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Original Article

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A study on the correlation of chronic obstructive pulmonary disease with metabolic syndrome and its components

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Abstract

***Background & Aims*:** Background & Aims: COPD and metabolic syndrome are highly prevalent and contribute significantly to morbidity and mortality worldwide. Limited evidence suggests a higher prevalence of metabolic syndrome in COPD patients, indicating a potential link between metabolic syndrome and impaired lung function. We aimed to study the correlation between COPD severity and metabolic syndrome components, and between CRP and COPD severity.

Materials & Methods: This cross-sectional observational study involved 100 COPD outpatients. Metabolic syndrome parameters were assessed using NCEP criteria. Patients were categorized per GOLD classification using MMRC grading and spirometry. We compared blood pressure, blood glucose, cholesterol, triglycerides, and waist circumference across GOLD stages, and clinical, metabolic, and spirometry parameters between those with and without metabolic syndrome. Analysis was performed using GraphPad Prism 9 and SPSS 26.0.

Results: 48% of COPD patients had metabolic syndrome. SBP, blood glucose and triglycerides were significantly higher in severe COPD compared to stages I and II. Among metabolic parameters, blood glucose and SBP were significant negative predictors of FEV1/FVC adjusted for age, smoking and BMI. CRP level, diabetes, hypertension, and abdominal adiposity were associated with airflow limitation severity. FEV1/FVC was significantly lower in extreme BMI groups. Those with metabolic syndrome had higher MMRC grade, exacerbation rate, and CRP, but lower FEV1/FVC and smoking history than those without.

Conclusion: This study emphasizes assessing and managing metabolic syndrome in COPD patients, and suggests links between inflammation, metabolic syndrome, and impaired lung function.

***Keywords*:** Chronic Obstructive Pulmonary Disease, Systolic Blood Pressure, Fasting Blood Glucose, Waist Circumference, Metabolic Syndrome, Forced Expiratory Volume

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Introduction

COPD is a chronic partially reversible respiratory obstructive airway disease caused by exposure to harmful particles/gas especially smoking (1). Other common risk factors include infections, pollution, occupational exposures (2)), and genetic associations like Alpha 1 Antitrypsin deficiency, polymorphisms of Microsomal epoxide hydrolase (EPHX1), and Glutathione S –transferase (3,4). Metabolic syndrome is twice as common in COPD (5). Obesity, as a part of metabolic syndrome, impacts lung function and increases respiratory dyspnea severity by deconditioning, additional restrictive disease and associated systemic inflammation. CRP serves as a marker of inflammation and tissue damage in COPD. It also has a role in predicting exacerbations COPD (6). It has been shown to directly activate the classical complement pathway contributing to further inflammation (7). An altered adipokine secretion pattern has been observed in COPD patients. The release of pro-inflammatory adipokine Leptin is increased, which causes TH1 differentiation and neutrophil activation while Adiponectin, which reduces the pro-inflammatory cytokine levels (8,9), is significantly decreased. Adverse adipokine profile along with increased release of IL6 and TNF-Alpha in obesity contributes to systemic manifestations of COPD. The Obesity Paradox was described in the meta–analysis by Cao et al. which analyzed data from 22 studies which included about 21,150 subjects. It showed that lower BMI in COPD patients was associated with higher mortality in these patients (10). The probable reasons may include loss of appetite, deconditioning and sarcopenia occurring in advanced stages contributing to a lower BMI. Effects of obesity, particularly abdominal obesity on lung function include abnormal ventilation/perfusion ratio, decreased chest wall and pulmonary compliance, increased work of breathing, reduction of ventilatory muscle strength and endurance and small airway dysfunction with expiratory flow limitation.

Hypertension incidence in COPD varies between 6 and 50%. Hypoxia-related vasoconstriction and endothelial dysfunction could contribute to the development of hypertension in these patients. Increased intrathoracic pressure because of airway obstruction could lead to persistent sympathetic overactivation and a subsequent decrease in baroreceptor sensitivity further increasing the risk of hypertension (11). Common risk factors include smoking, genetics, obesity, physical inactivity, and airflow limitation contributing to both COPD and metabolic syndrome. Inflammation is the shared pathway between COPD and metabolic syndrome comorbidities (12).

