Section: Respiratory Medicine

Original Research Article

SERUM CYSTATIN C VERSUS URINARY MICROALBUMIN AS A POTENTIAL EARLY PREDICTOR FOR ACUTE KIDNEY INJURY IN PATIENTS WITH ACUTE EXACERBATION OF COPD

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ABSTRACT

Background: Acute Kidney Injury (AKI) is a critical complication in patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), which often results in poor outcomes. Traditional biomarkers such as serum creatinine (SCr) are not suitable for the early detection of AKI, especially in COPD patients with muscle wasting. This study assesses the effectiveness of serum Cystatin C and urinary Microalbumin as early biomarkers for AKI in AECOPD patients admitted to a Respiratory Intensive Care Unit (RICU).

Materials and Methods: Over a period of one year, from May 2023–May 2024, a prospective cross-sectional study was performed at a tertiary care hospital. Sixty-five AECOPD patients were included by excluding patients who already had chronic kidney disease and other confounding diseases. Serum Cystatin C and urinary Microalbumin levels were measured at admission. AKI was diagnosed using KDIGO guidelines. Statistical analysis was done with ROC curves to assess biomarker predictive accuracy.

Results: The prevalence of AKI was 24.6%. Serum Cystatin C and urinary Microalbumin levels were significantly higher in AKI patients ($p < 0.001$). ROC analysis showed AUC values of 0.890 for Cystatin C (cutoff: 1 ng/µL; sensitivity: 87.5%, specificity: 93.9%) and 0.802 for Microalbumin (cutoff: 29.74 mg/L; sensitivity: 68.8%, specificity: 100%). AKI patients had higher mortality (37.5% vs. 2%) and required more mechanical ventilation (68.8% vs. 24.5%) and dialysis (18.8% vs. 0%) compared to non-AKI patients.

Conclusion: Serum Cystatin C and urinary Microalbumin are effective early biomarkers for AKI in AECOPD patients. Their integration into clinical practice could enable timely intervention, improving patient outcomes. Further multicenter studies are needed to validate these findings.

Keywords: Acute Kidney Injury, Chronic Obstructive Pulmonary Disease, Serum Cystatin C, Urinary Microalbumin, Biomarkers, AECOPD.

INTRODUCTION

The lung condition Chronic Obstructive Pulmonary Disease (COPD) consists of diverse airway and lung tissue changes which produce persistent respiratory symptoms including breathlessness and cough with sputum production together with recurrent worsening of illness. Airway diseases such as bronchitis and bronchiolitis together with alveoli damage that causes emphysema are responsible for generating COPD symptoms. The worsening nature of COPD results in permanent breathing obstruction which causes severe consequences to a patient's overall well-being. AECOPD stands as an urgent

medical situation which brings about a combination of worsening breathing difficulties and rising sputum levels during brief intervals of fewer than 14 days. The health issue leads to rapid and excessive breathing along with rapid heart rate when triggered by infections as well as environmental pollutants alongside airway bothersome substances that generate inflammation both locally and throughout the body.[1]

The combination of COPD with various other health conditions affects both the persistent nature of the disease and the treatment results for patients. The medical community neglects the clinically important relationship between Chronic Kidney Disease (CKD) and similar diseases despite its existence. Multiple studies demonstrate that COPD shows a direct connection with CKD specifically among the elderly patient population. The work of Corsonello et al. together with Incalzi et al. indicates that COPD patients experience elevated rates of CKD while revealing its negative effects on patients' death rates and illness severity. The established role of CKD as an AKI risk factor makes it possible that COPD patients would experience more cases of AKI than patients without CKD.[2-3]

The sudden decrease in kidney function defines AKI when doctors detect either rising serum creatinine levels or decreased urine output. Affiliation between moderate elevated SCr levels and negative patient results and decreased life expectancy does exist. The use of serum creatinine as a biomarker for detecting AKI proves inadequate most specifically in COPD patients. Collective kidney injury delays SCr elevation which leads to treatment delays because of misdiagnosis. The conversion of proteins into creatinine for SCr measurement becomes less accurate in patients with COPD because skeletal muscle wasting generates misleading GFR examination results. The prevalence of muscle loss reaches between 20% among stable outpatients and 50% among hospitalized patients who have COPD at the time of exacerbations. Doctors require additional biomarkers that provide better detection of AKI because conventional biomarkers prove insufficient during these situations.[4]

