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Cystatin C, E-Selectin, and Pulmonary Function as Markers of Renal Dysfunction in Chronic Obstructive Pulmonary Disease with Stable Ischemic Heart Disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) frequently coexists with ischemic heart disease (IHD), and this combination may amplify systemic inflammation, endothelial injury, and renal dysfunction. Sensitive markers capable of detecting early renal involvement in this multimorbid phenotype remain incompletely characterized.

Objective: To evaluate cystatin C, cystatin C-based estimated glomerular filtration rate (eGFR), E-selectin, and forced expiratory volume in 1 second (FEV_1) as markers of renal dysfunction in patients with COPD with stable IHD, and to examine their relationships with inflammatory and cardiac biomarkers.

Methods: This comparative observational study included 135 patients with GOLD II-IV COPD: 90 with stable IHD and 45 without IHD. Within each GOLD stage, 30 patients had COPD plus IHD and 15 had COPD alone. Spirometry, serum cystatin C, creatinine, E-selectin, tumor necrosis factor-alpha (TNF-α), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed. eGFR was calculated from cystatin C. Pearson correlation and receiver operating characteristic (ROC) analyses were performed.

Results: Cystatin C increased progressively from GOLD II to IV and was higher in COPD plus IHD than COPD alone at each stage (1.39±0.02 vs 1.20±0.03 mg/L; 1.72±0.04 vs 1.54±0.04 mg/L; and 2.00±0.04 vs 1.90±0.03 mg/L, respectively; $P<0.01$ for each comparison). Corresponding eGFR values were lower in the comorbid group at GOLD II (70.1±1.5 vs 81.8±1.7 mL/min/1.73 m^2; $P<0.001$) and GOLD III (61.4±1.2 vs 67.1±1.8; $P<0.05$), while both groups showed marked filtration impairment at GOLD IV (44.6±1.2 vs 46.6±1.4; $P>0.05$). E-selectin, TNF-α, and NT-proBNP were also higher in COPD plus IHD. FEV_1 was inversely correlated with NT-proBNP in the comorbid group, with stronger associations as COPD severity increased (r=-0.524, -0.578, and -

0.724 for GOLD II, III, and IV, respectively). For identifying renal dysfunction, ROC AUCs were 0.86 (95% CI 0.79-0.92) for cystatin C, 0.78 (0.70-0.85) for E-selectin, and 0.71 (0.63-0.79) for FEV_1.

Conclusion: Renal filtration impairment in COPD worsened in parallel with airflow limitation and was accentuated by coexisting stable IHD, particularly at moderate and severe stages. Cystatin C showed the strongest discriminatory performance, while E-selectin and FEV_1 provided complementary information reflecting endothelial and pulmonary contributions to the pulmonary-cardiac-renal continuum.

Keywords: chronic obstructive pulmonary disease; ischemic heart disease; cystatin C; estimated glomerular filtration rate; E-selectin; NT-proBNP; renal dysfunction; cardiorenal interaction

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory disorder with important extrapulmonary consequences. Contemporary GOLD guidance emphasizes multimorbidity as a core component of COPD assessment because concomitant chronic diseases materially influence symptoms, hospitalization, and prognosis [1]. Cardiovascular disease is particularly important. Population-based analyses have shown substantially increased cardiovascular morbidity among people with COPD, including a higher prevalence of coronary heart disease, angina, myocardial infarction, heart failure, and arrhythmia [2,3]. Stable ischemic heart disease (IHD) may also be underrecognized in patients with COPD because dyspnea, exercise limitation, and chest discomfort can overlap with respiratory manifestations [4].

The lung-kidney relationship is increasingly recognized as another clinically relevant component of COPD multimorbidity. A 2024 systematic review and meta-analysis found a significantly higher risk of chronic kidney disease (CKD) in patients with COPD and demonstrated that CKD is associated with worse short- and long-term mortality outcomes [5]. Earlier meta-analytic data likewise documented a meaningful prevalence of CKD in COPD populations [6]. The mechanisms are likely multifactorial and include shared vascular risk factors, chronic hypoxemia, systemic inflammation, oxidative stress, endothelial dysfunction, altered hemodynamics, and exposure to medications or acute illnesses that affect renal perfusion.