Higher Blood glucose levels probably lead to more systemic inflammation as well as direct hyperglycemia-induced lung function impairment in COPD patients (13–15). Patients with COPD have a higher prevalence of DM. A study by Engstrom et al. described that reduced lung function is an important risk factor for the development of diabetes in COPD (13). In a prospective Australian study, the Fremantle Diabetes Study, blood glucose was found to be a strong negative predictor of lung function (14). The association between impaired lung function and diabetes is thought to be the result of inflammation, oxidative stress, hypoxemia or direct damage caused by chronic hyperglycemia. (15). The Rho-kinase pathway activation in diabetes leads to glucose-induced bronchial hyper responsiveness (16). Moreover, T2DM also seems to be associated with impaired alveolar microvascular function which correlates with the level of glycemic control and extrapulmonary microangiopathy (17). There is also a risk of recurrent infection in diabetes patients further compromising lung function.

Contributory factors for dyslipidemia in COPD include physical inactivity, steroid use, coexisting diabetes, and systemic inflammation, however, the magnitude of its direct effect on lung function is conflicting. COPD patients with metabolic syndrome have severe disease, more dyspnea, lower FEV1, and require more inhalational glucocorticoids as compared to those without metabolic syndrome (18).

In this study, we aimed to compare the clinical, metabolic and spirometry parameters between those with and without metabolic syndrome, investigate for

any correlation between metabolic parameters and CRP with lung function, and determine if there is any significant difference in the mean levels of these parameters across GOLD stages (19).

Materials & Methods

The cross-sectional observational study enrolled 100 clinically stable COPD patients who visited the General Medicine and Chest Medicine OPDs at IPGME&R, Kolkata from February 2018 to August 2019. It was a hospital-based cross-sectional observational study. The inclusion criteria consisted of COPD patients without acute exacerbation or history of exacerbation in the previous 6 weeks, without any other systemic inflammatory disease, and not on any antidiabetic, antihypertensive, statins or oral steroids for >3 weeks. Exclusion criteria encompassed hospitalized COPD patients, those with coexisting other pulmonary diseases like pneumonia, pleural effusion, bronchiectasis or fibrosis, any systemic inflammatory diseases, or known ischemic heart disease. The study received ethical committee approval from the institutional ethics committee of IPGME&R.

The study utilized the revised NCEP criteria to define metabolic syndrome in the study population. To meet the criteria, individuals needed to have at least three of the following components: 1) abdominal obesity (waist circumference ≥90 cm for Asian men or ≥80 cm for Asian women), 2) triglycerides ≥150 mg/dL, 3) HDL cholesterol ≤40 mg/dL for men or ≤50 mg/dL for women, 4) systolic/diastolic blood pressure ≥130/85 mmHg, and 5) fasting plasma glucose ≥100 mg/dL. Diabetes was defined according to ADA guidelines. The patients were classified as Underweight (BMI<18.5), Normal (BMI 18.5-22.9), Overweight (BMI 23-24.9) and Obese (BMI≥25 Kg/m^2) according to the Indian Consensus guideline for Indians residing in Asia. Exacerbation was defined as acute worsening of respiratory symptoms requiring additional therapy. Short acting bronchodilators/oral steroid or requiring hospitalization. Apart from performing anthropometric measurements of weight, height and waist circumference recording of blood pressure following the protocol of AHA was done and serum levels of fasting blood glucose, lipid profile and CRP were measured, MMRC grading was done in each patient and Chest X-ray, Spirometry was performed. The same standard spirometer was used for all measurements to maintain uniformity. The patients were then categorized as per GOLD Staging (20).

Statistical analysis was performed using Graph pad Prism 9 and SPSS ver. 26.0, with data summarized as the mean and standard deviation for continuous variables and count and percentages for categorical variables. Shapiro Wilk test was performed to ascertain normality of parameters. Two-sample t-tests and Mann Whitney test were performed depending on whether the variables were parametric or nonparametric, respectively. One-way analysis of variance (ANOVA) was performed to compare means across groups and to determine correlation, Pearson correlation analysis was utilized. Multiple linear regression was for ascertaining significant metabolic predictors of FEV1/FVC after adjusting for age, BMI and pack years. Univariate logistic regression was performed to investigate for any association between metabolic syndrome parameters and severity of airflow limitation (GOLD Stage) and multivariate logistic regression was done with variables that attained statistical significance in univariate analysis. A $P\text{-}value \leq 0.05$ was considered statistically significant to reject the null hypothesis in favor of the alternative hypothesis.

