



Original Article

Clinical Markers of Major Esophageal Motor Disorders in Patients with Non-Cardiac Chest Pain

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ABSTRACT

Background: Non-cardiac chest pain is common and may reflect gastroesophageal reflux, esophageal motor dysfunction, or functional pain. Esophageal manometry is not required for every patient, and simple clinical markers that identify patients at higher risk of a major motor disorder could improve referral prioritization.

Methods: This post hoc secondary analysis included 100 adults with non-cardiac chest pain referred to a tertiary gastroenterology service after negative cardiac evaluation. All patients underwent upper gastrointestinal endoscopy and esophageal manometry. The primary outcome was a major esophageal motor disorder, operationally defined as achalasia types I-III, distal esophageal spasm, or hypercontractile esophagus. Associations with age, sex, heartburn, dysphagia, and weight loss were assessed using Welch's t test, Fisher's exact test, effect-size estimates, and Firth bias-reduced logistic regression. Diagnostic performance was reported with Wilson 95% confidence intervals.

Results: Major motor disorders were present in 26 of 100 patients: achalasia type I in 10, type II in two, type III in three, distal esophageal spasm in eight, and hypercontractile esophagus in three. Dysphagia was present in all 26 patients with a major disorder and in six of 74 without one (Fisher's exact $p < 0.001$; $\phi = 0.864$; Firth odds ratio 558.5, 95% confidence interval 29.7-10,508.7). Weight loss was present in 25 of 26 patients with a major disorder and three of 74 without one ($p < 0.001$; $\phi = 0.900$; Firth odds ratio 347.3, 95% confidence interval 47.7-2,530.3). Dysphagia had 100.0% sensitivity and 91.9% specificity; weight loss had 96.2% sensitivity and 95.9% specificity. Age, sex, and heartburn were not significantly associated with the primary outcome.

Conclusions: In this selected tertiary-care cohort, dysphagia and weight loss were strong clinical markers of major esophageal motor disorders, whereas age, sex, and heartburn were not discriminatory. These findings support early manometric evaluation after structural disease has been excluded in patients with non-cardiac chest pain accompanied by dysphagia or weight loss. External validation is required before these estimates are used as a stand-alone triage rule.

Keywords: achalasia; chest pain; dysphagia; esophageal manometry; esophageal motility disorders; hypercontractile esophagus; weight loss.

INTRODUCTION

Non-cardiac chest pain (NCCP) is generally defined as recurrent, angina-like retrosternal pain for which an appropriate cardiac evaluation has not identified a cardiac cause [1,2]. Although its prognosis with respect to cardiac mortality is usually favorable after adequate cardiac exclusion, persistent symptoms can lead to repeated emergency visits, extensive testing, impaired quality of life, work absenteeism, and continuing fear of undetected heart disease [1-3]. The syndrome

is etiologically heterogeneous. Gastroesophageal reflux disease (GERD) is the most frequent esophageal explanation, but esophageal motor disorders, visceral hypersensitivity, functional chest pain, musculoskeletal disease, and psychological comorbidity are also important [1-3].

The role of esophageal physiologic testing depends on the clinical setting. Current guidance supports endoscopy to exclude structural and mucosal disease when alarm symptoms are present and recommends esophageal manometry for patients with obstructive esophageal symptoms when a mechanical cause has not been identified [4]. Manometry also complements the evaluation of chest pain that remains unexplained after an appropriate reflux assessment [4]. High-resolution pressure topography and the Chicago Classification have improved the reproducibility of esophageal motor diagnosis by integrating the median integrated relaxation pressure, distal contractile integral, distal latency, pressurization pattern, and peristaltic integrity [5,6].

Not every patient with NCCP has a clinically actionable motor disorder. In many cohorts, manometry is normal or demonstrates isolated hypomotility or lower esophageal sphincter abnormalities of uncertain relevance to chest pain. By contrast, achalasia and clinically relevant spastic disorders can lead to targeted medical, endoscopic, or surgical treatment. Identifying symptoms that enrich the pre-test probability of these disorders is therefore clinically useful, particularly in settings where access to dedicated motility laboratories is limited.

