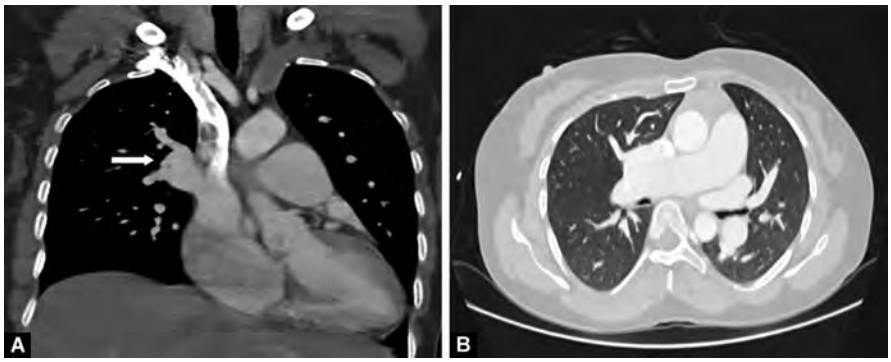
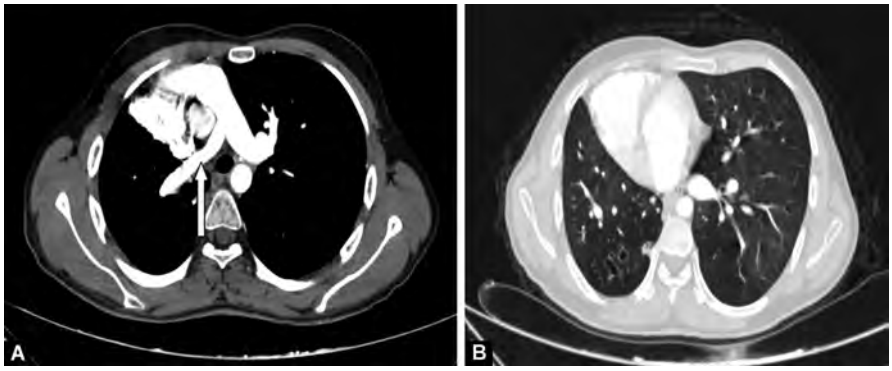


Figs 1A to D: (A) Axial section of CT cardio angiography showing the anomalous drainage of the right upper lobe pulmonary vein into the superior vena cava; also seen is the enlarged main pulmonary artery, which measured 31 mm in diameter; (B and C) Axial and sagittal section showing connection with the right atrium and left atrium immediately below the anomalous connection; (D) Saggital section showing the connection between the right atrium and left atrium through the septum secundum suggesting ostium secondum ASD



Figs 2A and B: (A) Coronal section of CT cardio angiography of the same patient showing the opening of the right upper lobe pulmonary vein into the superior vena cava; (B) Axial section of the same scan in pulmonary window depicting the subtle mosaic attenuation in bilateral lungs



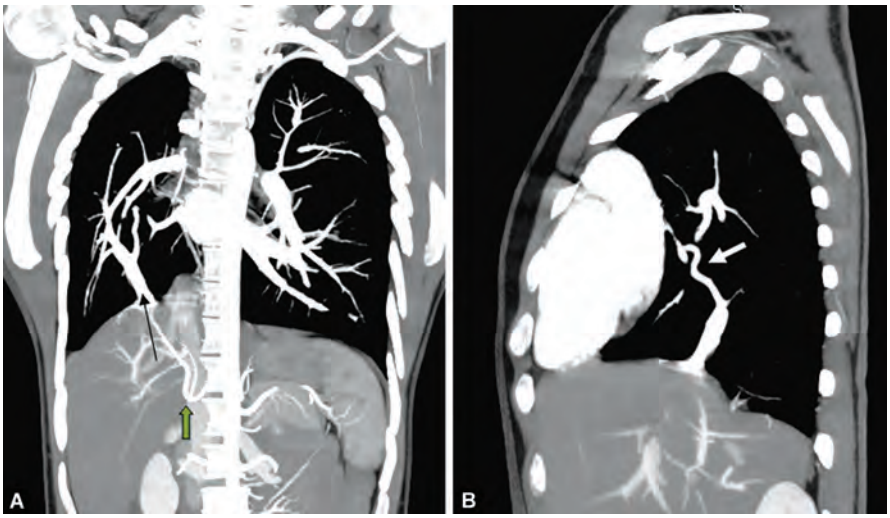
Figs 3A and B: (A) Axial section of CT angiocardiography of the patient in soft tissue window showing the dextrocardia, hypoplastic right pulmonary artery (white arrow); (B) Axial section in pulmonary window demonstrating the dextrocardia with ipsilateral mediastinal shift and hypoplastic right lung parenchyma; few areas of bronchiecetetic changes are also seen

