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Evaluation of Cystatin C Role as a Predictor of Acute Kidney Injury in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) had a prevalence of acute kidney injury (AKI) between 1.9% and 21.3%. It has been suggested that serum protein cystatin C (Cys C) can be used as a marker for the early detection of AKI.

Objective: This study aimed to assess the role of cystatin C in prediction of acute kidney injury in patients with chronic obstructive pulmonary disease (COPD).

Patients and methods: The study was conducted on 150 subjects divided into three groups: Group (1) included fifty patients with an AECOPD, group (2) included fifty patients with stable COPD without exacerbation and group (3) included fifty subjects as control subjects who were recruited from the general population and matched for age and sex. All participants were subjected to full history taking, clinical assessment and laboratory investigations. Serum creatinine at admission and after 48 hours was estimated. Pulmonary function test (PFT) was performed using a spirometry. Serum Cys C levels was measured for all subjects.

Results: There was a high statistically significant (p-value < 0.001) increase of Cys C level in AECOPD group (median = 0.95, IQR = 0.86 – 1) when compared to stable COPD group (median = 0.7, IQR = 0.64 – 0.79) and control group (median = 0.6, IQR = 0.58– 0.61). Serum Cys C can be used to discriminate between AECOPD group and stable COPD group at a cutoff level of > 0.79, with 96% sensitivity, 88% specificity, 88.9% PPV and 95.7% NPV (AUC = 0.97 & p-value < 0.001).

Conclusion: Patients with AECOPD who had serum cystatin C level more than 0.79 are thought to have a higher risk of developing HA-AKI. Serum Cystatin C level is negatively correlated with FEV1 and FEV1/FVC. We recommend using of serum Cystatin C for prediction of AKI in COPD patients.

Keywords: Cystatin C, AKI, Chronic obstructive pulmonary disease.

INTRODUCTION

Airflow limitation brought on by anomalies in the airways and/or lungs is what defines COPD, a widespread, preventable, and curable illness caused by prolonged contact with harmful particles or gases and affected by host variables including immature lungs [1].

The prevalence of AKI is rising globally, and it frequently leads to the progression of chronic kidney disease (CKD) and, eventually, end-stage renal failure [2]. AKI affects between 1.9 and 21.3% of patients diagnosed with AECOPD [3].

Cystatin C (Cys C) is the most significant endogenous cysteine protease inhibitor. Cys C regulates the production or leakage of proteases from lysosomes by forming complexes with cathepsins in dying or ill cells [4]. Patients with emphysema, inflammatory lung disease, and chronic renal disease all had elevated Cys C levels [5]. For the early detection of AKI, serum cystatin C shows great promise as a marker [6]. Our study's primary objective was to evaluate cystatin C's utility for predicting acute kidney damage in COPD patients.

PATIENTS AND METHODS

This research was performed at Chest Diseases Department, Al-Azhar Assiut University Hospital in the period from January 2021 to October 2021 to assess if COPD patients who had elevated serum cystatin C (Cys C) levels at admission who were more likely to have AKI. We aimed to determine the correlation between Cys C levels and pulmonary function test (PFT). The study was performed on 150 subjects 96 males and 54 females above age of 40 who were divided into three groups:

- **Group (1):** included fifty patients with an acute exacerbation of COPD (AECOPD).
- **Group (2):** included fifty patients with stable COPD without exacerbation.
- **Group (3):** included fifty age- and sex-matched healthy individuals worked as a control group.

COPD exacerbation is diagnosed by an acute worsening of respiratory symptoms that need further medication [1]. AKI was recognised by a rise in SCr: increase in SCr ≥ 0.3 mg/dL within 48 hours, according to Kidney Disease Improving Global Outcomes (KDIGO) recommendations [7].

Exclusion criteria: Patients with cystic fibrosis-associated acute renal injury, history of CKD and dialysis treatment prior to admission, or urinary tract infection were not included.