The field of nephrology now utilizes new biomarkers which perform better than standard tests during the early identification of acute kidney injury cases. Serum Cystatin C together with urinary Microalbumin now show potential as alternative biomarkers compared to SCr. All nucleated cells throughout the body produce Cystatin C which freely passes through glomeruli as a low-molecular-weight protein. The levels of Cystatin C do not depend on muscle mass size so it functions as a better kidney function indicator specifically for patients who experience muscle wasting conditions similar to COPD. The glomerular permeability of kidneys causes Microalbumin levels to rise in urine before SCr measurements show clear changes.[5-6]

The objective of this research is to assess serum Cystatin C and urinary Microalbumin as possible early biomarkers that detect AKI in AECOPD patients treated at the Respiratory Intensive Care Unit (RICU). This research examines serum Cystatin C and urinary Microalbumin with the intention of detecting early-stage AKI during admission to provide suitable intervention opportunities such as fluid therapy and hemodialysis. AKI detection in COPD patients through prompt biomarker recognition followed by correct treatment processes will lead to better clinical results and fewer medical complications and improved patient survival. The findings of this study emphasize how novel biomarkers should be implemented in regular clinical practice for optimizing COPD patient care because CKD represents a common COPD comorbidity

MATERIALS AND METHODS

This research took place in the ten-bed Respiratory Intensive Care Unit (RICU) which operates at the Department of Respiratory Medicine within S.C.B. Medical College and Hospital, an educational and medical institution located in Cuttack. The Institutional Ethics Committee granted approval for this study which followed all Declaration of Helsinki principles during the research period. A period of one year consisted of the analytical prospective cross-sectional design which enrolled 65 patients with AECOPD following their admission to the RICU based on established criteria from May 2023 through May 2024.

Study Population

Adult patients who had provided consent for the study were included if they received RICU admission for COPD acute exacerbation diagnosis beyond age 18. The research excluded patients with bronchial asthma, bronchiectasis, interstitial lung disease and lung carcinoma or pneumonia and pulmonary tuberculosis. The research excluded patients with pre-existing chronic kidney disease (CKD) as well as individuals undergoing dialysis before admission and those with urinary tract infections or who received nephrotoxic drugs. Patients with chronic liver disease and pregnant women as well as those with HIV infection fulfilled the exclusion criteria.

Data Collection

Telemedicine services collected comprehensive demographic and clinical information from each patient at entry which included age factors, sex findings, ideal body weight data, height results and body mass index (BMI) readings. Clinical staff performed an extensive examination of general and systemic body systems before obtaining radiographic images to determine how far the lungs were affected. All patients underwent laboratory examinations which enabled researchers to determine reference parameters by performing blood counts with sedimentation rates as well as testing liver and kidney function with electrolyte evaluation

of sodium and potassium. Serum protein and albumin assays combined with C-reactive protein (CRP) diagnosis along with the evaluation of procalcitonin measurements were included in biochemistry testing. A kidney function assessment included collecting serum creatinine measurements at admission and after an additional day along with tracking fluid consumption and measuring urine outputs during 24 hours.

The examination protocol included the evaluation of two biomarkers called serum Cystatin C and urinary Microalbumin for acute kidney injury (AKI) detection purposes. The researchers collected blood for testing serum Cystatin C levels and they also obtained spot urine samples to determine microalbumin concentrations. Staff recorded both invasive and non-invasive mechanical ventilation modes together with the need for hemodialysis and the final patient outcomes and survival rate and discharge status.