Results

Among 100 COPD patients included in the study, 94 were men and 6 were women. The median age of the patients was 65 years (Range-46-80 years). The mean post-bronchodilator FEV1/FVC in the study population was 57.45±7.96%. Based on the GOLD staging, 2% of patients belonged to Stage I, 77% to Stage II, and 21% to Stage III and none of the patients belonged to Stage IV.

Association of COPD severity with Triglyceride and HDL levels: Triglyceride levels were significantly higher in GOLD Stages II and III (149±30.25 mg/dL and 156±24.32 mg/dL, respectively) compared to Stage I

(112 mg/dL) (p<0.001). Hypertriglyceridemia was present in 45% and 66% of patients in GOLD Stages II and III, respectively. There was a moderate negative correlation between triglyceride levels and FEV1/FVC (r=-0.36). However, no significant association was found between hypertriglyceridemia and the severity of airflow limitation (p=0.27). A weak positive correlation (r=0.26) was observed between FEV1/FVC and HDL (p=0.009). There was no significant difference in mean HDL levels across GOLD Stages, and it was not associated with the severity of airflow limitation (p=0.39).

Association of BMI and Waist Circumference with COPD Severity: The study population had a mean BMI of 24.23±3.29, with 13% classified as underweight, 12% in the normal range, 26% overweight, and 49% obese. There was no significant difference in mean BMI across the GOLD stages. A weak negative correlation was found between BMI and FEV1 (r=-0.358, p<0.001), as well as between waist circumference and FEV1/FVC (r=-0.287, p<0.001). However, the association of BMI with airflow limitation severity was not statistically significant (p=0.15).

In terms of waist circumference, 35% of males had a waist circumference >90 cm, and 31% and 54% of patients in GOLD stages II and III, respectively, had increased waist circumference. Among females, all 6 patients had a waist circumference ≥80 cm. No significant difference in the mean waist circumference was observed across GOLD stages. Increased waist circumference (>80 cm in females and >90 cm in males) was significantly associated with airflow obstruction severity in severe COPD patients (GOLD II: OR=0.45, p<0.087; GOLD III: OR=2.72, p=0.037).

The mean FEV1/FVC ratio was significantly lower in both obese (p<0.001) and underweight individuals (p=0.021) compared to those with a normal BMI. This suggests that COPD patients at both extremes of the BMI spectrum have significantly more airflow limitation compared to those with a normal BMI.

Table 1. Distribution of FEV1 according to BMI

Classification by BMI	N	Mean FEV1	Std. Deviation
Underweight	13	56.31	6.59
Obese	49	54	6.77
Overweight	26	61.19	6.08
Normal	12	64.67	9.77
Total	100	57.45	7.97

Table 2. Distribution of BMI across GOLD Stages

Column1	GOLD Stage		
	I	II	III
BMI Category	% within BMI Cat	% within BMI Cat	% within BMI Cat
underweight	0%	69.23%	30.77%
obese	0%	67.35%	32.65%
overweight	0%	88.46%	11.54%
normal	16.67%	75%	8.33%

Association of Blood Pressure with COPD Severity: The mean systolic blood pressure (SBP) was 129.98±14.18 mmHg (Range: 100-160 mmHg), and the mean diastolic blood pressure (DBP) was 79.88±7.90 mmHg (Range: 70-100 mmHg). Among patients with hypertension, 68% were in GOLD Stages II and 32% were in GOLD Stage III. SBP was significantly higher in GOLD Stage III compared to Stage II (p<0.05). The

presence of hypertension was significantly associated with the severity of airflow obstruction in severe COPD patients (GOLD II: OR=0.47, p<0.118; GOLD III: OR=2.82, p=0.047). The mean diastolic blood pressure in GOLD Stages I, II, and III was 70 mmHg, 79.21±7.38 mmHg, and 82.75±8.80 mmHg, respectively. There was no significant difference in DBP across GOLD Stages. There was a significant negative correlation between SBP (r=-0.56, p<0.001) and DBP (r=-0.34, p<0.001). and FEV1/FVC.

