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ORIGINAL PAPER

Pancreatic Function in Chronic Proton Pump Inhibitor Use: Findings from a Cross-Sectional Study

Leo Francis CHALISSERY[a], Madhavi EERIKE[b], Lisha Francis CHALISSERY[c], V. SAKTHIVADIVEL[d], Sangeetha SAMPATH[e], Gajula SINDHURA[f]

[a]Senior Resident, Department of Pharmacology, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India, PIN-508126

[b]Additional Professor, Department of Pharmacology, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India, PIN-508126

[c]Assistant Professor, Department of Pharmacology, P.K. Das Institute of Medical Sciences, Vaniamkulam, Ottapalam, Palakkad, Kerala, India, PIN-679522

[d]Additional Professor, Department of General Medicine, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India, PIN-508126

[e]Professor, Department of Biochemistry, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India, PIN-508126

[f]Former Junior Resident, Department of General Medicine, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India, PIN-508126; presently Medical Officer, Manage, Rajendra Nagar, Hyderabad, Telangana, India, PIN-500030

ABSTRACT

Background: *Proton pump inhibitors (PPIs) are widely used for acid-related disorders. Recent evidence suggests potential associations between long-term PPI use and pancreatic dysfunction, though findings remain inconsistent. This study aimed to evaluate pancreatic function in patients on long-term PPI therapy.*

Methods: *A cross-sectional study was conducted in a tertiary care hospital from March 2023 to June 2024. Ninety-seven adults aged 18–65 years who were using PPIs (≥three doses/week for ≥eight weeks) were recruited from outpatient services. Patients with diabetes or those on medications affecting glucose metabolism were excluded. Blood samples were analyzed for C-peptide, amylase, glycated hemoglobin (HbA_{1c}) and random blood sugar (RBS). C-peptide levels were categorized as normal (≤4.20 ng/mL) or abnormal (>4.20 ng/mL). Other biochemical parameters were also similarly classified using standard laboratory cut-offs. Prevalence*

Address for correspondence:
Dr. Madhavi Eerike, Additional Professor
Department of Pharmacology, All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana, India, PIN-508126
Email: dr.madhavieerike@gmail.com

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of dysfunction was expressed as percentages. Associations between C-peptide levels and age, sex, amylase, HbA_{1c}, RBS, PPI type and duration were assessed using odds ratios and Chi-square/Fisher's exact tests.

Results: *Participants had a mean age of 51.2 years and 62.9% of them were females. The most common PPI was pantoprazole (76.3%). Abnormal C-peptide levels were observed in 10.3% of participants. Raised HbA_{1c} levels were noted in 48.5% of subjects. There were no significant associations with pancreatic function and age, sex, type and duration of PPI treatment.*

Conclusion: *No definitive association between chronic PPI usage and pancreatic dysfunction could be established. A possible association may be suspected due to the high prevalence of raised HbA_{1c} levels in long-term PPI users. Further studies are required to elaborate on these findings.*

Keywords: proton pump inhibitors, pancreatic function, C-peptide, diabetes, amylase.

INTRODUCTION

Proton pump inhibitors (PPIs) are widely prescribed for acid-related disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) (1, 2). They are also commonly available over-the-counter (OTC) for symptomatic relief of acidity. Proton pump inhibitors exert their effect by irreversibly inhibiting the H+/K+ ATPase proton pump located on the gastric parietal cells, suppressing gastric acid secretion (3).

Proton pump inhibitors are widely used due to their perceived safety, often leading to prolonged unsupervised use. Abrupt discontinuation can cause rebound hyperacidity, encouraging continued use. While generally well-tolerated, PPIs may cause headaches, nausea, diarrhea, abdominal pain and constipation. Long-term use is linked to gastrointestinal infections, micronutrient deficiencies, bone fractures, bacterial overgrowth, nutrient malabsorption and gut microbiota changes (4).