Dysphagia is biologically plausible as a marker of impaired esophageal emptying or disordered peristalsis. In a study of 177 patients with NCCP, dysphagia independently predicted an esophageal motor disorder, whereas older age predicted both reflux disease and motor abnormalities [7]. Indian manometry data have also shown dysphagia to be the symptom most consistently associated with esophageal motor diagnoses [9]. More recently, a tertiary-center cohort from the United Arab Emirates found that major motor disorders were more frequent among patients referred with dysphagia than among those without dysphagia [8]. Weight loss is an alarm feature in the evaluation of esophageal symptoms and may identify patients with prolonged dysphagia, impaired intake, or advanced outflow obstruction; however, its discriminatory value for motor disorders in NCCP has been less clearly quantified.

The parent study prospectively characterized 100 adults with NCCP using clinical assessment, upper gastrointestinal endoscopy, and esophageal manometry. The present secondary analysis was designed to determine whether readily available clinical variables - particularly dysphagia and weight loss - identify patients with achalasia or a spastic esophageal motor disorder. We hypothesized that dysphagia and weight loss would have stronger associations with major motor disorders than age, sex, or heartburn.

MATERIALS AND METHODS

Study design and setting

This manuscript reports a post hoc secondary analysis of a single-center cross-sectional study conducted in the Department of Medical Gastroenterology, Gandhi Medical College and Gandhi Hospital, Secunderabad, Telangana, India. The parent study enrolled 100 consecutive or consecutively available adult patients over an 18-month period after institutional ethics approval. Reporting was structured in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement [15].

Participants

Adults aged 18 years or older were eligible when they presented with recurrent chest pain or chest discomfort and had been referred from Cardiology or General Medicine after a negative cardiac evaluation. Cardiac assessment in the parent protocol included clinical review, electrocardiography, two-dimensional echocardiography, and treadmill testing, with additional testing guided by the treating cardiology team. Patients younger than 18 years, patients with confirmed cardiac chest pain, those with a mechanical cause of dysphagia, and postoperative patients were excluded.

All included patients underwent clinical evaluation, routine laboratory testing, upper gastrointestinal endoscopy, and esophageal manometry. Twenty-four-hour pH monitoring was performed when clinically indicated and was not used to define the primary outcome of this analysis.

Clinical variables

The clinical variables selected before the secondary analysis were age, sex, heartburn, dysphagia, and weight loss. Symptoms were abstracted as binary variables from the original case-record dataset. Chest pain was present in all included patients and therefore could not be evaluated as a predictor. The parent dataset did not consistently retain validated symptom-severity scores, duration categories, or quantitative weight change.

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed to identify mucosal or structural disease and to exclude a mechanical explanation for dysphagia. The original dataset recorded normal endoscopy, reflux esophagitis, and a dilated esophagus

among the principal findings. Endoscopic assessment was performed with a diagnostic upper gastrointestinal video endoscope system (Olympus CV-150 series, Olympus Corporation, Tokyo, Japan) with GIF-Q150 Esophageal manometry: equipment, protocol, and analysis

Esophageal manometry was performed after fasting using a 16-channel water-perfused manometry system (KangarooJeff, Royal Melbourne Hospital, Melbourne, Australia). The recordings were analyzed using Trace software, and manometric diagnoses were assigned according to Chicago Classification version 4.0. The catheter was passed transnasally after topical anesthesia, positioned to record the upper esophageal sphincter, esophageal body, lower esophageal sphincter, and proximal stomach, and the study protocol included baseline recording followed by standardized wet swallows

The recorded manometric variables were basal lower esophageal sphincter pressure (LESP), integrated relaxation pressure (IRP), distal contractile integral (DCI), and distal latency (DL). The parent dissertation stated that interpretation followed the Chicago Classification version 4.0 framework [5,6]. Under this framework, achalasia requires impaired esophagogastric junction relaxation (high IRP) with absent peristalsis and is subtyped by pressurization and spastic features; distal esophageal spasm (DES) requires clinically relevant symptoms with premature contractions; and hypercontractile esophagus requires clinically relevant symptoms with excessive contractile vigor after exclusion of obstruction [5,6]. Full Chicago Classification version 4.0 application also requires a standardized protocol incorporating position changes and provocative testing, with supportive testing for selected inconclusive diagnoses [5,6]. Because swallow-level tracings and all protocol details were not available for this secondary analysis, the original final manometric diagnoses were used without retrospective re-adjudication.

