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RENAL DYSFUNCTION AMONG CHRONIC OBSTRUCTIVE PULMONARY DISEASE VERSUS OTHER CHRONIC RESPIRATORY DISEASES –AN ANALYTICAL OBSERVATIONAL STUDY

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) and chronic kidney disease (CKD) are major global health concerns. Emerging evidence indicates potential link between these diseases via shared risk factors like systemic inflammation, oxidative stress, and environmental exposures. However, limited Indian studies have compared renal dysfunction in COPD with other chronic respiratory conditions. Hence, we aimed to compare renal between COPD patients and those with non-COPD chronic respiratory diseases in a tertiary care setting in Southern India.

Methods: A hospital-based analytical observational study was conducted from June 2019 to May 2020 among 90 adults (≥18 years) with chronic respiratory illness (45 COPD, 45 non-COPD), matched by age and sex. Spirometry confirmed COPD diagnosis as per GOLD criteria. Renal function was assessed using serum creatinine, eGFR (CKD-EPI), and spot urine microalbuminuria. CKD was defined as eGFR <60 mL/min/1.73m², persisting for ≥3 months. Comparative analyses were done using chi-square and Wilcoxon rank-sum tests. Unadjusted Odds ratio was calculated to determine association between COPD and CKD.

Results: Participants with COPD had a significantly higher prevalence of CKD

(51.1%) compared to those with other chronic respiratory conditions (28.9%, p=0.03), with an odds ratio of 2.57. No significant differences were observed in serum creatinine, eGFR, or microalbuminuria between groups, though values were worser in the COPD group. Lung function was significantly lower in COPD patients ($p<0.05$).

Conclusion: There was higher prevalence of chronic kidney disease among patients with COPD compared to those with other chronic respiratory conditions. Early identification of renal impairmentis essential among COPD patients.

Keywords: Chronic Obstructive Pulmonary Disease (COPD), chronic kidney disease (CKD), Renal Dysfunction, Estimated Glomerular Filtration Rate (eGFR), Microalbuminuria, Spirometry.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory condition characterized by reduced airflow and difficulty in breathing.[1]Globally, COPD is the fourth leading cause of death, contributing to nearly 5% of total deaths.[1] COPD not only contributes to high healthcare costs and reduced quality of life, but also represents a leading cause of disability, ranking second in terms of Disability Adjusted Life Years (DALYs) due to chronic respiratory diseases.[2,3] India accounted for nearly 32% of global COPD-related DALYs and contributed to 75.6% of DALYs from all chronic respiratory conditions in the country.[3]The high burden of COPD in low and middle-income countries, including India, is attributable to a combination of risk factors such as tobacco use, exposure to biomass fuels, ambient and occupational air pollution, and poor access to early diagnosis and treatment.[1,4]

Chronic kidney disease (CKD) is defined by the presence of kidney damage or decreased kidney function for a period of three months or more, regardless of the underlying cause. [5]CKD is a major public health concern worldwide and is ranked as one of the most common cause of death globally, with a documented rise in mortality over the past decade.[6]

Emerging evidence suggests that COPD and CKD may share common pathophysiological mechanisms and overlapping risk factors. Both conditions are influenced by aging, systemic inflammation, oxidative stress, and comorbidities such as diabetes mellitus, hypertension, and cardiovascular disease.[7]Moreover, environmental exposures such as tobacco smoke, air pollutants, and biomass fuel use can be contributors to both pulmonary and renal dysfunction. [8,9]

The presence of CKD in patients with COPD has been independently associated with poorer health outcomes, increased hospitalization, higher treatment burden, and elevated mortality risk.[7,10–12]Hence, early identification and management of renal dysfunction in COPD patients is of clinical importance.

However, studies examining the association between COPD and renal dysfunction are limited in the Indian setting. Limited studies have compared renal impairment in COPD versus non-COPD chronic respiratory conditions to assess whether the presence of airflow limitation, systemic inflammation in COPD may uniquely contribute to renal injury beyond the common comorbidities seen in other respiratory diseases.

Hence, we set our primary objective to compare the prevalence of CKD between adult COPD patients and patients with other chronic respiratory conditions in a tertiary hospital in Southern India. Our secondary objective was to compare renal function (serum creatinine ,estimated GFR) between the two groups.