Several studies have recently raised concerns about an increased risk of diabetes with long-term PPI use. Ciardullo *et al* reported a 56% increased risk of diabetes among PPI users, particularly when treatment duration was longer than eight weeks (5). Similarly, Yuan *et al* observed a 24% higher risk among regular users compared to non-users. Proposed mechanisms include PPI-induced gut dysbiosis and hypomagnesemia, both of which could contribute to glucose metabolism disturbances (6). However, contrasting evidence also exists. Lin *et al* (7) reported a decreased risk of diabetes among patients using PPIs for upper gastrointestinal disorders (7), and a retrospective study by Hsun Lin *et al* found that lansoprazole use was associated with a significantly reduced risk of type 2 diabetes mellitus (T2DM) (8). Possible explanations include rebound hypergastrinemia, stimulating insulin secretion and pancreatic beta-cell proliferation. Systematic reviews and meta-analyses (SRMAs) have also been inconclusive, with some indicating increased risk and others suggesting no association or even improved glycemic control (9-12). These inconsistencies underscore the need for further studies. Such studies are particularly important in the Indian context, given the high burden of diabetes and the distinct racial, dietary, lifestyle and socioeconomic factors that may influence disease patterns and drug responses.

Pancreatic dysfunction can be assessed using alteration in C-peptide and amylase levels. Glycated hemoglobin and blood sugar levels are also altered in pancreatic dysfunction indirectly.

In this study we aim to assess abnormalities in C-peptide, amylase, HbA_{1c} as well as random blood sugar levels in long-term PPI users and their association with PPI type, duration, age and sex. A cross-sectional design was chosen for feasibility and to generate preliminary data for future studies.

METHODOLOGY

This cross-sectional study was carried out in a tertiary care hospital from March 2023 to June 2024. It was initiated after getting approval from the Institutional Ethics Committee. Due to the high patient load, the Department of Medicine's Outpatient Department (OPD) was chosen for recruitment of participants.

Written informed consent was taken from all selected patients before enrolling them into the study. The study population comprised both male and female patients aged 18 to 65 years. Patients taking prescribed or over-the-counter (OTC) PPIs for at least three doses *per* week for a

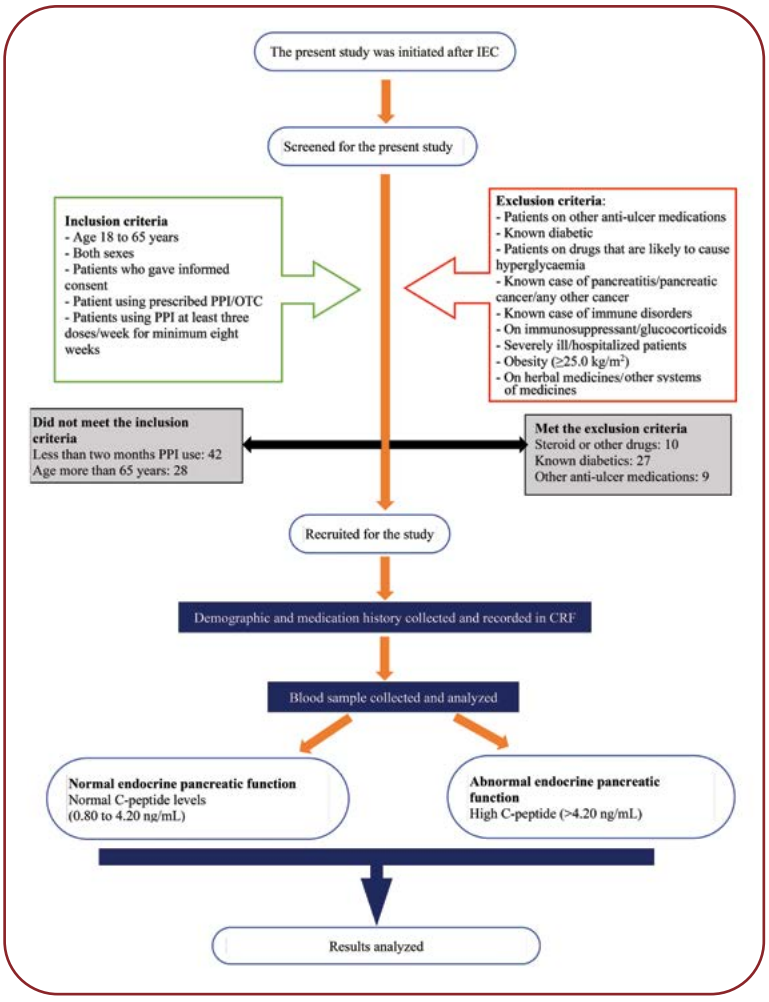

FIGURE 1. Flow chart illustrating the participant selection and study process

minimum of eight weeks (5) were included in the present study. Those who were previously diagnosed with diabetes, cancer, immune disorders, receiving drugs that may cause hyperglycemia or immunosuppression and users of herbal or other alternative systems of medicine were excluded (Figure 1).