Measurement of Serum Cystatin C

Healthcare professionals obtained venous blood from patients during admission for both Cystatin C analysis and standard blood test executions. The Cystatin C Fluid Stable Kit applied a particle-enhanced immunoturbidimetric technique for quantifying the measured samples. The methodology relies on an antigen-antibody reaction where particular antibodies targeted for human Cystatin C bind themselves to polystyrene particles. A photometric system can measure Cystatin C amounts because its presence in patient serum creates observable changes to optical density when mixed with the patient serum. An assay containing Tris-buffered saline (pH 7.5), sodium chloride, borate and human Cystatin C monoclonal antibodies constituted the reagents. The test reagents required storage at 2–8°C and kept under conditions protecting them from light to maintain their stability.

Measurement of Urinary Microalbumin

The spot urine microalbumin assessment depended on collecting a sterile urine sample in a 30 mL container during patient admission. The analysis system employed the Recombigen Microprotein Test Kit that implements the Pyrogallol Red method to determine the results. The colorimetric technique depends on the formation of blue-purple color complexes between proteins in urine and pyrogallol red ions with molybdate ions present. The intensity of the color measurement relies on the amount of microproteins found in each sample and allows for precise spectrophotometry detection of the concentration. The stored test reagents which included both microprotein reagent and calibration standard needed to be kept within 2–8°C to maintain their stability.

Study Procedure

Medical staff collected a detailed medical history when patients checked in followed by complete examinations to evaluate disease extent. The researchers distributed patients into groups according to their requirement of non-invasive or invasive mechanical ventilation according to their clinical evaluations. Medical staff performed all baseline laboratory tests that included blood and urine examinations during patient admission day. Healthcare specialists monitored serum creatinine and urea as renal function markers together with CRP and procalcitonin as inflammatory markers and electrolytes. Doctors measured total urine volume during a 24-hour period for fluid balance assessment. The study continued serum resource creatinine and urea testing together with fluids tracking on the following day.

The study used KDIGO guidelines combined with serum creatinine tests and urine output evaluation to distinguish AKI patients from other cases. Patients needed nephrology referral for either AKI diagnosis or high Cystatin C serum concentration and Microalbumin levels in urine tests. The patient received management treatments which combined fluid therapy along with dialysis according to nephrology guidance.

Statistical Analysis

The study presented percentages for categorical data while providing mean values with standard deviations as well as median values with interquartile ranges according to the data distribution. Chi-square test with Fisher's exact test served as tests for comparing categorical variables depending on their distribution. The evaluation used unpaired t-test for regular distributions while Mann–Whitney U-test was employed for irregular distributions to analyze continuous variables between groups.

Univariate binary logistic regression analysis examined every potential factor for AKI risk including patient characteristics such as age and sex as well as comorbidities and laboratory results and treatment approaches. The investigation proceeded by adding variables with $p < 0.2$ levels from the univariate analysis to a multivariable binary logistic regression model. Analysis of ROC curves enabled the assessment of predictive capabilities for AKI by calculating the AUC from measurements of serum Cystatin C and urinary Microalbumin. Studies compared the AUC values between independent variables obtained from both categorical and continuous information sets. The research used <0.05 as the threshold determining statistical significance. A version 21.0 of SPSS software enabled the data analysis at SPSS Inc. headquarters in Chicago Illinois USA.

This research investigated whether Serum Cystatin C alongside Urinary Microalbumin served as early biomarkers for AKI diagnosis in patients with AECOPD by determining their availability for clinical use to improve patient results and early detection and intervention strategies.

RESULTS

Researchers studied 65 patients who needed care at the RICU's Respiratory Intensive Care Unit due to

COPD exacerbation during May 2023 and May 2024. This research team studied how common and what factors lead to Acute Kidney Injury (AKI) through measuring RICU patients' medical data. This report uses tables and charts to present our research conclusions about the study participants.