MATERIALS AND METHODS:

Study design and setting

This hospital-based, analytical observational study was conducted at the Department of Pulmonary Medicine, a tertiary care teaching hospital in South India. The study was carried out over a one-year period, from June 2019 to May 2020.

Study population

The study population consisted of adult patients (≥18 years) presenting to the outpatient department (OPD) or admitted to the inpatient wards under the Department of Pulmonary Medicine, who were previously diagnosed with chronic respiratory illness.

Eligibility criteria

Inclusion criteria: Both male and female adults aged at least 18 years who were diagnosed with chronic respiratory condition were included

Exclusion criteria employed in our study were: (a) recent diagnosis of ischemic heart disease within the preceding three months, (b) active haemoptysis at the time of recruitment, (c) history of recent thoracic or abdominal surgery, (d) pregnancy, (e) HIV-positive patients (confirmed via rapid card testing), (f) individuals with known chronic kidney disease prior to onset of respiratory illness, and (g) individuals with positive RT-PCR test for SARS CoV2.

Sample size calculation:

The sample size calculation was done based on serum creatinine values in COPD group (1.02 ± 0.19 mg/dl) and non-COPD group (0.91 ± 0.17 mg/dl) as reported by Chen et al.[11] The alpha was assumed to be 5% and power was assumed to be 80%. The calculated sample size was 43 per group which was rounded off to 45 participants per group.

Sampling strategy:

A total of 90 participants were enrolled in the study using a non-probability purposive sampling technique. We recruited 45 participants each into two groups:

- Group 1: Patients with a confirmed diagnosis of COPD. The diagnosis of COPD was based on clinical history, risk factor exposure, and spirometry findings consistent with persistent airflow limitation, defined as a post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC) <0.70, as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[13]
- Group 2: Patients diagnosed with other chronic respiratory diseases.

The COPD group (Group 1) was recruited followed by selection of Group 2 comprising non-COPD respiratory disease to match Group 1 by age and sex. Individual matching was done in 1:1 ratio. The matching criteria used were: (a) Age (with a difference of less than 5 years from the COPD case), and (b) Sex

Study procedure

Following written informed consent, a detailed clinical history was obtained including symptom duration, comorbidities (diabetes mellitus, hypertension, heart disease), and substance use (tobacco and alcohol). Height and weight were measured using a stadiometer and calibrated weighing scale,respectively.Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Pulmonary function was assessed using spirometry, performed as per American Thoracic Society (ATS) and European Respiratory Society (ERS) standards.[14] The following parameters were recorded. Forced expiratory volume in 1 second (FEV1), Forced vital capacity (FVC), FEV1/FVC ratio and forced expiratory flow during 25–75% of FVC (FEF25–75%). Each participant underwent pre- and post-bronchodilator spirometry. Post-bronchodilator values were obtained 15 minutes after administering 400 µg of salbutamol via metered dose inhaler with spacer.

The severity of airflow obstruction among COPD patients was graded using the GOLD classification(post bronchodilator FeV1) :GOLD 1 (mild): FEV1 ≥80% predicted; GOLD 2 (moderate): FEV1 50–79% predicted; GOLD 3 (severe): FEV1 30–49% predicted; and GOLD 4 (very severe): FEV1 <30% predicted.[13]

Venous blood samples were collected twice – once during recruitment and once after 3 months of recruitment. A total of 5 mL of venous blood was collected each time based on standard procedure under aseptic precautions. Serum creatinine levels were estimated using the Jaffe method for both the samples.

Based on Serum creatinine levels, Glomerular Filtration Rate (GFR) was estimated using the CKD-EPI equation:[15]

$$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$$

Where S.cr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males,α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1.

Renal function was categorized based on KDIGOclassification:[16]

- Stage 1: GFR ≥90 mL/min/1.73 m^2
- Stage 2: GFR 60–89 mL/min/1.73 m^2
- Stage 3: GFR 30–59 mL/min/1.73 m^2
- Stage 4: GFR 15–29 mL/min/1.73 m^2
- Stage 5: GFR <15 mL/min/1.73 m^2

Chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2 which was persistent for 3 months (present in both the samples).[5]

Urine sample (2^{nd} urine sample from the morning) was collected during the time of recruitment after providing standard instructions to the participant for proper collection of urine samples. Microalbuminuria was assessed through spot urine analysis using immunoturbidimetric assay.