Outcome definition

The primary outcome was the presence of a major esophageal motor disorder, operationally defined for this analysis as achalasia type I, achalasia type II, achalasia type III, distal esophageal spasm, or hypercontractile esophagus. These disorders were selected because they represent esophagogastric junction outflow failure or clinically relevant spastic/hypercontractile physiology and are more likely than isolated hypomotility to alter treatment. The comparison group included normal manometry, isolated hypotensive lower esophageal sphincter findings, gastroesophageal reflux-related diagnoses, functional chest pain, and ineffective esophageal motility/hypomotility. Esophagogastric junction outflow obstruction and absent contractility were not recorded in the cohort.

Statistical analysis

All 100 participants in the parent dataset were included; no additional sample-size calculation was performed for this secondary analysis. Continuous variables were summarized as mean $\pm$ standard deviation and categorical variables as number and percentage. Age was compared using Welch's independent-samples t test, with Cohen's d as the standardized effect size. Categorical variables were compared using two-sided Fisher's exact tests because of sparse or zero cells. Pearson chi-square statistics and phi coefficients were additionally reported as measures of association for descriptive completeness.

Odds ratios with 95% confidence intervals were estimated using Firth bias-reduced logistic regression because dysphagia completely separated the outcome groups and conventional maximum-likelihood logistic regression would have produced an infinite estimate [13,14]. Dysphagia and weight loss were evaluated in separate exploratory models because weight loss was almost completely nested within dysphagia. Each model adjusted for age (per 10-year increase) and sex; the small number of outcome events precluded a larger model. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated with Wilson 95% confidence intervals. Positive and negative likelihood ratios, accuracy, and Youden's index were also calculated. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

The reanalysis was performed using Python version 3.13.5 (Python Software Foundation, Wilmington, Delaware, United States), pandas version 2.2.3, SciPy version 1.17.0, and statsmodels version 0.14.6. Firth regression was implemented using the adjusted-score method described by Firth and by Heinze and Schemper [13,14].

Ethical considerations

The parent study was conducted after approval by the Institutional Ethics Committee of Gandhi Medical College. Written informed consent was obtained from participants before study procedures. The present analysis used de-identified study data and did not introduce additional patient contact or intervention.

RESULTS

The analysis included all 100 participants. The mean age was 46.97 $\pm$ 13.06 years; 55 participants were male and 45 were female. Heartburn was reported by 67 patients, dysphagia by 32, and weight loss by 28. The baseline distribution of clinical variables according to the primary outcome is presented in Table 1.

Table 1. Baseline clinical characteristics according to the presence of a major esophageal motor disorder

Characteristic	Overall (n=100)	Major motor disorder (n=26)	No major motor disorder (n=74)
Age, years	46.97 +/- 13.06	47.19 +/- 13.46	46.89 +/- 13.01
Male sex	55 (55.0)	18 (69.2)	37 (50.0)
Heartburn	67 (67.0)	20 (76.9)	47 (63.5)
Dysphagia	32 (32.0)	26 (100.0)	6 (8.1)
Weight loss	28 (28.0)	25 (96.2)	3 (4.1)

Values are mean +/- standard deviation or number (percentage). A major motor disorder was defined as achalasia type I, II, or III; distal esophageal spasm; or hypercontractile esophagus. Percentages in the two outcome columns use the respective column denominators.

A major esophageal motor disorder was recorded in 26 patients. The outcome comprised achalasia type I in 10 patients, achalasia type II in two, achalasia type III in three, distal esophageal spasm in eight, and hypercontractile esophagus in three (Table 2). The remaining 74 participants had no major motor disorder by the operational definition used for this analysis.

Table 2. Composition of the major esophageal motor disorder outcome

Recorded diagnosis	Number	Percentage of full cohort	Percentage of major-disorder group
Achalasia type I	10	10.0	38.5
Achalasia type II	2	2.0	7.7
Achalasia type III	3	3.0	11.5
Distal esophageal spasm	8	8.0	30.8
Hypercontractile esophagus	3	3.0	11.5
Total	26	26.0	100.0

Diagnoses are those recorded in the individual-level study dataset.