Anomalous drainage of the right pulmonary vein into the suprahepatic infradiaphragmatic IVC was noted. The main pulmonary artery was normal in calibre (measures up to 18 mm) in this patient. In addition, a meandering vein was seen connecting this anomalous vein with a small caliber right pulmonary vein draining into the left atrium. Systemic supply to the right lower lobe was noted from a hypertrophied right phrenic artery arising from the abdominal aorta at the level of the body of the D11 vertebra. An aberrant supply from the right phrenic artery was noted to a portion of segment VII of the right lobe of the liver, which revealed early opacification of the branch of the right portal vein during late arterial phase suggests arterioportal shunt with perfusion abnormality. Tracheobronchial abnormality was noted in the form of division of the right main bronchus into four divisions with no perceptible fissure. Few fibrotic and bronchiectatic changes were noted in the right paracardiac region additional 13th pair of ribs was also noted. Possibilities such as TB, allergic bronchopulmonary aspergillosis or Kartagener syndrome were ruled out (Figs 3 and 4).

Discussion

Partial anomalous pulmonary venous connection (PAPVC) is a rare cardiopulmonary congenital anomaly and is characterized by an anomalous pulmonary venous return, where pulmonary venous channels are seen draining into the systemic vein rather than the left atrium.[7,8] The incidence of complex pulmonary malformation is approximately one to three in 100,000 live births with a 2:1 female preponderance.[1,9] Based on the age of presentation and associated congenital cardiac malformations, PAPVC has been classified into two types: infantile and adult. The infantile form is more symptomatic and commonly associated with congenital cardiac defects, whereas the adult form is mostly asymptomatic and may only present with recurrent chest infections and has a relatively good prognosis.

This anomaly can be asymptomatic clinically and may be incidentally detected on imaging. There is more common involvement of the right lung with a characteristic finding of the anomalous pulmonary vein draining into the systemic circulation, usually the infradiaphragmatic IVC, which is called Scimitar syndrome.[4] However, other rarer drainage sites are the superior vena cava, right atrium, hepatic vein, portal vein, and azygous vein.[4,9] On a chest radiograph, a demonstration of a curvilinear opacity in the right lung that starts from the hilum and widens inferiorly toward the diaphragm, paralleling the cardiac border resembling a scimitar (i.e., Turkish sword) is a radiological clue to the presence



Figs 4A and B: (A) Coronal MIP image of the arterial phase of the CT cardio angiography of the same patient showing a curvilinear anomalous vein (black arrow) draining into the infradiaphragmatic suprahepatic IVC giving the appearance of Scimitar (a Turkish sword); also seen in the image is the aberrant right phrenic artery supplying segment VII of the liver (green arrow) and showing early opacification suggesting arterioportal shunt; (B) Saggital MIP reconstruction of the arterial phase of CTA showing a meandering vein was seen connecting the anomalous vein with small caliber right pulmonary vein draining into the left atrium

of an abnormal pulmonary venous channel.[2,10] Similar curvilinear opacities can be seen in upper lung zones in the supracardiac type.[11,3]