Table 1: Demographic and Clinical Characteristics of the Study Population

Parameter	Value
Total Patients	65
Gender Distribution	Male: 49 (75.38%), Female: 16 (24.62%)
Age Distribution	50-60 years: 21 (32.3%), 60-70 years: 18 (27.7%), 70-80 years: 22 (33.8%), >80 years: 4 (6.2%)
BMI Distribution	Underweight: 15 (23.1%), Normal: 29 (44.6%), Overweight: 5 (7.7%), Obese Class I: 14 (21.5%), Obese Class II: 2 (3.1%)
Comorbidities	T2DM: 12 (18.4%), HTN: 10 (15.4%), Cor Pulmonale: 3 (4.6%), No Comorbidities: 33 (50.7%)
Exposure History	Smoking: 21 (32.3%), Biomass Fuel: 10 (15.4%)
Prevalence of AKI	16 (24.6%)

Table 2: Comparison of Laboratory Parameters Between AKI and Non-AKI Groups

Parameter	AKI Group (N=16)	Non-AKI Group (N=49)	P Value
Hemoglobin (g%)	9.7 (IQR: 1.95)	10.4 (IQR: 1.9)	0.077
Total Leucocyte Count	15 (IQR: 4.33)	10 (IQR: 2.74)	<0.0001
Serum Cystatin C (ng/uL)	1.18 (IQR: 0.37)	0.75 (IQR: 0.24)	<0.001
Urinary Microalbumin (mg/L)	30.8 (IQR: 13.33)	15.03 (IQR: 10.25)	<0.001
Serum Urea (mg/dL)	61 (IQR: 41.3)	40 (IQR: 18)	<0.001
Serum CRP(Q) (mg/L)	107.86 (IQR: 61.2)	56.2 (IQR: 53.4)	0.003
Serum Procalcitonin (ng/mL)	0.93 (IQR: 1.09)	0.23 (IQR: 0.4)	<0.001

Table 3: Diagnostic Efficiency of Biomarkers for Predicting AKI

Biomarker	Cut-Off Value	Sensitivity	Specificity	AUC (95% CI)
Serum Cystatin C (ng/uL)	1.0	87.5%	93.9%	0.890 (0.751-1.0)
Urinary Microalbumin (mg/L)	29.74	68.8%	100%	0.802 (0.629-0.976)

Graphs for Visualization

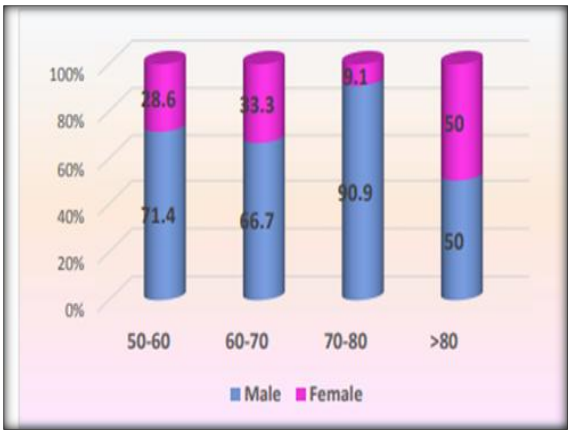


Figure 1: Age and Gender Distribution of Patients

Bar graph showing the percentage of males and females in different age groups (50-60, 60-70, 70-80, >80 years).

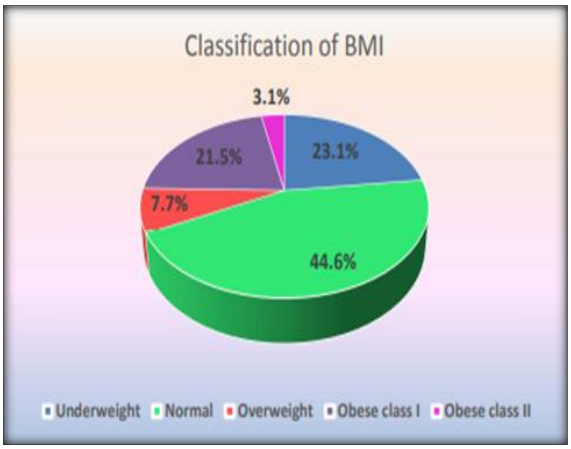


Figure 2: Distribution of BMI Among Patients

Pie chart showing the percentage of patients in each BMI category (Underweight, Normal, Overweight, Obese Class I, Obese Class II).