Association of Fasting Blood Glucose with COPD Severity: Of the diabetic patients, 59% were in GOLD Stages II and 41% were in Stage III. Patients without diabetes had higher FEV1 values (M = 60.05, SD = 7.67) compared to diabetic patients (M = 52.41, SD = 5.9, p<0.001). There was a statistically significant difference in mean fasting blood sugar (FBS) across the GOLD stages, with Stage III having significantly higher mean FBS compared to Stages I and II. There was a significant negative correlation between FBS and FEV1/FVC (r=-0.649, p<0.001). The presence of diabetes was significantly associated with the severity of airflow obstruction in moderate and severe COPD (GOLD II: OR=0.32, p=0.015; GOLD III: OR=3.92, p=0.005). Pearson correlation analysis showed a significant correlation between FBS and exacerbation rate (r=0.7, p<0.001).

Table 3. Comparison of metabolic syndrome parameters among GOLD Stages

GOLD Stage	Triglyceride(mg/dl) Mean±SD	SBP (mm Hg) Mean±SD	Waist Circumference (cm) Mean±SD	FBS (mg/dl) Mean±SD	BMI Mean±SD
I	112	115±7.07	84	88	22.5
II	149±30.25	127.7±13.61	83.6±7.06	109.14±16.52	24.05±3.13
III	156±24.32	138.25±12.95	84.3±7.21	124.91±14.60	24.92±3.85

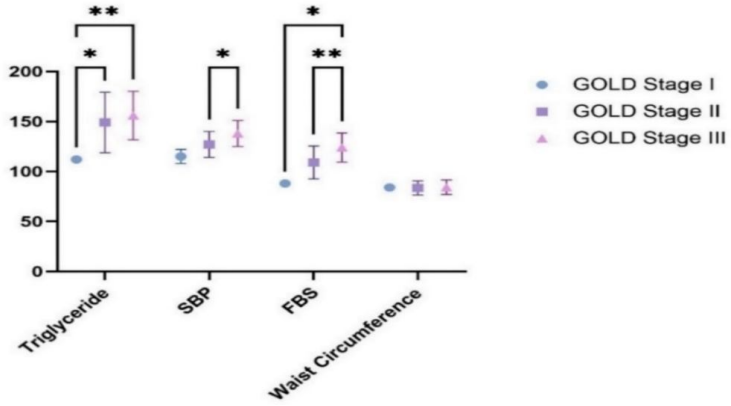

Fig. 1. Distribution of metabolic syndrome parameters across GOLD stages

COPD severity and CRP: Patients with metabolic syndrome had higher CRP levels compared to those without. There was a strong negative correlation between CRP and FEV1/FVC, and CRP was significantly associated with the severity of airflow limitation (GOLD III: OR=2.19, p<0.001; GOLD II: OR=0.58, p=0.002). Additionally, there was a significant correlation between CRP and exacerbation rate.

Comparison of the groups of COPD patients with and without metabolic syndrome: 48% of the COPD population met the criteria for metabolic syndrome. Among those with metabolic syndrome, 62% were in GOLD stages II and 37.7% were in GOLD stage III, while in those without metabolic syndrome, 83% were in GOLD stage II and 12% were in GOLD stage III (Chi Square, p=0.005). The most common comorbidities in COPD patients were hypertension (56%), hypertriglyceridemia (50%), and diabetes (30%). Patients with metabolic syndrome had lower mean FEV1/FVC and mean Pack years ($p<0.001$ and $p<0.05$, respectively). They also had higher mean SBP, DBP, FBS, Waist Circumference, and Triglyceride levels, but no significant difference in HDL levels. Patients without metabolic syndrome had lower exacerbation frequency and MMRC values compared to those with metabolic syndrome (p=.007, r= 0.31). The presence of metabolic syndrome was significantly associated with airflow limitation severity (GOLD II: OR=3.1, p=0.018; GOLD III: OR=0.24, p=0.005).