Serum creatinine remains widely used for renal assessment, but it may be influenced by muscle mass and body composition, which are particularly relevant in advanced COPD. Cystatin C offers an alternative filtration marker, and current kidney guidelines support its use when creatinine-based estimates may be less accurate [7]. A meta-analysis of COPD studies found higher serum cystatin C concentrations in COPD and inverse associations with FEV_1 percent predicted and FEV_1/FVC [8]. These findings suggest that cystatin C may capture a clinically meaningful interaction between pulmonary impairment and renal dysfunction.

Endothelial injury provides a plausible biological bridge between pulmonary, cardiovascular, and renal abnormalities. E-selectin is an endothelial adhesion molecule involved in leukocyte recruitment and vascular inflammation. Prior studies have demonstrated altered circulating endothelial markers in COPD, although individual E-selectin findings have varied across populations [9]. In parallel, NT-proBNP may reflect myocardial wall stress and occult cardiopulmonary load; in stable COPD it has been associated with subsequent exacerbation risk and varies with disease severity and cardiovascular comorbidity [10,11].

The present study therefore evaluated renal filtration, endothelial activation, systemic inflammation, cardiac stress, and pulmonary function across GOLD II-IV COPD in patients with and without stable IHD. The primary objective was to compare cystatin C and cystatin C-based eGFR across these groups and to assess the discriminatory performance of cystatin C, E-selectin, and FEV_1 for renal dysfunction. Secondary objectives were to characterize TNF-α and NT-proBNP patterns and to examine the relationship between FEV_1 and NT-proBNP.

Materials and Methods

Study Design and Participants

This comparative observational study was derived from the dissertation cohort and included 135 patients with COPD. Ninety patients had COPD with stable ischemic heart disease/stable exertional angina (main group), and 45 had COPD without IHD (comparison group). According to the GOLD 2024 spirometric severity classification used in the dissertation, patients were stratified into GOLD II, III, and IV groups. Each stage contained 30 patients with COPD plus IHD and 15 patients with COPD alone. GOLD I patients were not included because the dissertation cohort was hospital-based and focused on patients requiring more intensive clinical evaluation.

The mean ages of the COPD plus IHD groups were 60.2±2.3, 62.5±2.8, and 61.4±2.8 years in GOLD II, III, and IV, respectively. Corresponding ages in the COPD-only groups were 58.3±3.5, 59.4±2.6, and 60.5±3.5 years. Body mass index ranged from 27.6 to 30.4 kg/m² across stage-defined groups. Smoking prevalence increased with disease severity and was higher in the comorbid group at GOLD IV.

Clinical and Instrumental Assessment

All participants underwent clinical assessment, routine blood and urine testing, biochemical investigations, 12-lead electrocardiography, transthoracic echocardiography, and spirometry. Spirometry was performed with a Spirometer SP100 (Contec Medical Systems, China). The principal respiratory variables were FEV_1, FEV_1/FVC, and peripheral oxygen saturation. Electrocardiography was performed with a SCHILLER Cardiovit AT-1 system. Echocardiography was performed using a Philips Affiniti 70 platform with a sector transducer, with standard M-mode, two-dimensional, and Doppler assessment.

Renal and Biomarker Measurements

Routine biochemical parameters, including serum creatinine, were measured using Human reagents on a Mindray BA-88 biochemical analyzer. Serum cystatin C was measured by enzyme-linked immunosorbent assay (ELISA) using a Mindray MR-96A semi-automated microplate reader. Cystatin C-based eGFR was calculated using the CKD-EPI approach specified in the dissertation protocol.