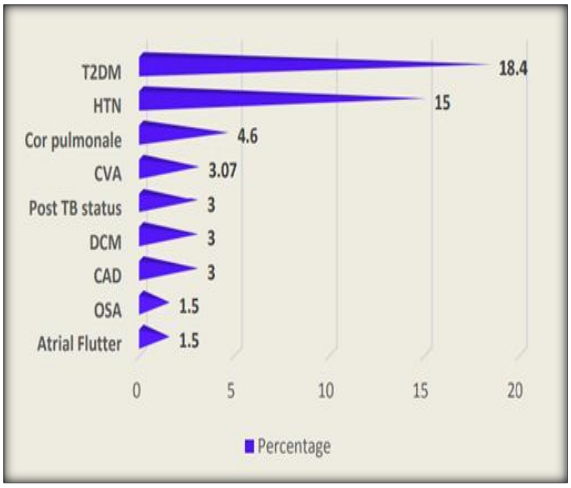
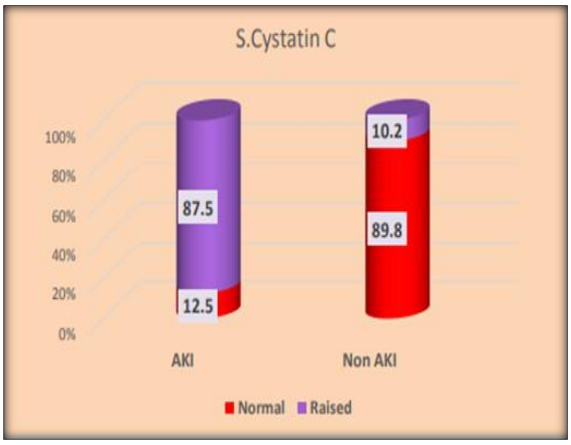


Figure 3: Prevalence of Comorbidities

Bar graph showing the frequency of comorbidities (T2DM, HTN, Cor Pulmonale, etc.) among the study population



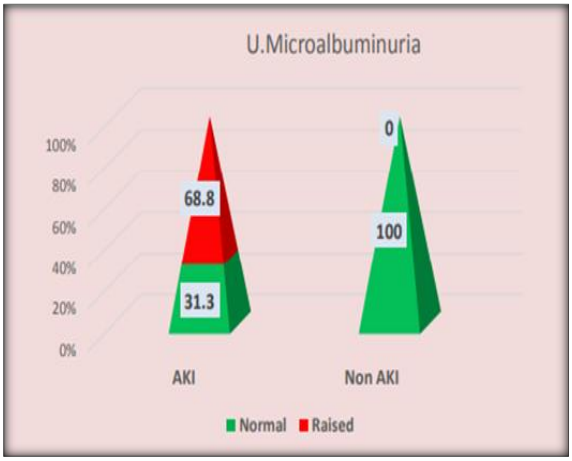
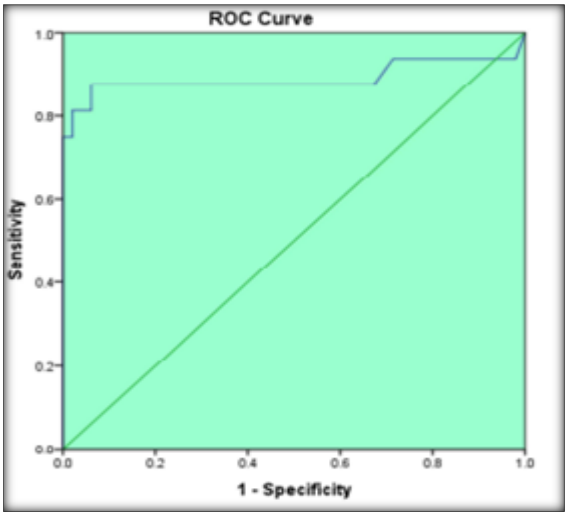
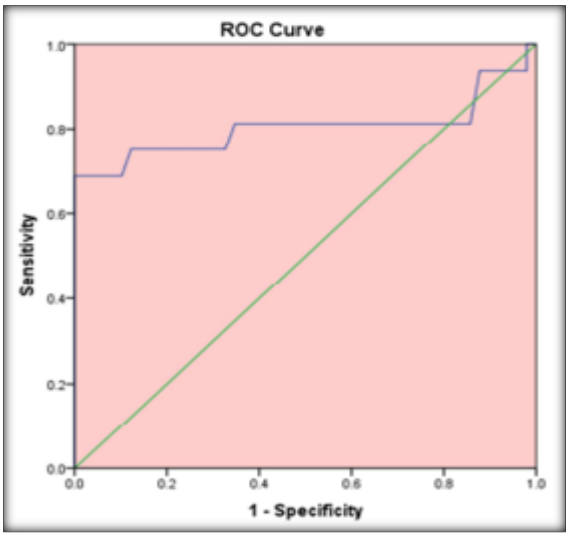