Table 4. Comparison of Metabolic syndrome parameters, MMRC Grade, Exacerbation rates, FEV1, and CRP between patient groups with and without Metabolic Syndrome

Parameters	Group	N	Mean	Std. Deviation	p-value
FEV1	1	48	53.92	6.575	<0.001
	2	52	60.71	7.795	
SBP	1	48	140.79	8.493	<0.001
	2	52	120.00	10.598	
Pack Years	1	48	23.60	7.756	<0.001
	2	52	20.10	6.664	
DBP	1	48	84.04	6.983	<0.001
	2	52	76.04	6.715	
FBS	1	48	123.48	12.470	<0.001
	2	52	102.38	15.433	
HDL	1	48	43.02	3.091	0.3
	2	52	43.94	4.968	
LDL	1	48	111.71	14.870	<0.001
	2	52	100.92	10.177	
TG	1	48	173.13	21.581	<0.001
	2	52	129.92	17.583	
WC	1	48	89.42	4.099	<0.001
	2	52	79.19	6.322	
BMI	1	48	26.69	1.847	<0.001
	2	52	21.96	2.655	
CRP	1	48	4.95	.773	<0.001
	2	52	2.70	1.189	
Exacerbation Rate	1	48	3.02	0.69	<0.001
	2	52	1.85	0.97	
MMRC Grade	1	48	3 (Median)		0.007
	2	52	2 (Median)		

SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, FBS-Fasting Blood Sugar, HDL-High Density Lipoprotein, LDL-Low Density Lipoprotein, TG-Triglyceride, WC-Waist Circumference, BMI-Body Mass Index, N-Number of patients, GROUP 1: Patients with metabolic syndrome, GROUP 2: Patients without metabolic syndrome

Multiple linear regression for predictors of FEV1/FVC was performed with the independent variables comprising principal components of metabolic syndrome (df=7, F=11.49, $p<0.001$, $R^2=0.43$) – SBP, FBS, Triglyceride, Waist Circumference after adjustment for age, BMI and Pack years. It revealed Fasting blood glucose (β-0.46, $p<0.001$) followed by Systolic Blood Pressure (β:0.3, $p=0.009$) are the strongest negative predictors of FEV1/FVC among the metabolic syndrome components. Other metabolic syndrome components did not reach statistical significance in the regression model.

Discussion

These study highlights the associations between BMI, metabolic syndrome, FBS levels, and blood pressure parameters in COPD patients and their potential impact on disease severity and comorbidities.

In our study, the majority of participants were males with a median age of 65 years and majority of patients belonged to GOLD stages II and III. In terms of metabolic syndrome, our study found a prevalence of 48%, which aligns with the findings of previous studies (18,21), where 40.3% and 47.5% of COPD patients met the criteria for metabolic syndrome respectively.

It was observed that patients with metabolic syndrome exhibited a significantly lower mean FEV1 compared to those without metabolic syndrome, which is consistent with the findings of Fekete M et al's study conducted on over 400 COPD patients (22,23). However, these results contradict the findings of Díez-Manglano J et al. (24). The lower mean FEV1 in patients with metabolic syndrome may indicate a higher level of airflow limitation in this particular subgroup of patients.

Furthermore, systolic blood pressure (SBP) was significantly higher in COPD patients with metabolic syndrome, particularly in advanced stages of COPD (24). It demonstrated a strong negative correlation with FEV1 and was associated with a greater degree of airflow limitation in severe COPD (GOLD III). Hypertension was found to be the most common comorbidity among our patients. Previous studies have also shown significantly higher SBP in COPD patients with metabolic syndrome (25), a negative correlation of SBP/DBP ((23), or pulse pressure and FEV1 (26). Several factors may contribute to this association, including the use of steroids, systemic inflammation, endothelial dysfunction, vasoconstriction, obesity, and smoking. While this association may not be causal, it certainly contributes to the patients' morbidity, especially in more advanced stages of the disease.

There was no statistically significant difference in mean waist circumference across the GOLD stages ($p=0.227$), which is consistent with previous observations. It exhibited a negative correlation with FEV1/FVC but no correlation with GOLD stages, similar to the findings of Foumani et al. (27). Increased waist circumference was significantly associated with airflow limitation in GOLD Stage III but not in Stage II in univariate analysis, as observed in the study by Lam K et al. (28). However, this association did not reach significance in the multivariate model. These findings suggest that waist circumference alone may not contribute to airflow limitation in COPD, but its association with other metabolic components and systemic inflammation serve as stronger predictors of airflow limitation severity.