Statistical analysis

Data were entered into Microsoft Excel and analysed using STATA version 14.0. Categorical variables (distribution of co-morbidities, sex, substance use, presence of microalbuminuria, CKD) were described as frequencies and percentages.Continuous variables were presented as mean ± standard deviation (SD) if normally distributed (age, dynamic lung capacity values). Since estimated GFR and serum creatinine were not normally distributed, they were expressed as median with interquartile range. Shapiro-Wilk test was used to assess the normality of continuous variables.Unadjusted Odds ratio was calculated to determine association between COPD and CKD.

The following tests were applied for comparative analyses between COPD and other chronic respiratory condition groups: (a) unpaired t-test for normally distributed continuous variables, (b) Wilcoxon rank sum test for non-normally distributed variables, (c) Chi-square test for categorical variables.A P-value <0.05 was considered statistically significant.

Ethical considerations

Ethical approval was obtained from the Institutional Human Ethics Committee prior to commencement of the study. All participants provided written informed consent in their preferred language after detailed explanation of study objectives, procedures, and patient rights in this study. Patients found to have abnormal renal function were referred to the nephrology department for further evaluation and management.

RESULTS

A total of 90 participants were included in this study. This constituted 41 (45.6%) male and 49 (54.4%) female participants. The mean age of the participant was 50.3 ± 16.6 years. Out of the total, half of the participants (n=45) belonged to the COPD group and half belonged to other respiratory conditions (n=45).

Among participants with COPD, 13.3% (n=6) of participants with COPD were at GOLD stage 1, 55.6% (n=25) were at stage 2, 28.9% (n=13) at stage 3 and one participant (2.2%) was at stage 4.

Other respiratory conditions included Bronchiectasis (n=15) (33.3%), bronchial asthma (n=9) (20.0%), obstructive sleep apnoea (OSA) (n=7) (15.6%), interstitial lung disease (n=6), (13.3%), post TB fibrosis (n=2) (4.4%), other obstructive diseases (n=3) (6.7%), Allergic Broncho Pulmonary Aspergillosis (ABPA) (n=1) (2.2%), Obesity Hypoventilation Syndrome (OHS) (n=1) (2.2%), and upper airway cough syndrome (n=1) (2.2%).

Table 1 presents a comparison of demographic and clinical characteristics between participants diagnosed with COPD and those with other respiratory conditions. The characteristics were similar for both the groups. The mean age of COPD patients was slightly higher (52.4 ± 16.5 years) compared to those with other respiratory conditions (48.1 ± 16.5 years), although the difference was not statistically significant (p=0.21). There was no significant gender-based difference. Tobacco and alcohol use similar between the two groups. The prevalence of comorbidities such as diabetes mellitus (22.2% vs. 17.8%; p=0.60), hypertension (15.6% vs. 17.8%; p=0.78), and heart disease (13.3% in both groups; p=1.00) was also comparable between the two groups.

Table 2 compares the pulmonary function parameters between participants with COPD and those with other respiratory conditions (N=90). At pre-bronchodilator stage, participants with COPD had significantly lower lung function. The FEV1/FVC ratio was significantly reduced in COPD patients (61.9 ± 7.1) compared to others (79.5 ± 8.5; p=0.01). Post-bronchodilator values continued to show significant impairment in COPD patients. FEV1/FVC ratio (62.0 ± 10.6 vs. 81.7 ± 7.3; p=0.01) continued to show significant reductions in the COPD group compared to other respiratory conditions.

Serum creatinine levels, microalbuminuria, and estimated GFR levels were not significantly different between COPD group and non-COPD group. The prevalence of chronic kidney disease (CKD) was significantly higher in the COPD group (51.1%) than in the other respiratory conditions group (28.9%) (p=0.03). Those with COPD had 2.57 times increased odds of having CKD than compared to those with other respiratory conditions.