Figure 4: Comparison of Serum Cystatin C and Urinary Microalbumin Between AKI and Non-AKI Groups

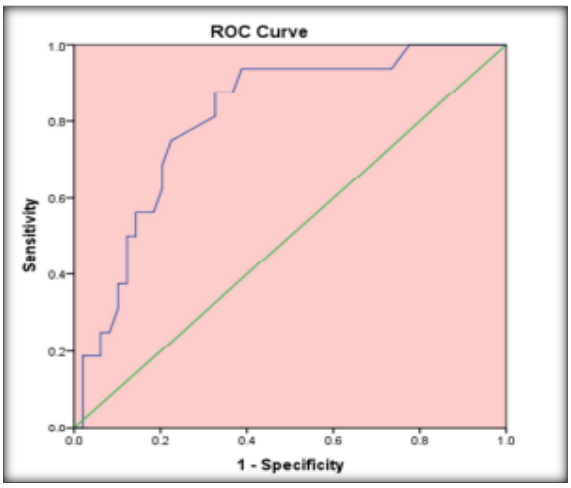
Bar graphs comparing median values of serum cystatin C and urinary microalbumin in AKI vs. Non-AKI patients



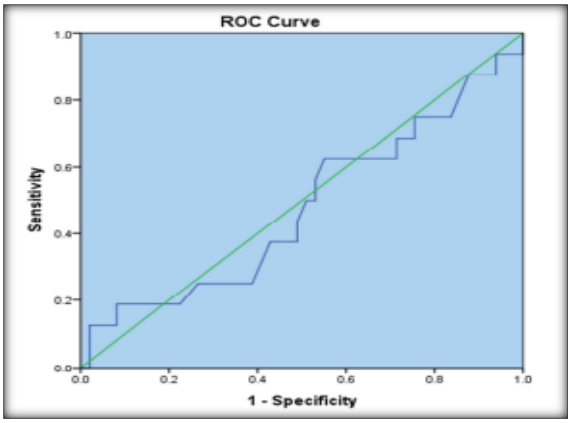
serum cystatin C



urinary microalbumin



serum urea



platelet count

Figure 5: ROC Curves for Biomarkers Predicting AKI

ROC curves for serum cystatin C, urinary microalbumin, serum urea, and platelet count, showing their diagnostic efficiency in predicting AKI.

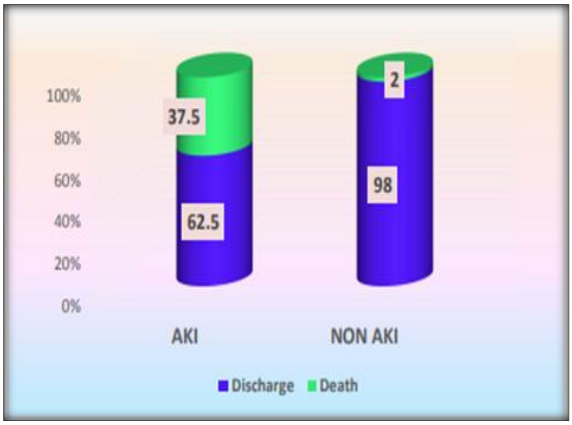


Figure 6: Outcomes in AKI vs. Non-AKI Patients

Bar graph comparing discharge and mortality rates between AKI and Non-AKI groups.