Serum TNF-α was measured by ELISA using a Human ELISA kit (Elabscience Biotechnology Inc., USA). Serum soluble E-selectin was measured using the Human sE-Selectin/CD62E Quantikine ELISA system (R&D Systems/Bio-Techne, USA). NT-proBNP was measured by ELISA using Vector-Best reagents (Russia), with an analytical measurement range reported in the dissertation as 0-2500 pg/mL and analytical sensitivity of 20 pg/mL.

Statistical Analysis

Statistical analyses in the source dissertation were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean±standard error as reported in the dissertation, and categorical variables as counts or percentages. Between-group comparisons used nonparametric procedures where appropriate, including Mann-Whitney and Kruskal-Wallis tests; categorical variables were compared using chi-square or Fisher exact tests. Pearson correlation coefficients were used for correlation analysis. ROC analysis was used to assess the discriminatory performance of cystatin C, E-selectin, and FEV_1 for renal dysfunction. Statistical significance was defined as $P<0.05$.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Ethics Committee of Tashkent State Medical University. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants were informed about the objectives, procedures, potential risks, and intended scientific use of the collected data. Written informed consent was obtained from all participants before enrollment. Participant confidentiality was maintained throughout the study.

Results

Renal Function Across COPD Severity

Renal filtration markers worsened progressively with increasing COPD severity. Cystatin C was consistently higher in patients with COPD plus stable IHD than in those with COPD alone. At GOLD II, mean cystatin C was 1.39±0.02 versus 1.20±0.03 mg/L ($P<0.001$); at GOLD III, 1.72±0.04 versus 1.54±0.04 mg/L ($P<0.01$); and at GOLD IV, 2.00±0.04 versus 1.90±0.03 mg/L ($P<0.01$). Within the comorbid group, stagewise differences were highly significant ($P<0.001$).

The cystatin C-based eGFR showed the reciprocal pattern. Patients with COPD plus IHD had lower eGFR at GOLD II (70.1±1.5 vs 81.8±1.7 mL/min/1.73 m²; $P<0.001$) and GOLD III (61.4±1.2 vs 67.1±1.8; $P<0.05$). At GOLD IV, eGFR was markedly reduced in both groups (44.6±1.2 vs 46.6±1.4; $P>0.05$), indicating advanced renal filtration impairment irrespective of IHD status. Serum creatinine discriminated the groups less consistently, with a significant difference at GOLD II but not GOLD III or IV.

Table 1. Renal function according to COPD severity and stable ischemic heart disease status

Parameter	GOLD II COPD+IHD (n=30)	GOLD II COPD (n=15)	GOLD III COPD+IHD (n=30)	GOLD III COPD (n=15)	GOLD IV COPD+IHD (n=30)	GOLD IV COPD (n=15)
Cystatin C, mg/L	1.39±0.02	1.20±0.03	1.72±0.04	1.54±0.04	2.00±0.04	1.90±0.03
P, IHD vs no IHD	<0.001		<0.01		<0.01	

Parameter	GOLD II COPD+IHD (n=30)	GOLD II COPD (n=15)	GOLD III COPD+IHD (n=30)	GOLD III COPD (n=15)	GOLD IV COPD+IHD (n=30)	GOLD IV COPD (n=15)
Creatinine, µmol/L	98.3±2.2	83.5±2.2	97.7±1.9	91.3±3.6	115.0±1.92	109.4±4.2
P, IHD vs no IHD	<0.001		>0.05		>0.05	
eGFR, mL/min/1.73 m²	70.1±1.5	81.8±1.7	61.4±1.2	67.1±1.8	44.6±1.2	46.6±1.4
P, IHD vs no IHD	<0.001		<0.05		>0.05	

Data are mean±standard error as reported in the dissertation. eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease.