The sample size was calculated using the statulator software. The confidence level was taken as 95% and absolute precision as 0.5 for the calculation. Since no data from a similar study previously conducted in the Indian population was available, the expected prevalence was assumed as maximum, *i.e.*, 50%. The final sample size for this cross-sectional study was 97.

The demographic history and drug history of all enrolled participants were recorded in the case report forms. The demographic history comprised patient initials, age, sex, address, contact number, comorbidities, history of alcoholism/smoking, education and occupation. The drug history included the drugs presently taken by the patient and their dose, frequency, duration, indications and whether the PPI was prescribed by a physician or acquired as OTC. A 10 mL blood sample was collected by a trained phlebotomist for the estimation of C-peptide, amylase, HbA_{1c} and RBS levels.

Pancreatic dysfunction may be related to the endocrine function measured through C-peptide levels and exocrine function was assessed through amylase indirectly.

Although fasting samples are generally preferred, random blood sugar and C-peptide levels were used in our study. In our setting, since the patients visited the OPD at varying times between 9:00 am and 1:00 pm, standardized fasting sample collection was not feasible. Also, as participants were unwilling to return on a separate day for fasting sample collection and due to time constraints of the study, the analysis was performed using random blood sugar and C-peptide levels.

Random C-peptide estimation is known to be one of the easiest and more flexible methods to test C-peptide levels in an inpatient or outpatient setting. Also, it is reliable and correlates well with other C-peptide tests like fasting C-peptide and post glucose stimulation test (13-15).

Biochemical parameters, including C-peptide, amylase, HbA_{1c} and RBS, were categorized as normal or abnormal based on standard laboratory cut-offs. C-peptide >4.20 ng/mL, amylase >80 U/L, HbA_{1c} ≥5.7% and RBS ≥140 mg/dL were considered abnormal levels.

Similarly, other study variables were categorized for analysis as follows: duration of PPI use was classified as <one year or ≥one year; type of PPI was grouped into pantoprazole or other PPIs; age was categorized as <60 years or ≥60 years; and sex was classified as male or female.

Data were entered into Microsoft Excel and analyzed using GraphPad InStat Version 3™ software. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as counts and percentages.

Participants were grouped into two groups based on normal and raised C-peptide levels. Associations between pancreatic function and

variables such as age, sex, type of PPI and duration of PPI use were analyzed using contingency tables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of associations. Fisher's exact test was used for categorical comparisons as it provides more accurate results for small sample sizes where expected frequencies in any cell of the 2x2 table was less than 5. A p-value <0.05 was considered statistically significant.

RESULTS

The present cross-sectional study enrolled 97 participants after screening a total number of 224 patients. Reasons for screen failure (n=127) included PPI use of less than two months (n=42), age above 65 years (n=28), unwillingness to give a blood sample (n=11), currently on steroid or other drugs causing hyperglycemia (n=10), known diabetics (n=27) and users of other anti-ulcer medications (n=9).

The study participants were predominantly females (62.9%) and had a mean age of 51.2 years, with most participants falling within the 45–65 age group (70.1%). Around one-third of all participants lacked formal education and about one-third were unemployed. Common comorbidities included hypertension (36.1%) and hypothyroidism (6.2%) (Table 1).

TABLE 1. Demographic details of participants enrolled in the present study

Parameter	N (%)
Total screened	224
Total enrolled	97 (100)
Sex distribution	
Females	61 (62.9)
Males	36 (37.1)
Age groups	
18 - 29 years	7 (7.2)
30 - 44 years	22 (22.7)
45 - 59 years	34 (35.1)
60 - 65 years	34 (35.1)
Education	
No formal education	35 (36.1)
Primary	12 (12.4)
Secondary	33 (34.0)
Higher secondary	8 (8.3)
Bachelors' degree	9 (9.3)
Occupation	
Unemployed	33 (34.0)
Agriculture	22 (22.7)
Homemaker	15 (15.5)
Skilled	11 (11.3)
Service	8 (8.3)
Business	5 (5.2)
Comorbidities	
Hypertension	35 (36.1)
Hypothyroidism	6 (6.2)
Others	11 (11.3)
No comorbidities	45 (46.4)