Table 1: Comparison of demographic and clinical characteristics between participants with COPD and other respiratory conditions (N=90)

Variable	**COPD N=45**	**Other respiratory conditions N=45**	**P value**
Age (in years) (Mean ± SD) *	52.4 ± 16.5	48.1 ± 16.5	0.21
Males, n (%)	22 (48.9)	22 (48.9)	1.00
Tobacco use. n (%)	16 (35.6)	12 (27.3)	0.36
Alcohol use, n (%)	11 (24.4)	9 (20.0)	0.61
Diabetes Mellitus, n (%)	10 (22.2)	8 (17.8)	0.60
Hypertension, n (%)	7 (15.6)	8 (17.8)	0.78
Heart disease, n (%)	6 (13.3)	6 (13.3)	1.00

*For age, unpaired t test was used to assess any difference between the two groups. For other variables, chi square test was used to compare between the two groups.

Table 2: Comparison of pulmonary function between participants with COPD and other respiratory conditions (N=90)

Dynamic lung capacities	**COPD N=45** (Mean ± SD)	**Other respiratory conditions N=45** (Mean ± SD)	**P value**
Pre-bronchodilator level			
%predicted FEV1	53.1 ± 17.6	72.7 ± 14.6	**0.01**
%predicted FVC	68.8 ± 20.5	77.2 ± 16.3	**0.03**
FEV1/FVC (%)	61.9 ± 7.1	79.5 ± 8.5	**0.01**
%predicted FEF 25-75	28.1 ± 14.8	49.0 ± 18.4	**0.01**
Post-bronchodilator level			
%predicted FEV1	56.8 ± 17.1	76.4 ± 15.5	**0.01**

%predicted FVC	71.9 ± 19.0	79.0 ± 17.8	0.07
FEV1/FVC (%)	62.0 ± 10.6	81.7 ± 7.3	**0.01**
%predicted FEF 25-75	30.4 ± 14.1	53.3 ± 17.7	**0.01**

*Unpaired t test was used for comparison between the two groups.

Table 3: Comparison of renal function between participants with COPD and other respiratory conditions (N=90)

Variable	**COPD N=45**	**Other respiratory conditions N=45**	**P value**
Serum creatinine (mg/dL) (Mean ± SD) *	1.02 (0.80-1.33)	0.94 (0.76-1.15)	0.23
Microalbuminuria, n (%) ^	17 (37.8)	13 (28.9)	0.37
Estimated GFR (L/min) (Mean ± SD) *	53.0 (64.0-97.8)	75.0 (55.2-107.2)	0.24
Chronic Kidney Disease (CKD), n (%) ^	23 (51.1)	13 (28.9)	**0.03**

*For serum creatinine and estimated GFR, the data was non-normally distributed based on Shapiro Wilk test ($p<0.05$). Hence, Wilcoxon rank sum test was used to assess difference between the two groups

^Chi square test was used for comparison between the two groups.

DISCUSSION

Our study found that the prevalence of CKD was significantly higher among COPD patients (51.1%) compared to non-COPD patients (28.9%) (p=0.03). Those with COPD had 2.57 times increased odds of having CKD than compared to those with other respiratory conditions. Although the median serum creatinine and eGFR values showed a trend toward worsened renal function in the COPD group, the differences were not statistically significant. These findings might suggest that COPD, through its systemic inflammatory and hypoxemic burden, may independently contribute to renal impairment beyond shared risk factors such as diabetes, hypertension, and aging.

Multiple studies support the association between COPD and CKD. In a systematic review and meta-analysis by Gaddam et al. (2016), which included nine studies and adjusted for major confounders, patients with COPD had more than double the odds of having CKD compared to non-COPD controls (OR = 2.20; 95% CI: 1.83–2.65).[12]A more recent meta-analysis by Liu et al. (2024) observed similar findings and demonstrated a pooled OR of 1.54 (95% CI: 1.28–1.84) for CKD in COPD patients compared to the general population.[10]

Indian studies align with these observations. A cross-sectional study by Saravanan et al. (2023) from a government respiratory hospital in South India found that 83.6% of their COPD patients had renal function defects based on creatinine clearance and eGFR, with the severity of COPD and disease duration significantly correlating with renal impairment.[17] Similarly, a study conducted at Kolkata by Mondal et al. (2024) demonstrated a statistically significant decline in eGFR with increasing COPD severity.[18]