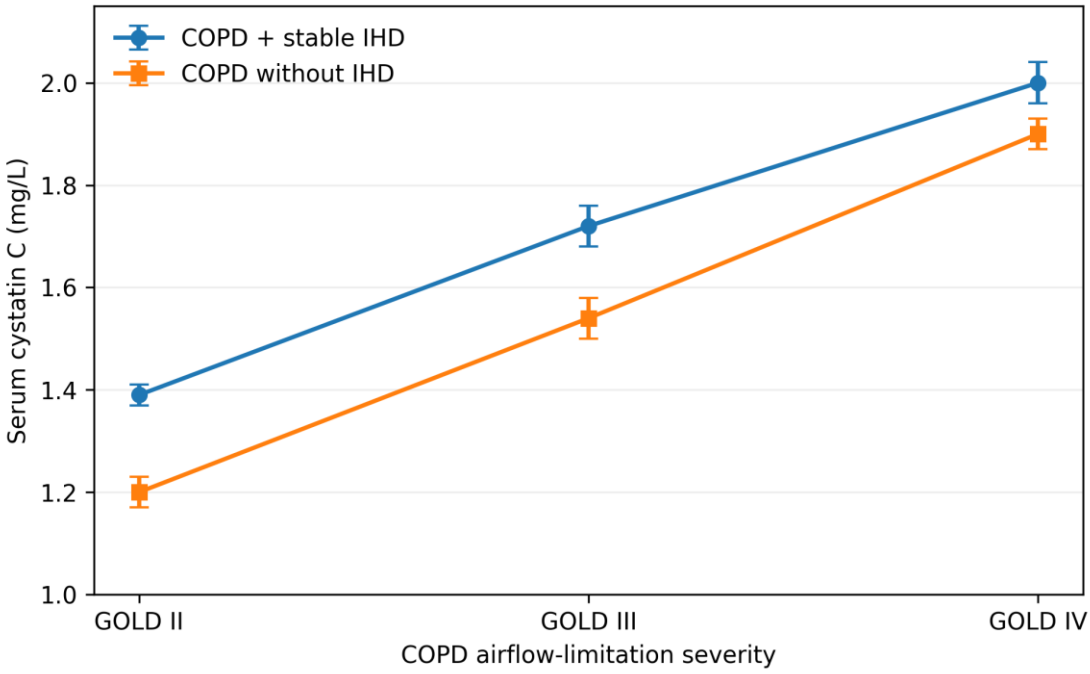

Figure 1. Serum cystatin C across GOLD II-IV COPD in patients with and without stable ischemic heart disease. Error bars represent the reported standard error.

Endothelial, Inflammatory, and Cardiac Biomarkers

E-selectin increased with COPD severity in both groups. Values were significantly higher in COPD plus IHD at GOLD II (64.5±1.6 vs 50.0±2.2 ng/mL; P<0.001) and GOLD III (74.0±2.1 vs 62.4±1.7 ng/mL; P<0.001). At GOLD IV, E-selectin was high in both groups (86.0±1.7 vs 81.5±3.9 ng/mL), and the between-group difference was no longer statistically significant (P>0.05). This pattern suggests that severe COPD itself is associated with substantial endothelial activation, while stable IHD adds a clearer signal at earlier stages.

TNF-α was higher in the comorbid group across all stages: 16.7±1.4 versus 10.8±1.3 ng/mL at GOLD II (P<0.01), 24.6±2.1 versus 15.2±1.9 ng/mL at GOLD III (P<0.001), and 32.5±2.2 versus 20.2±1.7 ng/mL at GOLD IV (P<0.001). NT-proBNP likewise showed large between-group differences: 365.4±13.9 versus 116.7±19.1 pg/mL at GOLD II, 487.4±23.8 versus 170.7±23.7 pg/mL at GOLD III, and 601.9±21.4 versus 232.5±10.6 pg/mL at GOLD IV (all P<0.001).