TABLE 2. Medication details and indications of participants enrolled in the present study

Parameter	N (%)
Type of PPI	
Pantoprazole	74 (76.3)
Omeprazole	8 (8.3)
Esomeprazole	7 (7.2)
Rabeprazole	8 (8.3)
Duration of PPI use	
2-6 months	19 (19.6)
6-12 months	27 (27.8)
1-2 years	14 (14.4)
2-5 years	19 (19.6)
> five years	18 (18.6)
Type of prescription	
Prescribed	76 (78.4)
OTC	21 (21.7)
Indications	
Gastritis	82 (84.5)
Peptic ulcer disease	10 (10.3)
Co-prescribed with NSAIDs	5 (5.2)
Other medications	
Telmisartan	19 (19.6)
Amlodipine	8 (8.3)
Thyroxine	7 (7.2)
Atenolol	5 (5.2)
Metoprolol	3 (3.2)
Aspirin	3 (3.1)
Gabapentin	3 (3.1)
Statin	2 (2.1)
Propranolol	2 (2.1)

NSAIDs: non-steroidal anti-inflammatory drugs

The present study primarily assessed the use of PPIs, with pantoprazole being the most frequently prescribed drug (76.3%). The most common duration of PPI use was 6-12 months (27.8%); 78.4% of participants received prescribed PPIs, while 21.7% of subjects obtained them over the counter. Gastritis was the main indication for PPI use (84.5%). The medication details, including those of PPI, are mentioned in Table 2.

C-peptide levels had a mean of 2.2 ± 3.1 ng/mL, with 87 (89.7%) participants having C-peptide values within the normal range and 10 (10.3%) abnormally raised values i.e. >4.20 ng/mL.

Glycosylated hemoglobin, which reflects long-term glycemic control, showed that 50 (51.6%) participants were within the normal range (<5.7%), 42 (43.3%) in the prediabetes range

Lab parameter	Category	Range	N (%)	Mean±SD
C-peptide	Overall		97 (100%)	2.2 ±3.1
	Normal	≤4.20 ng/mL	87 (89.7%)	1.3±1.2
	High	> 4.20 ng/mL	10 (10.3%)	9.7±4.3
HbA_{1c} (in %)	Overall		97 (100%)	5.7±0.7
	Normal	<5.7%	50 (51.6%)	5.4± 0.2
	Prediabetes	5.7% to 6.5%	42 (43.3 %)	5.9±0.2
	Diabetes	>6.5%	5 (5.2%)	8.0±1.9
	Diabetes + prediabetes		47 (48.5 %)	6.1±0.9
RBS (in mg/dL)	Overall		97 (100%)	111.3±36.9
	Normal	<140 mg/dL	90 (92.8%)	103.5±13.6
	Prediabetes	≥140 mg/dL to 200 mg/dL	4 (4.1%)	166.5±11.3
	Diabetic	200 mg/dL	3 (3.1%)	270.3±101.1
	Diabetes + prediabetes		7 (7.2%)	211±80.9
Amylase (in U/L)	Overall		97 (100%)	46.5±17.6
	Normal	≤80 U/L	94 (96.9 %)	44.8±14.3
	Abnormal	> 80 U/L	3 (3.1%)	102±23.9

TABLE 3. Biochemical parameters of study participants on long term PPI therapy

Parameter	Subgroups	High C peptide (>4.20 ng/mL)	Normal C-peptide	p	Odds ratio	Confidence interval
Age	≥ 60	3	31	1.00	0.78	0.19 to 3.210
	<60	7	56			
Sex	F	4	57	0.17	0.35	0.09 to 1.34
	M	6	30			
Duration of PPI use	≥ one year	6	69	0.23	0.39	0.10 to 1.53
	< one year	4	18			
Type of PPI	Pantoprazole	10	64	0.11	7.65	0.43 to 35.86
	Other PPIs	0	23			

TABLE 4. Association of abnormal C-peptide levels with gender, age, duration of PPI use and type of PPI

(5.7% to 6.4%) and five subjects (5.2%) had levels suggestive of diabetes (≥6.5%). Glycated hemoglobin had an overall mean of 5.7 ± 0.7%.