DISCUSSIONS

The prevalence and burden of chronic obstructive pulmonary disease (COPD) are projected to rise in the coming decades due to a combination of continued exposure to risk factors such as smoking and air pollution, as well as the aging global population. Globally, the prevalence of COPD is estimated at 10.3% (95% CI: 8.2–12.8%). Acute exacerbation of COPD (AECOPD) is a critical event characterized by worsening dyspnea, increased sputum production, and systemic inflammation, often triggered by infections, pollution, or other airway insults. COPD is frequently accompanied by comorbidities, including heart failure, hypertension, diabetes, and metabolic syndrome, which significantly impact prognosis. However, renal comorbidities in COPD have been relatively understudied, despite their potential to influence outcomes. The role of noxious gases, such as cigarette smoke, in COPD pathogenesis is well-established. Nicotine and other toxins activate the sympathetic nervous system, exacerbate endothelial dysfunction, and contribute to oxidative stress and hypoxia, all of which can worsen renal function. Given the higher prevalence of chronic kidney disease (CKD) in COPD patients and the increased risk of acute kidney injury (AKI) in individuals with CKD, it is plausible that AKI rates are elevated in COPD patients compared to the general population. This study aimed to evaluate the potential of two biomarkers—serum cystatin C and urinary microalbumin—for predicting AKI in patients with AECOPD admitted to a respiratory intensive care unit (RICU) in a tertiary care hospital in eastern Odisha.[7-8]

The study included 65 patients with AECOPD, with a mean age of 67.5 years (±9.38 years). The majority of patients were in the 70–80-year age group (33.8%), followed by the 50–60-year (32.3%) and 60–70-year (27.6%) groups. Only 6.1% of patients were above 80 years of age. The male-to-female ratio was approximately 3:1, with 75.4% males and 24.6% females, consistent with previous studies. The mean body mass index (BMI) was 21.67 kg/m² (±4.30), with 44.6% of patients having a normal BMI, 23.1% underweight, 21.5% in obese class I, 7.7% overweight, and 3.1% in obese class II. Comorbidities were prevalent, with type 2 diabetes mellitus (18.7%) and systemic hypertension (15.4%) being the most common. Other comorbidities included cor pulmonale (4.6%), coronary artery disease (3.0%), cerebrovascular accidents (3.0%), and post-tuberculosis status (3.0%). Notably, 50.7% of patients had no comorbidities. Exposure history revealed that 32.3% were smokers, and 15.4% had biomass fuel exposure, while 52.4% had no significant exposure history.[9-10].

The prevalence of AKI in this cohort was 24.6%, consistent with findings from other studies. For instance, Barakat et al. reported an AKI incidence of 128 per 100,000 person-years in COPD patients, while C Cao et al. found an AKI prevalence of 21.3% in AECOPD patients. Similarly, studies by Incalzi et al. and Chen et al. reported AKI prevalence rates of 20.8% and 7.6%, respectively. These variations may be attributed to differences in study populations, diagnostic criteria, and regional factors. In this study, laboratory parameters were compared between AKI and non-AKI groups. Hemoglobin levels did not differ significantly between the two groups, with median values of 9.7 g/dL (IQR: 1.95) in the AKI group and 10.4 g/dL (IQR: 1.9) in the non-AKI group ($p = 0.077$). However, total leukocyte counts were significantly higher in the AKI group (median: 15, IQR: 4.33) compared to the non-AKI group (median: 10, IQR: 2.74; $p < 0.001$). Platelet counts and neutrophil ratios did not show significant differences between the groups. Renal function tests revealed significantly higher serum urea levels in the AKI group (median: 61 mg/dL, IQR: 41.3) compared to the non-AKI group (median: 40 mg/dL, IQR: 18; p