In a study by Kim et al. (2017) in Korea, CKD was significantly more prevalent in COPD patients (8.7%) compared to those with normal lung function (2.2%).[19] Multivariate logistic regression confirmed CKD as an independent risk factor associated with COPD, even after adjusting for age, sex, smoking, education, and comorbidities. The Taiwanese population-based cohort study by Chen et al. (2016) found that the adjusted hazard ratio of CKD in COPD patients was 1.61 (95% CI: 1.52–1.72). [11]

A study by Yoshizawa et al. (2015) observed a higher prevalence of CKD among COPD patients (53%) compared to controls (15%)based on cystatin C, a more reliable marker of renal function unaffected by muscle mass. However, CKD was notably underdiagnosed when only creatinine-based eGFR was used (31% vs. 8%).[20] This finding might be important for COPD patients, who often suffer from sarcopenia and low muscle mass, leading to underestimation of renal impairment when relying solely on serum creatinine levels. This non-differential misclassification might explain why there was not statistically significant difference with serum creatinine levels between the two groups.

Similar observation was made by Gaddam et al. (2016) who observed in their meta-analysis that some studies failed to detect elevated creatinine levels despite an increased prevalence of CKD in COPD patients.[12] Similarly, Mondal et al. (2024) found that patients with higher GOLD stage COPD had significantly lower eGFR, yet their serum creatinine levels remained within normal ranges for a majority of participants. [18]This discrepancy was attributed to the diminished creatinine generation from reduced muscle bulk in advanced COPD cases, particularly those in GOLD stages III and IV.

Romundstad et al. (2014) provided longitudinal evidence over 12 years showing increased microalbuminuria in COPD patients, an early marker of glomerular endothelial dysfunction. [21]Their findings support our study's results regarding higher microalbuminuria prevalence in COPD patients, though the statistical significance was not achieved probably being a small sized study.

From a pathophysiological perspective, multiple mechanisms may underlie the observed association between COPD and renal dysfunction. Bidirectional relationship is possible between CKD and COPD. Chronic systemic inflammation in COPD may accelerate atherosclerosis and microvascular damage in the renal vasculature. Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and TGF-β may involve in both pulmonary and renal tissue remodelling. Hypoxemia and hypercapnia, especially in advanced COPD, may impair renal blood flow and increase oxidative stress, contributing to glomerular injury. Additionally, activation of the renin-angiotensin-aldosterone system (RAAS) due to chronic hypoxia may further exacerbate renal injury. [7]

In our study, COPD patients showed significantly lower lung function indices compared to non-COPD chronic respiratory disease patients. This aligns with existing evidence.[22]The severity of airflow limitation among COPD patients might correlate with the degree of systemic hypoxemia, oxidative stress, and hormonal activation. These mechanisms might contribute to glomerular hyperfiltration, endothelial dysfunction, and ultimately, structural kidney damage. Observations by other studies may align with this logic. Casanova et al. (2010) had observed a link between hypoxemia in COPD and microalbuminuria.[23]Similarly, Gaddam et al. (2016) observed that airflow limitation may be independently associated with CKD risk after adjusting for age and comorbidities.[12]

Strengths and limitations:

Adequate sample size was achieved to assess differences in serum creatinine, but sample size might be insufficient for comparison of proportion of CKD between the two groups. Individual matching by age and sex was done to address confounding. However, residual confounding could be still possible in our study.

Spirometry was used to diagnose COPD which has good sensitivity and specificity. [24]Bidirectional relationship might be possible between COPD and CKD, but temporality and causal direction could not be ascertained in our study. Urine albumin was measured instead of albumin - creatinine ratio which would have reduced misclassification of proteinuria. Since our study was conducted in a single hospital setting, generalizability may be limited to similar settings with similar study populations.

CONCLUSION

This study highlights higher prevalence of chronic kidney disease among patients with COPD compared to those with other chronic respiratory conditions. Early identification of renal impairment is essential among COPD patients to prevent long-term complications.

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