Complete history collection, clinical examination, and laboratory investigation were performed for all individuals (including CBC, serum albumin, serum sodium, serum creatinine, estimated GFR, serum total bilirubin and international normalized

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ratio (INR)). Serum creatinine at admission and after 48 hours was measured. Subjects' serum levels of cystatin C were tested.

Spirometry was used for the pulmonary function test (PFT). All spirometry tests were performed in compliance with the European Respiratory Society (ERS) standards [8].

Ethical approval: The Ethical Committee of Al-Azhar Assiut Faculty of Medicine approved this study and permitted us to review patients' medical data. All eligible participants were informed about study's objectives, methodology, and possible side effects. Each subject provided written informed permission before being included in the research. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

SPSS version 25 (IBM, Armonk, NY, USA) was used to tabulate and analyse the data gathered. To analyze the differences between the groups, we utilized the Chi-square and Kruskall-Wallis tests. Sensitivity (capability for detecting the true positive cases with minimal false negatives), Specificity (capability for detecting the true negative cases with minimal false positives), and PPV (positive predictive value) (probability that a person with a test result of positive has the condition) were used to determine the validity of point of care US.

To determine the correlation between two quantitative factors within the same group, Spearman correlation coefficients were employed. The confidence interval was set at 95%, while the allowed margin of error was set at 5%. P values ≤ 0.05 were considered significant.

RESULTS

There were 150 patients in all that participated in this trial, and statistically significant (p-value = 0.002) increased age in AECOPD group (median = 66.5, IQR = 57 – 72 years) when compared to stable COPD group (median = 60, IQR = 57 – 64 years) and control group (median = 59, IQR = 55 – 66 years). With regards to sex, the groups did not differ significantly from one another (Table 1).

Table (1): Comparisons of the studied groups' demographic information

		Groups						Stat. test	P-value
		AECOPD (n = 50)		StableCOPD (n = 50)		Control (n = 50)			
Sex	**Male**	32	64%	34	68%	30	60%	X^2 = 0.69	0.707 NS
	Female	18	36%	16	32%	20	40%		
Age (years)	**Median**	66.5		60		59		KW = 12.9	**0.002 S**
	IQR	57 – 72		57 - 64		55 - 66			

NS: p-value > 0.05 is considered nonsignificant.S: p-value < 0.05 is considered significant.

The results showed a statistically significant (p-value = 0.002) increased percentage of AKI in AECOPD group (6 patients; 12%) as compared to stable COPD group and control group (Table 2).

Table (2): Comparisons of the study groups' AKI

		Groups						Stat. test	P-value
		AECOPD (n = 50)		StableCOPD (n = 50)		Control (n = 50)			
AKI	**No**	44	88%	50	100%	50	100%	**X^2 =12.5**	**0.002 S**
	Yes	6	12%	0	0%	0	0%		

S: p-value < 0.05 is considered significant.

The results showed a statistically significant (p-value < 0.001) increased Cys C level in AECOPD group (median = 0.95, IQR = 0.86 – 1) when compared to stable COPD group (median = 0.7, IQR = 0.64 – 0.79) and control group (median = 0.6, IQR = 0.58– 0.61) (Table 3).

Table (3): Comparisons of the study groups' cystatin C levels

		Groups			Stat. test	P-value
		AECOPD (n = 50)	StableCOPD (n = 50)	Control (n = 50)		
Cystatin C	**Median**	0.95	0.7	0.6	KW = 112.8	**< 0.001 HS**
	IQR	0.86 – 1	0.64 - 0.79	0.58 - 0.61		

HS: p-value < 0.001 is considered highly significant.

The levels of albumin and TLC varied significantly amongst the groups (p <0.001). There was no statistically significant variation in the baseline and 48-hours S. creatinine, T. bilirubin, INR, Hb, PLTs, eGFR, and Na levels between the groups (Table 4).