Dysphagia showed the strongest association with a major motor disorder. All 26 patients with a major disorder had dysphagia, compared with six of 74 patients without a major disorder (100.0% vs 8.1%). Fisher's exact p value was <0.001, the Pearson chi-square statistic was 74.66, and phi was 0.864. Firth regression yielded an unadjusted odds ratio of 558.5 (95% confidence interval 29.7-10,508.7). Weight loss was present in 25 of 26 patients with a major disorder and three of 74 without a major disorder (96.2% vs 4.1%; Fisher's exact p<0.001; Pearson chi-square=80.95; phi=0.900). The corresponding Firth odds ratio was 347.3 (95% confidence interval 47.7-2,530.3). Associations for all prespecified clinical variables are summarized in Table 3.

Age did not differ between patients with and without a major disorder (47.19 +/- 13.46 vs 46.89 +/- 13.01 years; Welch's t=0.10; p=0.922; Cohen's d=0.023). Male sex was more frequent in the major-disorder group, but the association did not reach statistical significance (69.2% vs 50.0%; Fisher's exact p=0.111; phi=0.170). Heartburn was also not significantly associated with the primary outcome (76.9% vs 63.5%; Fisher's exact p=0.236; phi=0.125).

Table 3. Association of prespecified clinical variables with major esophageal motor disorders

Clinical variable	Major disorder	No disorder	major	Effect estimate (95% confidence interval)	Statistical test and p value	Effect size
Dysphagia present	26/26 (100.0%)	6/74 (8.1%)		Firth odds ratio 558.5 (29.7-10,508.7)	Fisher exact p<0.001; Pearson chi-square=74.66	Phi=0.864
Weight loss present	25/26 (96.2%)	3/74 (4.1%)		Firth odds ratio 347.3 (47.7-2,530.3)	Fisher exact p<0.001; Pearson chi-square=80.95	Phi=0.900
Male sex	18/26 (69.2%)	37/74 (50.0%)		Firth odds ratio 2.18 (0.85-5.57)	Fisher exact p=0.111; Pearson chi-square=2.87	Phi=0.170
Heartburn present	20/26 (76.9%)	47/74 (63.5%)		Firth odds ratio 1.83	Fisher exact	Phi=0.125

Clinical variable	Major disorder	No disorder	major	Effect estimate (95% confidence interval)	Statistical test and p value	Effect size
				(0.66-5.03)	p=0.236; Pearson chi-square=1.56	
Age, per 10-year increase	47.19 +/- 13.46 years	46.89 +/- 13.01 years		Firth odds ratio 1.02 (0.72-1.43)	Welch t=0.10; p=0.922	Cohen d=0.023

Odds ratios are Firth bias-reduced estimates. Categorical p values are from two-sided Fisher's exact tests; Pearson chi-square statistics are shown as supplementary test statistics. Phi is the effect-size measure for 2 x 2 tables. Age was compared using Welch's t test, with Cohen's d as the standardized mean difference. Confidence interval indicates 95% confidence interval.

In an exploratory Firth model adjusted for age and sex, dysphagia remained strongly associated with a major motor disorder (adjusted odds ratio 533.2, 95% confidence interval 31.4-9,061.2; Wald p<0.001). In a separate model adjusted for age and sex, weight loss was also strongly associated with the outcome (adjusted odds ratio 554.5, 95% confidence interval 34.7-8,851.3; Wald p<0.001). The very wide confidence intervals reflect sparse data and near-complete separation and should not be interpreted as precise estimates of effect magnitude.

The diagnostic performance of dysphagia and weight loss is shown in Table 4. Dysphagia had a sensitivity of 100.0% (95% confidence interval 87.1%-100.0%), specificity of 91.9% (83.4%-96.2%), positive predictive value of 81.3% (64.7%-91.1%), and negative predictive value of 100.0% (94.7%-100.0%). Weight loss had a sensitivity of 96.2% (81.1%-99.3%), specificity of 95.9% (88.7%-98.6%), positive predictive value of 89.3% (72.8%-96.3%), and negative predictive value of 98.6% (92.5%-99.8%).