Table 2. Endothelial, inflammatory, and neurohormonal biomarkers

Biomarker	GOLD II COPD+IHD	GOLD II COPD	GOLD III COPD+IHD	GOLD III COPD	GOLD IV COPD+IHD	GOLD IV COPD
E-selectin, ng/mL	64.5±1.6	50.0±2.2	74.0±2.1	62.4±1.7	86.0±1.7	81.5±3.9
P, IHD vs no IHD	<0.001		<0.001		>0.05	
TNF-α, ng/mL	16.7±1.4	10.8±1.3	24.6±2.1	15.2±1.9	32.5±2.2	20.2±1.7
P, IHD vs no IHD	<0.01		<0.001		<0.001	
NT-proBNP, pg/mL	365.4±13.9	116.7±19.1	487.4±23.8	170.7±23.7	601.9±21.4	232.5±10.6
P, IHD vs no IHD	<0.001		<0.001		<0.001	

Pulmonary Function and NT-proBNP Correlations

FEV_1 declined across GOLD stages. In the COPD plus IHD group, mean FEV_1 was 58.4±1.2% at GOLD II, 49.7±2.4% at GOLD III, and 33.7±2.0% at GOLD IV. Corresponding values in COPD without IHD were 59.8±2.2%, 54.5±3.1%, and 41.6±1.1%. The between-group difference was not significant at GOLD II or III but became significant at GOLD IV (P<0.01).

In patients with COPD plus IHD, FEV_1 correlated inversely with NT-proBNP at all three severity stages, and the association strengthened with advanced airflow limitation: r=-0.524 (P<0.05) at GOLD II, r=-0.578 (P<0.05) at GOLD III, and r=-0.724 (P<0.001) at GOLD IV. In COPD without IHD, the corresponding correlations were weaker at GOLD II (r=-0.312; P>0.05) and GOLD III (r=-0.383; P>0.05), but became significant at GOLD IV (r=-0.536; P<0.001).

Table 3. FEV_1 and its correlation with NT-proBNP

GOLD stage	FEV_1, % COPD+IHD	FEV_1, % COPD	P for FEV_1	r(FEV_1, NT-proBNP) COPD+IHD	P	r(FEV_1, NT-proBNP) COPD	P
II	58.4±1.2	59.8±2.2	>0.05	-0.524	<0.05	-0.312	>0.05
III	49.7±2.4	54.5±3.1	>0.05	-0.578	<0.05	-0.383	>0.05
IV	33.7±2.0	41.6±1.1	<0.01	-0.724	<0.001	-0.536	<0.001

ROC Analysis for Renal Dysfunction

ROC analysis demonstrated the highest discriminatory performance for cystatin C, with an AUC of 0.86 (95% CI 0.79-0.92). E-selectin provided moderate discrimination (AUC 0.78; 95% CI 0.70-0.85), while FEV_1 showed modest discrimination (AUC 0.71; 95% CI 0.63-0.79). The dissertation did not report validated cutoffs, sensitivity, or specificity values for these ROC analyses; therefore, no threshold estimates are introduced in this manuscript.

Table 4. Discriminatory performance for renal dysfunction in COPD with stable IHD

Marker	AUC	95% CI	Interpretation
Cystatin C	0.86	0.79-0.92	Good discrimination
E-selectin	0.78	0.70-0.85	Moderate discrimination
FEV_1	0.71	0.63-0.79	Modest discrimination