Table (4): Comparisons of study groups in terms of additional laboratory results

		Groups			Stat. test	P-value
		AECOPD (n = 50)	StableCOPD (n = 50)	Control (n = 50)		
Basal S.creatinine (mg/dl)	**Median**	0.85	0.9	0.95	KW = 4.26	0.119 NS
	IQR	0.7 - 1.1	0.7 – 1	0.8 - 1.1		
S.creatinine after 48 hour (mg/dl)	**Median**	0.9	0.9	0.95	KW =3.76	0.152 NS
	IQR	0.77 - 1.1	0.7 – 1	0.8 - 1.1		
Albumin (g/dl)	**Median**	3.3	3.7	3.95	KW = 28.8	**< 0.001 HS**
	IQR	2.9 - 3.8	3.5 - 3.8	3.6 - 4.1		
T. Bilirubin (mg/dl)	**Median**	0.58	0.6	0.75	KW = 3.2	0.2 NS
	IQR	0.4 - 0.8	0.47 -0.73	0.6 - 0.9		
INR	**Median**	1	1.1	1	KW = 1.73	0.419 NS
	IQR	1 – 1	1 - 1.2	1 - 1		
Hb (g/dl)	**Median**	12.8	13.3	13.2	KW = 0.58	0.748 NS
	IQR	12 - 14.2	12 - 15	12 - 14		
PLTs (x10³/ul)	**Median**	295	300	225	KW = 4.15	0.125 NS
	IQR	186.8 - 350	252.3 -350	200 - 316		
TLC (x10³/ul)	**Median**	12	7.5	7.45	KW = 28.9	**<0.001 HS**
	IQR	7.9 - 15	6.5 - 10.2	6.4 - 8.4		
eGFR	**Median**	82	81.5	85	KW = 5.03	0.081 NS
	IQR	65 - 94	76.3 -98.8	53 - 96		
Na	**Median**	140	140	138.5	KW = 4.7	0.094 NS
	IQR	138 - 141	138 - 140	137 - 140		

Median and IQR: Non-parametric test.
NS: p-value > 0.05 is considered non-significant.
S: p-value < 0.05 is considered significant.
HS: p-value < 0.001 is considered highly significant.
The results showed a statistically significant (p-value < 0.001) decreased FEV1 in AECOPD group (median = 49, IQR = 43 – 56) as compared to stable COPD group (median = 62, IQR = 59.8 – 66) and control group (median = 84.5, IQR = 80 – 91). Also, there was a high statistically significant (p-value < 0.001) decrease of FEV1/FVC in AECOPD group (median = 44, IQR = 39 – 48) as compared to stable COPD group (median = 48, IQR = 45 – 51) and control group (median = 87.5, IQR = 86 – 89) (Table 5).

Table (5): FEV1 and FEV1/FVC comparisons between study groups

		Groups			Stat.test	P-value
		AECOPD (n = 50)	Stable COPD (n = 50)	Control (n = 50)		
FEV1	**Median**	49	62	84.5	KW =120.5	**< 0.001 HS**
	IQR	43 – 56	59.8 - 66	80 - 91		
FEV1/FVC	**Median**	44	48	87.5	KW =106.07	**< 0.001 HS**
	IQR	39 – 48	45 - 51	86 - 89		

A negative correlation (r = -0.41) between serum Cys C and FEV1 was found to be statistically significant (p = 0.003), while a very significant (p 0.001) negative correlation (r = -0.58) was found between serum Cys C and FEV1/FVC. Using ROC curve, it was shown that serum Cys C can be used to differentiate between AECOPD group and stable COPD group at a cutoff level of > 0.79, with 88% specificity, 96% sensitivity, 95.7% NPV and 88.9% PPV (AUC = 0.97 & p-value < 0.001) (Table 6).

Table (6): Serum Cys C diagnostic performance in differentiating between AECOPD and stable COPD groups

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
Cys C	**> 0.79**	**0.97**	**96%**	**88%**	**88.9%**	**95.7%**	**< 0.001**

PPV: positive predictive value NPV: negative predictive value. AUC: Area under curve

DISCUSSION

Poor prognosis, including in-hospital mortality, and high clinical burden, are linked to severe acute kidney injury. There is evidence from prior research that AKI raises the risk of death while hospitalized for individuals with AECOPD [9].