Other radiographic signs include hypoplastic right lung and decreased right pulmonary vascularity. The scimitar sign can also be seen in other benign vascular anomalies, such as meandering pulmonary veins and an anomalous single unilateral pulmonary vein.[12] Anomalous courses of one of the pulmonary veins draining the left atrium are called meandering pulmonary veins, whereas when a single pulmonary trunk drains, all the bronchopulmonary segments to the left atrium are referred to as anomalous single unilateral pulmonary veins.[12]

It is important to differentiate these benign entities clinically from scimitar syndrome in order to avoid unnecessary imaging and intervention. Other differentials are pulmonary sequestration, middle lobe collapse, pulmonary venous varix, and intrapulmonary collaterals due to obstruction of the main pulmonary vein; hence, the presence of scimitar signs is not diagnostic and secondary signs such as hypoplasia of lung and cardiac dextroposition should be looked for.[9] Further evaluation can be carried out in the form of a CT chest, which is used to demonstrate the anatomy of an anomalous pulmonary vein, its site of drainage, pulmonary sequestration, anomalous arterial supply from the aorta to the lung, and features of pulmonary hypertension aortopulmonary collateral.[5,9]

Echocardiography can also aid in delineating the direction of flow and anatomy and also look for cardiac defects.[13] Magnetic resonance (MR) imaging is also an excellent nonionizing and noninvasive diagnostic tool for evaluating pulmonary veins anatomy and assessment of ventricular volume and function.[13] Although cardiac angiography and catheterization remain the confirmatory gold standard, but have a limited role in cases of pulmonary atresia or high-grade stenosis where noninvasive CT and MR angiocardiography have been proven to be better and safe modalities for preoperative evaluation.[13] The aim of preoperative imaging includes (1) to determine total or partial anomalous pulmonary venous return; (2) to look for pulmonary hypertension; (3) to determine the fraction of left-to-right shunt; (4) associated congenital heart defects; (5) to look for aortopulmonary collaterals; and (6) anomalous arterial supply to hypoplastic lung. Treatment depends upon the age and symptoms of the patient.

Infants and patients of pulmonary arterial hypertension are seen to have guarded prognosis and higher mortality and complication rates.[14] However, if the defect is treated in time before the development of pulmonary hypertension, the prognosis is greatly improved.[15]

Detailed assessment of the morphology of the defect, along with the quantification of shunt and right ventricular functional assessment, is essential for management decision-making. Right ventricular enlargement with a pulmonary flow/systemic flow (Qp/Qs) ratio of >1.5 is considered to be significant.[16] Surgical repair aims to reestablish the flow from the pulmonary veins into the left atrium. Surgical repair is indicated only if the shunt fraction (Qp:Qs) is >2.[8] Direct reimplantation of the anomalous vein and intracardiac baffle repair are two safe and efficient surgical options.[17]

Post-operative complications of partial anomalous pulmonary venous return include altered venous flow dynamics and rare occurrence of superior vena cava syndrome in the form of new onset varices post surgery.[3]

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Cutis Verticis Gyrata—Unfolding the Folds

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A 45-year-old gentleman presented with severe headaches and visual disturbances. On examination, he had spade-like hands, large feet, prognathism, and prominent supraciliary ridges suggestive of acromegaly. His scalp showed prominent convoluted skin folds with deep furrows that did not reduce on traction resembling cerebral gyrations. This cutaneous anomaly is called cutis verticis gyrata (CVG) (Fig. 1). This observation may be seen in conditions primarily affecting the skin either due to inflammation like psoriasis, eczema, localized infiltrative or neoplastic dermatoses like melanocytic nevi, hamartomas, or neurofibromas.[1] CVG may also be seen as part of systemic disorders including acromegaly[2] (as in our patient), myxedema, and amyloidosis. Syndromic association of CVG includes anecdotal reports in Noonan and Turner syndromes. Pachydermoperiostitis is an uncommon familial condition in which CVG may be observed, and the gyrations are usually horizontal.[3] In addition to the above, this condition may be seen as primary CVG without any association with other diseases.[4]