< 0.001). Serum creatinine levels were also higher in the AKI group (median: 1.1 mg/dL, IQR: 0.7) than in the non-AKI group (median: 0.8 mg/dL, IQR: 0.9), but this difference was not statistically significant (p = 0.234). Serum electrolytes showed no significant differences in sodium levels, but potassium levels were higher in the AKI group (median: 4.1 mEq/dL, IQR: 0.8) compared to the non-AKI group (median: 3.5 mEq/dL, IQR: 0.9; p = 0.030). Inflammatory markers, including C-reactive protein (CRP) and procalcitonin, were significantly elevated in the AKI group, with median CRP levels of 107.86 mg/L (IQR: 61.2) versus 56.2 mg/L (IQR: 53.4) in the non-AKI group (p = 0.003), and median procalcitonin levels of 0.93 ng/mL (IQR: 1.09) versus 0.23 ng/mL (IQR: 0.4) in the non-AKI group (p < 0.001).[11-12]

The diagnostic accuracy of serum cystatin C and urinary microalbumin for predicting AKI was assessed in the study. The serum cystatin C level was found to be significantly elevated in the AKI group (median: 1.18 ng/uL, IQR: 0.37) compared to the non-AKI group (median: 0.75 ng/uL, IQR: 0.24; p < 0.001). Receiver operating characteristic (ROC) curve analysis showed an area under the curve (AUC) of 0.890 (95% CI: 0.751–1.0), with 87.5% sensitivity and 93.9% specificity at a cutoff value of 1 ng/uL for serum cystatin C. These results are consistent with earlier studies reported by Chen et al. and Soto et al., with AUC values of 0.803 and 0.86, respectively, for serum cystatin C to predict AKI. Likewise, the urinary microalbumin level was found to be significantly elevated in the AKI group (median: 30.8 mg/L, IQR: 13.33) compared to the non-AKI group (median: 15.03 mg/L, IQR: 10.25; p < 0.001). ROC analysis for urinary microalbumin found an AUC of 0.802 (95% CI: 0.629–0.976) with a sensitivity of 68.8% and specificity of 100% at a cutoff value of 29.74 mg/L. These results are consistent with reports by Zhang et al. and Yin et al., which presented urinary microalbumin and albumin-to-creatinine ratio (ACR) as predictors of AKI.[13-14]

The consequences of AKI in this group were alarming. Hemodialysis was needed in 4.6% of patients, with 18.8% of AKI patients requiring renal replacement therapy (RRT) versus none in the non-AKI group (p = 0.002). Mechanical ventilation was needed more often in AKI patients, with 68.8% needing invasive ventilation versus 24.5% in the non-AKI group (p < 0.001). Mortality was substantially higher in the AKI group (37.5%) compared to the non-AKI group (2%; p < 0.001). These results are in line with research conducted by Xin Wan et al. and Barakat et al., where higher mortality and greater necessity for mechanical ventilation and RRT were reported among AKI patients.[15]

In summary, this study reiterates the high incidence of AKI among AECOPD patients and the predictive role of serum cystatin C and urinary microalbumin as early biomarkers for AKI. The differences in inflammatory markers, renal function tests, and clinical outcomes between AKI and non-AKI groups are significant and further support the attention needed for early detection and intervention to enhance prognosis. These results are in accordance with global evidence, further supporting the integration of renal function monitoring into AECOPD patient care. Future research is needed to confirm these biomarkers and investigate their role in informing therapeutic approaches to minimize morbidity and mortality among this vulnerable population.

CONCLUSION

This study highlights the very high incidence of acute kidney injury (AKI) among patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and the contribution of AKI to clinical outcomes, including increased needs for invasive mechanical ventilation, dialysis, and death. Given the limitation of serum creatinine in early detection of AKI, this study highlights the contribution of new biomarkers such as serum Cystatin C and urinary microalbumin in the assessment. The study indicates that serum Cystatin C, with a cutoff of 1 ng/µL, is highly sensitive and specific (87.5% and 93.9%, respectively) for AKI prediction, and urinary microalbumin, with a cutoff of 29.74 mg/dL, also possesses high predictive accuracy (sensitivity 68.8% and specificity 100%). The findings suggest that these biomarkers, if incorporated into routine clinical practice, may enable early diagnosis and early intervention for AKI among patients with AECOPD, thereby improving prognosis and avoiding complications. However, because this was a single-center study with a small sample size, further multicentric studies with larger populations are needed to validate these findings and explore other biomarkers for the improvement of AKI prediction and care among this group of patients.

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