Table 4. Diagnostic performance of dysphagia and weight loss for identifying a major esophageal motor disorder

Clinical marker	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Accuracy
Dysphagia	100.0% (87.1%-100.0%)	91.9% (83.4%-96.2%)	81.3% (64.7%-91.1%)	100.0% (94.7%-100.0%)	12.33	0.00	94.0%
Weight loss	96.2% (81.1%-99.3%)	95.9% (88.7%-98.6%)	89.3% (72.8%-96.3%)	98.6% (92.5%-99.8%)	23.72	0.04	96.0%

Values in parentheses are Wilson 95% confidence intervals. Sensitivity, specificity, and predictive values are based on the operational outcome definition used in this study. Predictive values depend on the 26% outcome prevalence in this tertiary-care cohort and should not be directly transferred to populations with different prevalence.

DISCUSSION

In this secondary analysis of 100 adults referred with NCCP, dysphagia and weight loss were strongly associated with achalasia or a spastic/hypercontractile esophageal motor disorder. Every patient with a major disorder reported dysphagia, and all but one reported weight loss. In contrast, age, sex, and heartburn showed little discriminatory value. The high sensitivity and negative predictive value of dysphagia and the high specificity and positive likelihood ratio of weight loss suggest that these symptoms may help prioritize manometry after structural disease has been excluded. The estimates, however, arise from a selected tertiary-care cohort and should be considered hypothesis-generating rather than a validated prediction rule.

The association between dysphagia and major motor disorders is clinically and physiologically coherent. Achalasia impairs esophagogastric junction relaxation and progressively compromises bolus clearance, whereas distal esophageal spasm and hypercontractile esophagus can produce both dysphagia and chest pain through abnormal timing or vigor of contraction [5,6]. The American College of Gastroenterology recommends high-resolution manometry when obstructive esophageal symptoms persist without a mechanical cause [4]. Our findings reinforce that recommendation in the specific context of NCCP: chest pain accompanied by dysphagia should not be attributed to reflux or functional pain without considering a motor disorder.

The findings are directionally consistent with previous studies, although the magnitude of association in the present dataset was substantially larger. Gomez Cifuentes and colleagues evaluated 177 patients with NCCP and reported that dysphagia predicted esophageal motor disorders with an odds ratio of 3.8, while older age was also associated with

abnormal testing [7]. Goyal and colleagues reported that dysphagia was the symptom with the clearest positive predictive value for an esophageal motor disorder in an Indian high-resolution manometry cohort [9]. In the 2026 United Arab Emirates study, patients with dysphagia were more likely to have a major motor disorder than those without dysphagia [8]. The complete separation observed in our cohort - no major disorder among 68 patients without dysphagia - may reflect a more selected referral pathway, differences in diagnostic grouping, or recording practices rather than a universally applicable biological threshold.

Weight loss performed nearly as well as dysphagia and was more specific in this cohort. This may reflect prolonged impairment of oral intake among patients with achalasia or severe dysphagia. It is important, however, not to interpret weight loss as statistically independent of dysphagia: all 28 participants with weight loss also had dysphagia, and the two variables could not be entered together into a stable multivariable model. Clinically, weight loss should remain an alarm feature that prompts endoscopy and appropriate imaging before a primary motor disorder is assumed. Once structural and malignant causes are excluded, the combination of NCCP, dysphagia, and weight loss should substantially lower the threshold for esophageal manometry.

Heartburn was common in both outcome groups and was not useful for discrimination. This is unsurprising because heartburn can coexist with achalasia and spastic disorders, may reflect stasis or fermentation rather than true reflux, and is common in patients with NCCP more generally. Manometry should not be used as a stand-alone diagnostic test for gastroesophageal reflux disease; contemporary reflux guidelines emphasize endoscopic evidence and ambulatory reflux monitoring when objective confirmation is required [4,16]. The absence of a significant association with sex and age in our dataset also differs from some previous reports [7,8]. With only 26 outcome events, the study had limited power to detect modest demographic associations.

The distribution of major diagnoses also deserves attention. Achalasia accounted for 15% of the full cohort, including all three subtypes, while distal esophageal spasm accounted for 8% and hypercontractile esophagus for 3%. Earlier conventional-manometry studies reported high frequencies of legacy diagnoses such as nutcracker esophagus and hypotensive lower esophageal sphincter [11]. A more recent NCCP cohort from Abu Dhabi found ineffective esophageal motility to be the most frequent abnormality and reported major disorders less often [10]. Differences across studies may reflect referral thresholds, equipment, protocol, classification version, ethnic and regional factors, and whether isolated lower esophageal sphincter abnormalities or ineffective motility are counted as major disorders.