Further evaluation of our patient showed elevated IGF1 besides secondary hypothyroidism, hypocortisolism, and hypogonadism. Perimetry revealed bitemporal hemianopia, and magnetic resonance imaging of the head revealed a pituitary macroadenoma with compression of the optic chiasm. After appropriate hormonal replacement with thyroxine, hydrocortisone, and testosterone, he underwent transnasal transsphenoidal adenomectomy. His headache disappeared after surgery, and he was clinically feeling better. However, CVG did not show any significant change postoperatively. He was advised local scalp hygiene to avoid secondary infections as he was currently unwilling for any surgical intervention.

Fig. 1: Cutis verticis gyrata in a case of acromegaly

Learning Points

- Cutis verticis gyrata is a benign process and is quite distinctive.
- Clinically, it provides a visual clue to a possible underlying pathological condition.

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Cochlear Implants: An Attempt to Restore Hearing

Deepa A Valame[1], Geeta Gore[2], Jayant Pai-Dhungat[3]

Achievement in technology—improvised Bionic ear. Australia, 1982

Budapest Congress, 1972. Hungary, 1972

Indian National Society for the Deaf. Cinderella, issued in 1950 to appeal for help, 1950

Cochlear implants (CIs) are prostheses that are surgically placed in the cochlea and stimulate the spiral ganglion of the auditory nerve to give the percept of hearing.

The first CI was a single-channel implant carried out by otologist Dr. William House and neurosurgeon Dr. Boyle in California (1961). The first commercial multichannel implantation was done by Dr. Graeme Clark in Australia (1978), under the name "Cochlear/Nucleus." Otologist Dr. Ramalingam in Chennai was the first to do CI in India (1994). Presently, there are seven commercial developers of CIs in India.

A typical CI has external and internal components. The internal components are the electrode array inserted into the scala tympani and the receiver-stimulator. The receiver stimulator receives the electromagnetic signals from the speech processor and transmits it to the electrode array, which then transduces the signals into biphasic electric charges to stimulate the ganglion cells. The internal magnet communicates with the external components of the cochlear implant. The external components are usually worn behind the ear and over the head. They include the speech processor that encodes the sounds in the environment, the coil cable, and the coil with a magnet that sends the coded sound signals across the skull to the internal magnet in the form of radio waves. Currently, wearing options such as only above the head are available. Further, totally implantable cochlear implant (TICI) is under clinical trials and will soon be the future of CI.

The surgical implantation is done using cochleostomy, posterior tympanotomy, or Veria procedure. Once the wound heals, the audiologist conducts "switch-on" usually 2–3 weeks postsurgery. It is here that the world of sound is introduced to the implantee by mapping the processor using speech processing strategies.

Cochlear implantation for severe to profound bilateral congenital hearing loss should be done as early as possible since congenital profound hearing loss is a neurodevelopmental emergency. If left undiagnosed and untreated, it has serious consequences on the development of language and speech. This affects the overall social skills development of the child. The critical age for auditory language development is the first 3 years of life; therefore, cochlear implantation must be done within this period to facilitate normal development. Early implantation, regular mapping of the device according to the schedules of mapping, and intensive aural habilitation for at least 3 years are the prerequisites for auditory language development in children with bilateral severe to profound sensorineural hearing loss. In this journey of the child from silence to hearing, the importance of CI surgeon and the team of audiologists and speech-language therapists, the educator, and most importantly, the parents cannot be overemphasized.

Cochlear implants also work wonders for adults and elderly individuals with bilateral postlingual severe to profound hearing loss where the person loses hearing in adulthood after language is fully developed. This may be caused due to various causes. Cochlear implantation, mapping, and listening training for 6 months can help to restore hearing in these individuals.