Among the 10 participants with high C-peptide values, eight subjects had raised HbA_{1c} values (six in the prediabetes and two in the diabetes range).

Amylase levels had a mean of 46.55 ± 17.56 U/L. Most participants (n=94) had normal levels, while three subjects showed elevated levels.

Among all participants, four (4.1%) exhibited RBS levels between 140 to 200 mg/dL, indicating a potential prediabetes condition, and 3 (3.1%) showed RBS >200 mg/dL, indicating potential cases of undiagnosed diabetes. The remaining 92.8% subjects had levels within normal threshold (Table 3).

Out of the 97 participants, two (2.0%) had elevated levels of all three parameters, including C-peptide, HbA_{1c} and RBS.

In our study, participants' age did not show any significant association with pancreatic dysfunction. Participants aged 60 years or older were just as likely to have abnormal pancreatic function as those younger than 60 years. The analysis also revealed no significant association between the sex of the participant and abnormal pancreatic function. Likewise, the duration of PPI use (p=0.23, OR = 0.39, CI 0.10 to 1.34) as well as the type of PPI used (p=0.11, OR=7.65, CI 0.43 to 135.86) did not significantly affect pancreatic function (Table 4). ❑

DISCUSSION

Proton pump inhibitors (PPIs) are among the most widely used drugs in India, often taken over-the-counter (OTC). Mittal *et al* (2) reported a 29.4% prevalence of PPI use in a tertiary center. Long-term PPI use is associated with side effects such as megaloblastic anemia, hypergastrinemia, osteoporosis, hypomagnesemia and infections like pneumonia and *Clostridium difficile*. Some studies have linked PPI use to

both increased diabetes risk and improved glycemic control in type 2 diabetes mellitus (T2DM) patients.

In our study, 62.9% of participants were female, likely due to greater availability for hospital or Mobile Medical Unit (MMU) visits. Similarly, Czarniak *et al* (6) found 58.3% female participants and Shanika (16) reported 56% female PPI users globally. Mondal *et al*.(17) found a lower figure (40%) in Bangalore. The mean age in our study was 51.2 years, lower than Czarniak *et al* (6) (64.8 years) and Ciardullo *et al* (5) (66.2 years), likely because we capped the upper age limit at 65 to minimize confounding by age-related pancreatic changes. Seventy percent of participants were aged 45 years or older. Higher age is associated with increased polypharmacy, where PPIs may be co-prescribed to manage gastrointestinal side effects. The median PPI dose was seven *per* week. Paul *et al* noted high OTC drug use among the elderly (51%) in rural India(18). Similarly, Sudhakar *et al* (2019) reported that 75% of PPI users were over 40 years.(19)

Despite the availability of many PPIs in India (1), only four (pantoprazole, omeprazole, esomeprazole and rabeprazole) were commonly used by our participants. Pantoprazole was the most prescribed PPI (76.3%), consistent with findings by Mondal *et al* (17) and Venkatraman *et al* (20). The popularity of pantoprazole may be due to its wide availability (21) and minimal drug interactions (22). Additionally, MMU outreach programs provided pantoprazole for free, likely influencing usage patterns. In our study, 21.7% of participants self-medicated with OTC PPIs even though CDSCO has not approved the use of OTC PPIs, they remain accessible without a prescription.

Most participants (84.5%) used PPIs for acidity or gastritis. Our exclusion of patients on antacids or other ulcer drugs might explain the lower prevalence of peptic ulcer disease (10.3%) compared to Chavan *et al* (38.1%) (23) and Mayabhate *et al* (19.1%) (24). Co-prescription with NSAIDs (5.2%) was similar to Sudhakar *et al*'s findings (7.5%) (19). Quick symptom relief and once-daily dosing make PPIs preferable to H2 blockers.

Long-term PPI use carries risks. Commonly reported adverse effects include anemia, osteoporosis and infections (25). Emerging evidence also linked PPIs to glycemic changes, which prompted us to investigate pancreatic function *via* C-peptide levels. C-peptide is crucial for assessing insulin reserve. In type 1 diabetes mellitus (T1DM), low C-peptide levels indicates β-cell failure, while in T2DM, C-peptide reduction marks β-cell dysfunction (14).