The diagnostic framework requires caution. Chicago Classification version 4.0 deliberately tightened criteria for clinically relevant esophagogastric junction outflow obstruction, distal esophageal spasm, hypercontractile esophagus, and ineffective esophageal motility, and it emphasizes symptom compatibility, supine and upright swallows, provocative maneuvers, and supportive tests in selected cases [5,6]. The present secondary analysis used the final diagnoses recorded in the parent dataset because complete swallow-level tracings and all technical protocol elements were unavailable. Consequently, the study should not be interpreted as a formal retrospective reclassification under the complete Chicago Classification version 4.0 protocol.

From a practical perspective, the results support a symptom-informed but not symptom-only pathway. After adequate cardiac assessment, patients with NCCP should be evaluated for alarm features and undergo upper gastrointestinal endoscopy when indicated. If endoscopy does not identify a mechanical explanation and dysphagia persists - particularly when accompanied by weight loss - manometry should be prioritized. Patients without dysphagia may still require reflux monitoring or other assessment according to the broader clinical picture; the apparent 100% negative predictive value in this dataset should not be used to deny testing in other populations without prospective validation.

A strength of this analysis is the availability of individual-level data for a relatively large NCCP-focused cohort from an Indian tertiary center. The analysis distinguished treatment-relevant achalasia and spastic/hypercontractile disorders from isolated hypotensive lower esophageal sphincter findings and ineffective motility, reported effect sizes and diagnostic performance rather than p values alone, and used bias-reduced regression to address complete separation. The direct clinical question is also readily applicable to referral decisions in settings with limited access to motility testing.

Limitations

1. It was a single-center tertiary-care study of referred patients, creating referral and spectrum bias; the prevalence of major motor disorders and the diagnostic performance of symptoms may be substantially different in primary care or unselected emergency populations.
2. This was a post hoc secondary analysis. Dysphagia and weight loss were recorded as binary variables without validated severity scores, symptom duration, food consistency, or objectively measured weight change. Misclassification and recall bias are therefore possible.
3. Only 26 patients met the operational outcome definition. Dysphagia completely separated the groups, and weight loss was almost completely nested within dysphagia. Although Firth regression provides finite estimates

in separated data, the very large odds ratios and wide confidence intervals are unstable and should not be interpreted as precise causal effects. The study could not construct or internally validate a multivariable clinical prediction score.

4. Complete swallow-level manometry data, original pressure-topography plots, and all details of the acquisition protocol were not available for re-review. The recorded diagnoses could not be independently adjudicated using the full Chicago Classification version 4.0 protocol, and supportive tests such as timed barium esophagography or functional lumen imaging probe measurements were not systematically available.
5. The exact hardware configuration, channel spacing, calibration procedure, patient position, standardized swallow protocol, provocative maneuvers, and Trace software version must be confirmed from laboratory records before submission. Variation in water-perfused system thresholds can affect integrated relaxation pressure interpretation.
6. pH monitoring was selective rather than universal, and psychological comorbidity and esophageal hypersensitivity were not systematically assessed. These limitations restrict conclusions about the overall cause of NCCP, although they do not directly change the manometric primary outcome.
7. Treatment and longitudinal symptom outcomes were not available. External prospective validation with standardized high-resolution manometry, blinded diagnostic adjudication, and predefined symptom measures is required.

CONCLUSIONS

Among adults referred to a tertiary gastroenterology service with NCCP, dysphagia and weight loss were strong clinical markers of achalasia or a spastic/hypercontractile esophageal motor disorder. Dysphagia was highly sensitive, while weight loss was highly specific, but the near-perfect separation produced imprecise effect estimates and may reflect the selected referral population. After cardiac and structural causes have been addressed, NCCP accompanied by dysphagia or weight loss should prompt early esophageal manometry. These findings require prospective external validation before adoption as a formal triage rule.

Declarations

Ethics approval and consent to participate: Approved by the Institutional Ethics Committee of Gandhi Medical College. Written informed consent was obtained from all participants.

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Conflicts of interest: The authors declare no conflicts of interest.

Data availability: The de-identified data used for this secondary analysis are available from the corresponding author on reasonable request, subject to institutional and ethics requirements.

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