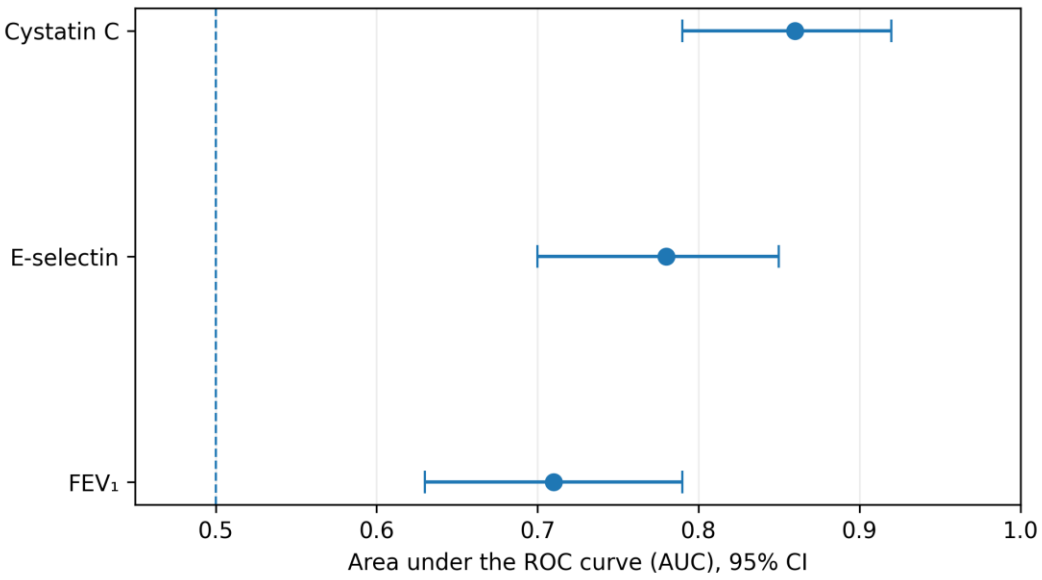

Figure 2. Area under the ROC curve for cystatin C, E-selectin, and FEV_1. Points indicate AUC estimates; horizontal error bars indicate 95% confidence intervals.

Discussion

This study identifies a coherent pulmonary-cardiac-renal pattern across increasing COPD severity. The principal finding was a progressive rise in cystatin C with a corresponding decline in cystatin C-based eGFR from GOLD II through GOLD IV. Stable IHD amplified these abnormalities at GOLD II and III, whereas by GOLD IV renal filtration was substantially impaired in both groups. This convergence at the most advanced COPD stage is biologically plausible: severe airflow obstruction, sustained hypoxemia, systemic inflammation, hemodynamic stress, and vascular dysfunction may become dominant determinants of renal impairment even in the absence of clinically defined IHD.

The renal findings are consistent with broader epidemiologic evidence. Liu et al. recently reported that COPD is associated with an increased risk of CKD and that coexisting CKD worsens both short- and long-term mortality [5]. Gaddam et al. previously demonstrated a clinically relevant CKD burden in COPD populations [6]. Importantly, the present data should be interpreted as evidence of renal dysfunction or reduced filtration rather than automatically equating every reduced eGFR value with CKD, because formal CKD diagnosis requires evidence of chronicity and/or markers of kidney damage in accordance with kidney guidelines [7].

Cystatin C was more informative than creatinine in this cohort. Creatinine differed between COPD plus IHD and COPD alone at GOLD II but not at GOLD III or IV, whereas cystatin C remained significantly different at each stage and showed a clear severity gradient. This pattern is compatible with the known limitations of serum creatinine in individuals with altered muscle mass. COPD is frequently accompanied by sarcopenia or changes in body composition, which can weaken the relationship between creatinine and true filtration. The meta-analysis by Chai et al. further supports the relevance of cystatin C in COPD, showing higher cystatin C concentrations in COPD and inverse correlations with both FEV_1 percent predicted and FEV_1/FVC [8].

The endothelial findings add mechanistic context. E-selectin increased as COPD severity advanced, and levels were markedly higher with coexisting IHD at GOLD II and III. E-selectin is expressed by activated endothelium and contributes to leukocyte adhesion and inflammatory trafficking. COPD has long been associated with abnormalities in circulating endothelial markers [9]. The loss of a statistically significant between-group difference at GOLD IV, despite high values in both groups, may represent a ceiling-like phenomenon in which severe COPD itself produces pronounced endothelial activation. However, this interpretation remains hypothesis-generating because the study was not designed to establish causal pathways.

TNF-α also increased with worsening COPD and was consistently higher in the comorbid group. This supports a systemic inflammatory phenotype linking airway disease, atherosclerotic vascular disease, and renal injury. The combination of elevated TNF-α, E-selectin, and cystatin C is compatible with an inflammatory-endothelial mechanism in which systemic cytokine activity and vascular dysfunction accompany declining renal filtration. Nevertheless, biomarker co-variation alone cannot distinguish whether endothelial activation is a cause, consequence, or parallel manifestation of multimorbidity.