In our study, approximately 49% of COPD patients had hypertriglyceridemia, which is consistent with the findings of Ameen et al, where elevated triglyceride levels were observed in 51.4% of COPD patients (25). We did not find a statistically significant difference in mean triglyceride levels across GOLD stages (29). We also identified a significant moderate negative correlation between triglyceride levels and FEV1 which is supported by the study conducted by Ameen et al., where a negative correlation between triglyceride levels and FEV1 was reported (r=-0.3, p-value 0.047) (30). Hypertriglyceridemia was not associated with airflow limitation severity. We did not observe any significant correlation between HDL and FEV1 and no association with airflow limitation severity. The results of previous studies are consistent with our findings (29,31). These results suggest that even though Triglyceride levels are significantly higher in more advanced stages it is not directly associated with airflow limitation severity. BMI

was significantly higher in the patient group of COPD with metabolic syndrome (32). It had a weak negative correlation with FEV1 contrary to the finding of Wu et al (33). The mean FEV1 was significantly lower in obese as well as underweight patients compared to those with normal BMI however there was no significant statistical difference was observed between normal-weight and overweight individuals. The presence of higher degree airflow limitation in extremes of BMI may have the following explanations- Obese individuals are more likely to have small airway dysfunction, OSA and other comorbidities, sedentary habits and systemic inflammatory state contributing to greater dyspnea as well as airflow limitation. On the other hand, severely underweight COPD patients may have ongoing systemic inflammation contributing to loss of muscle mass, loss of appetite and poor functional status and are hence more likely to have advanced disease (34). We didn't find any association of BMI with airflow limitation severity and the mean BMI did not differ significantly across GOLD stages which contrasts the findings of Saha A. et al which showed significant decrease of BMI in advancing GOLD stages. This difference is because stage IV COPD patients was not considered. Hence BMI itself may not be a predictor of severity but patients in extremes of BMI require special medical attention.

The prevalence of diabetes in COPD patients was found to be 30%, making it the third most common comorbidity after hypertension and hypertriglyceridemia. This finding is comparable to the study by Mahishale V et al., where the prevalence of diabetes mellitus in COPD patients was 25.63% (35). Diabetic patients had significantly lower FEV1, and higher fasting blood sugar (FBS) levels were associated with airflow limitation severity in both moderate and severe COPD patients (25,36). FBS emerged as the strongest negative predictor of FEV1 among all metabolic syndrome parameters and had a strong correlation with exacerbation rate. Managing glycemic status is crucial in COPD patients, as dysglycemia is associated with airway hyperresponsiveness, pulmonary microvascular damage, and recurrent infections (23,37).

Patients with metabolic syndrome had higher levels of C-reactive protein (CRP), which showed a significant negative correlation with FEV1 and was higher in more advanced stages (38). Previous studies also demonstrated higher CRP levels in individuals with metabolic syndrome (18). CRP was strongly associated with airflow limitation severity and exacerbation rates, supporting the link between systemic inflammation and COPD progression (39).

COPD patients with metabolic syndrome had lower mean FEV1, more severe dyspnoea, and higher exacerbation rates compared to those without metabolic syndrome. These findings differ from the study by Deez Manglano et al., where COPD patients with metabolic syndrome had more dyspnoea but higher mean FEV1 and exacerbation rates (24). Most patients with metabolic syndrome in our study belonged to GOLD stage II, similar to the findings of Ghatas et al. (39). This discrepancy may be due to the underrepresentation of GOLD stages I and IV in our study population. Therefore, this subset of COPD patients requires closer attention and effective management of comorbidities to limit airflow dysfunction progression and reduce exacerbations.

It is important to acknowledge certain limitations of our study, including relatively small sample size, underrepresentation of patients in GOLD stages I and IV, and the absence of a control group. Self-reported history of exacerbations and the cross-sectional nature of the study introduce potential biases.

Conclusion

This study emphasizes the association between metabolic syndrome parameters and COPD severity, including their impact on airflow limitation. It highlights the importance of managing comorbidities in COPD patients, as it can directly affect disease progression. Comprehensive management should address both airflow limitation and systemic comorbidities associated with metabolic syndrome to improve patient outcomes and quality of life.

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Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Conflict of interest

None of the authors have any interest that conflicts with this study.

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Ethical consideration

This study has been approved with ethics code IPGME&R/IEC/2019/009.

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