The outcomes from CIs depend on a myriad of factors. In congenital hearing loss, the age of identification of hearing loss, age of implantation, access to audiological services, parental motivation, and financial support all affect outcomes. Although CI is not contraindicated in children with multiple disabilities, outcomes may be less than optimal in such cases. The CI offers a chance to develop a sense of hearing and is a boon if done at the right age. It is then that the miracle unfolds, and a child with hearing loss can listen, speak, reason, and live a productive life.

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Its High Time to Correct Vitamin D Levels to the Optimum

Abhijit Trailokya

Head Medical Affairs, Department of Medical Affairs, Indoco Remedies Ltd., Mumbai, Maharashtra, India

Dear Editor,

I recently had the opportunity to read an article titled "A Review on Vitamin D Deficiency and Related Disorders: What is the Right Serum Vitamin D Level?" published in May 2023 issue of *Journal of the Association of Physicians of India*, cited as Bantwal G. A Review on Vitamin D Deficiency and Related Disorders: What is the Right Serum Vitamin D Level? J Assoc Physicians India 2023;71(5):75–79.

I wanted to take a moment to express my appreciation for the informative and well-researched content.

The article not only provided a comprehensive understanding of the importance of vitamin D but also effectively communicated its impact on overall health. The clarity of your writing and the depth of the information made it a valuable read for me.

The global prevalence of vitamin D deficiency is documented in both regions with limited sunlight and those with ample sunlight. Nevertheless, it remains a highly underdiagnosed and undertreated nutritional deficiency on a global scale.

The prevalence of vitamin D deficiency in India varies widely according to different studies, with community-based research reporting rates between 50 and 94% among apparently healthy individuals, while hospital-based studies indicate rates from 37 to 99%. This disparity in findings may be attributed to the absence of universally adopted guidelines for defining deficiency.[1]

Vitamin D deficiency is associated with various infectious diseases including upper respiratory tract infections. Many studies demonstrated the links between vitamin D deficiency and other diseases, such as muscle weakness, chronic diseases such as diabetes, hypertension, metabolic syndrome, cardiovascular disease (CVD) malignancies, autoimmune diseases, and skeletal disorders (hip or vertebral fractures) in later life.[2]

In India, the primary causes of vitamin D deficiency often stem from factors such as a rise in indoor activities, particularly prevalent in urban areas due to modern lifestyles. Shifts in dietary habits also play a role, leading to lower intake of calcium and vitamin D. Additionally, pollution can hinder the synthesis of vitamin D in the skin by reducing exposure to ultraviolet (UV) rays.

The optimal and safe range for serum 25-hydroxyvitamin D [25(OH)D] levels is typically considered to be between 30 and 100 ng/mL. At a level of 30 ng/mL, intestinal calcium absorption peaks, and levels of parathyroid hormone (PTH) continue to decrease until this threshold of 25(OH)D is reached.[1] Setting a goal of 50 ng/mL for serum 25(OH)D levels can indeed offer physiological benefits to patients. This contrasts with the conventional mindset of aiming for 30 ng/mL for vitamin D sufficiency. Utilizing a loading dosage regimen of 60,000 IU can be effective in achieving and maintaining the desired serum levels.[1] Following the Endocrine Society's recommendation, Khawaja et al. administered 50,000 IU of vitamin D bimonthly to sustain serum levels of 25(OH)D above 30 ng/mL.[3]

In a time where health awareness is crucial, the article serves as a valuable resource for readers seeking to understand the significance of vitamin D in maintaining well-being. To address the condition and alleviate its burden, several measures can be implemented:

- Food fortification with vitamin D: Incorporating vitamin D into food products can help increase intake and combat deficiency.
- Educational programs: Creating awareness about vitamin D deficiency through educational initiatives is crucial, as it is often underdiagnosed and undertreated. Both healthcare professionals and the public should be educated about its implications.
- Accessible vitamin D supplements: Ensuring availability of high-quality vitamin D supplements at discounted rates can facilitate supplementation, especially for vulnerable populations.
- Affordable testing facilities: Making testing facilities for vitamin D levels accessible and affordable, particularly for high-risk groups such as pregnant women, children, and the elderly, is essential for early detection and intervention.
- Revision of Recommended Dietary Allowance (RDA): The Indian Council of Medical Research (ICMR) should consider revising the RDA for vitamin D to reflect current knowledge and address deficiency effectively.
- Support for research: Government support for research groups to investigate and monitor the impact of supplementation programs and fortification strategies can provide valuable insights for public health interventions.[1]

To conclude, vitamin D deficiency in India is a prevalent health concern attributed to various factors. Insufficient exposure to sunlight, lifestyle changes, and dietary habits contribute to this issue. Despite abundant sunlight, many people have limited outdoor activities, leading to lower vitamin D synthesis in the skin. Modern lifestyles often result in inadequate dietary sources of vitamin D, further exacerbating the problem. This deficiency is associated with various health issues, including weakened bones, immune system complications, and increased susceptibility to certain diseases.

Addressing this concern requires public health initiatives, increased awareness, and promotion of vitamin D-rich foods or supplements. Regular monitoring and education on the importance of sunlight exposure are essential steps in mitigating vitamin D deficiency in India.

Thank you for your dedication to delivering high-quality content. I look forward to reading more of your insightful pieces in the future.

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Perspective of Indian Medical Students toward the Practice and Teaching of Integrative Medicine

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Complementary and alternative medicine (CAM), which includes methods that are not part of our standard practice, has widespread use in the field of medical care. Illnesses are complex to treat and often require a multipronged holistic approach that incorporates the best from all specialties of medicine. There have been debates in the past for and against the use of integrative medicine practices. We aim to explore the readiness and perception of Indian medical students, who are the future clinicians, toward the practice of integrative medicine and various factors that

can influence their perception of the same. Our study also focuses on learning about significant barriers faced toward practicing and integrating CAM.

Medical students of different study years in various medical colleges were asked to fill out the Integrative Medicine Attitude Questionnaire (IMAQ)[1] via Google Forms. CAM was defined as medical products and practices not included in standard medical care such as Ayurveda, Siddha, Unani, Yoga, and Homeopathy.

A total of 380 (69% response rate) questionnaires were filled, wherein 33.42% were in their first year of medical college, 29.47% were in second year, 19.73% were in third year, 15% were in fourth year, and 2.36% were interns. After running statistical tests such as Mann–Whitney and Kruskal–Wallis, the results corroborated.

Participants scored higher in the relationship subscale, and students whose family member was a physician had a positive inclination toward the practice of integrative medicine. Year-wise perception among participants was not significantly different, which can be explained possibly by a lack of academic exposure to treatment modalities other than conventional medicine. The results obtained in the openness subscale also did not reveal a major difference across demographic variables. Our study also found that medical students who had used CAM in the past and those who are willing to use it in the future are of the view that they would form a better patient–physician relationship as they can address the needs and concerns of the patients in an enhanced way.

With the advent of social media and increased patient awareness, there has been an increased demand for an integrative medical approach to treating disease. In view of this trend, the study conducted by us suggests that even medical students who have had experience using CAM have an insufficient understanding of the use and application of conventional medicine with CAM. Another study highlighted the fact that medical students were of the opinion that current knowledge deficits about CAM use are causing a major hindrance in their ability to better help patients in choosing CAM as their treatment modality.[2,3]

The participants appeared flexible toward inculcating the best of all streams for the welfare of the patients, leading us to believe that introductory courses about integrative medicine might help in bridging the gap between modern medicine and complementary medicine, with around 63.6% participants who were willing to use CAM in the future. Developing countries such as India have evidence-based AYUSH practices that can be used for chronic conditions and reduce the pharmacoeconomic burden on the patient and their family.

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