NT-proBNP was substantially higher in patients with stable IHD at every COPD severity stage and showed progressively stronger inverse correlations with FEV_1. This finding is consistent with evidence that NT-proBNP can be elevated in stable COPD and may reflect cardiopulmonary stress even beyond overt heart failure [10,11]. In the SPIROMICS cohort, higher baseline NT-proBNP predicted future COPD exacerbations even after accounting for cardiovascular disease [10]. A 2023 meta-analysis likewise found higher NT-proBNP in stable COPD, more severe airflow limitation, acute exacerbations, pulmonary hypertension, and chronic heart failure [11]. Thus, the strong FEV_1-NT-proBNP correlation in GOLD IV COPD plus IHD may reflect the combined effects of impaired ventilation, hypoxic pulmonary vascular load, and myocardial ischemic burden.

The ROC findings are clinically relevant but should be interpreted cautiously. Cystatin C achieved an AUC of 0.86, outperforming E-selectin (0.78) and FEV_1 (0.71). This supports cystatin C as the most useful of the three evaluated markers for identifying renal dysfunction in this cohort. E-selectin may add biological information on endothelial injury, while FEV_1 provides a nonrenal functional indicator of the systemic severity of COPD. Because the source dissertation did not provide prespecified or externally validated thresholds, sensitivity, or specificity for these ROC analyses, the AUC estimates should be viewed as exploratory rather than as ready-to-use diagnostic rules.

The findings also align with the broader cardiovascular implications of impaired lung function. COPD is independently associated with cardiovascular morbidity [2], and prospective data indicate that declining lung function is associated with subsequent cardiovascular events [12]. In patients already carrying stable IHD, the simultaneous assessment of lung function and renal filtration may therefore help identify a higher-risk multimorbid phenotype that is not fully captured by a single-organ approach.

Clinical Implications

The data support a practical multimorbidity-oriented assessment strategy in patients with GOLD II-IV COPD and stable IHD. Spirometry should be interpreted alongside renal filtration rather than as an isolated pulmonary measure. Cystatin C-based eGFR may be particularly informative when creatinine appears relatively preserved or when low muscle mass may reduce creatinine sensitivity. Elevated E-selectin and TNF-α are best considered research indicators of endothelial and inflammatory activation, while NT-proBNP can help characterize concurrent cardiac stress. These biomarkers should complement, not replace, standard cardiovascular and renal evaluation.

Study Limitations

- The analysis is observational and cannot establish causality or temporal direction among airflow obstruction, ischemic heart disease, endothelial activation, and renal dysfunction.

- The cohort was relatively small, particularly after stratification by GOLD stage, and external validation in independent multicenter populations is required.

- The dissertation does not provide albuminuria data or documentation of renal abnormality persisting for at least 3 months; therefore, the findings should not be interpreted as establishing CKD in every participant with reduced eGFR.

- The ROC analysis reports AUC and confidence intervals but not validated decision thresholds, sensitivity, or specificity, limiting immediate clinical implementation.

- Potential confounding by smoking burden, hypertension, diabetes, medication exposure, body composition, and other cardiovascular risk factors was not addressed using a multivariable model in the presented analysis.

- The source dissertation contains limited reporting of ethics approval details and study dates; these administrative elements must be verified from the original protocol before submission.

Conclusions

Among patients with GOLD II-IV COPD, renal dysfunction became progressively more pronounced with increasing airflow limitation. Coexisting stable ischemic heart disease was associated with higher cystatin C, lower eGFR at earlier stages, greater endothelial activation, stronger systemic inflammation, and substantially higher NT-proBNP. Cystatin C demonstrated the best discriminatory performance for renal dysfunction (AUC 0.86), followed by E-selectin (AUC 0.78) and FEV_1 (AUC 0.71). These findings support an integrated pulmonary-cardiac-renal model of COPD multimorbidity and justify prospective validation of cystatin C-centered renal screening strategies in patients with COPD and cardiovascular disease.

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