Pancreatic dysfunction may be related to the exocrine or endocrine function. Pancreatic function tests used to study exocrine pancreatic function include direct tests like the secretin test, cholecystokinin (CCK) test, secretin-CCK test, indirect tests like qualitative fecal fat analysis, and fecal elastase level analysis. Since it was not feasible to do these tests in our hospital, as it was a newly established not yet fully equipped centre, these tests were not included in our study. We included serum amylase levels as an indirect marker for exocrine pancreatic function as abnormal levels of amylase are indicative of pancreatic dysfunction. Endocrine pancreatic function was tested by random C-peptide levels.

In our study, 10 participants had raised C-peptide levels (>4.2 ng/mL, mean 9.7±4.3 ng/mL) and 87 subjects had normal C-peptide levels. Elevated levels of C-peptide suggest development of insulin resistance or hypersecretion of insulin due to other causes. Verma *et al* (26) showed significant C-peptide increases in T2DM patients on PPIs, which they attributed to hypergastrinemia. Gastrin enhances β-cell neogenesis and insulin secretion through CCK-2 receptor stimulation (Takebayashi *et al*) (27). Ortiz *et al* also reported increased insulin secretion after pantoprazole therapy (28). However, Hove *et al* (29) found no significant insulin increase despite a nine-fold rise in gastrin. Differences may stem from population variations, blood glucose levels, GI hormone interactions, or dietary changes post-acidity relief.

The 10 participants with raised C-peptide levels might reflect mechanisms such as gut dysbiosis, hypomagnesemia, pregnane X receptor activation, reduced IGF-1 production, or immune changes, which are all proposed explanations for PPI-associated diabetes risk (Czarniak *et al*) (6). Overall, our findings do not show any definitive association with long term PPI usage and pancreatic dysfunction. This is in contrast with earlier studies linking PPIs to increased diabetes risk, such as Ciardullo *et al* (5). Further long-term observational studies are needed to clarify these associations.

Our cross-sectional study on the effect of long-term PPI of a minimum of eight weeks on pancreatic function showed that there was an increase in the C-peptide and HbA_{1c} levels. These findings were not associated with age or sex, duration or the type of PPI used.

Our study has several strengths, including being the first to assess pancreatic function in non-diabetic individuals in India using C-peptide levels, a direct indicator of endocrine pancreatic activity. By evaluating multiple biochemical markers like RBS, HbA_{1c}, amylase and C-peptide, and exploring associations with demographic characteristics and comorbidities, the present study offers a comprehensive approach that could inform future public health policies. However, as a cross-sectional study without a control group, it cannot establish causality and limitations such as a non-representative sample skewed towards older individuals and female sex, use of consecutive sampling method, potential confounders like diet and socioeconomic status, and the absence of BMI measurement and additional pancreatic biomarkers may impact the generalizability and robustness of our findings. ❑

CONCLUSION

Our preliminary research found an increased prevalence of raised C-peptide levels (10.3%) and HbA_{1c} levels (48.5%) in the study population. No definitive associations between chronic PPI usage and pancreatic dysfunction were observed in our study. More robust studies using multiple biomarkers for pancreatic function could be planned in the future for further exploration. Since India is the diabetic capital of the world with a high prevalence of PPI use, new studies such are necessary to rule out or confirm the suspected association of chronic PPI usage and pancreatic dysfunction. ❑

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Authors' contributions: Leo Francis Chalissery – conceptualization, investigation, methodology, formal analysis, project administration, validation, visualization, writing (original draft); Madhavi Eerike – conceptualization, investigation, methodology, formal analysis, project administration, supervision, validation, visualization, writing (review and editing); Lisha Francis Chalissery – visualization, review and editing; V. Sakthivadivel, Sangeetha Sampath and Gajula Sindhura – investigation, review and editing.

Ethical considerations: This study was approved by the Ethics Committee of AIIMS Bibinagar (AIIMS/BBN/IEC/JULY/2022/198 dated 02/08/2022. This research was ethically conducted in accordance with the World Medical Association Declaration of Helsinki, ICMR National Ethical Guidelines for Biomedical Research 2017.

Informed consent: All participants provided written informed consent prior to enrolment in the present study.

Conflicts of interest: none declared.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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