Our first objective was to determine whether blood cystatin C (Cys C) on admission in individuals with COPD is a useful predictor of AKI severity.

We observed highly statistical significant (p-value < 0.001) decrease of serum albumin in AECOPD group (median = 3.3, IQR = 2.9 – 3.8 g/dl) when compared to stable COPD group (median = 3.7, IQR = 3.5 – 3.8 g/dl) and control group (median = 3.95, IQR = 3.6 – 4.1 g/dl). In a recent meta-analysis by **Zinellu *et al.*** [10] 26 studies were found, with a total of 2554 COPD patients and 2055 control subjects. Patients with stable COPD had considerably decreased blood albumin concentrations compared to non-COPD controls, according to a recent systematic review and meta-analysis. This provides more evidence that people with COPD have a weakened anti-inflammatory and antioxidant defense system. Hospitalization duration for COPD patients during acute exacerbations, abrupt respiratory failure, and death have all been shown to be correlated with hypoalbuminemia [11].

Results of current study showed that the prevalence of AKI among AECOPD group was 12% (6/50). Results obtained in this study are in agreement with **Wang *et al.*** [9] who evaluated 4898 patients hospitalized for acute exacerbated COPD. Of these people, 349 (12.0%) had AKI obtained in the hospital, whereas 205 (7.1%) had CA-AKI. Percentage of occurrences of CA- and Hospital acquired-acute kidney injury (HA-AKI) were 7.1 and 12.0%, respectively. Adult inpatients with AECOPD were surveyed retrospectively by **Cao *et al.*** [12]. They were 1,768 people; of those, 280 were found to have CA-AKI and another 97 to have HA-AKI. There was 15.8% prevalence of CA-AKI and 5.5% prevalence of HA-AKI.

With the help of the Healthcare Inpatient Database from seven different locations throughout the United States, we were able to analyse huge amounts of population-based data. **Hirayama *et al.*** [13] conducted a retrospective cohort research. Hospitalized AECOPD patients were 356,990. Age at median was 71, and men made up 41.9% of the population. Acute kidney injury was also diagnosed in 24,833 (7.0%) of these people. These diverse sample sizes and study designs may account for the substantial variances across these studies, or ethnic variations. This may be related to the underlying causes and comorbidities as CKD, nephrotoxic drugs and DM. A possible explanation for this might be a lack of adequate interventions and health care.

This study showed highly statistically significant (p-value < 0.001) increase of serum Cys C in AECOPD group (median = 0.95, IQR = 0.86 – 1) when compared to stable COPD group (median = 0.7, IQR = 0.64 – 0.79) and control group (median = 0.6, IQR = 0.58 – 0.61). We found that Cys C to be a sensitive predictor of AKI in patients with AECOPD. Results obtained in this study are in agreement with **Chen *et al.*** [2] who conducted a retrospective study that involved data of 1035 patients with AECOPD. Patients' mean age at admission was 76.5 years (SD = 9.2), and 77% of them were men. Seventy-nine individuals (7.6%), were diagnosed with HA-AKI. They discovered that in those with AECOPD, Cystatin C was a potent independent predictor of AKI (CI 2.49-10.95 OR 5.22; 95%; p< 0.001). Similarly, thirty prospective cohort studies were included in the meta-analysis by **Yong *et al.*** [14] (including 4247 individuals across 15 countries, with 982 cases of acute kidney injury) to assure the serum cystatin C's overall diagnostic efficacy for AKI. According to this comprehensive research, serum Cys C has a good diagnostic sensitivity for detecting AKI of any aetiology. In addition, according to a research by **Zhang *et al.*** [15] who evaluated serum and/or urine Cys C for AKI diagnosis, serum Cys C proved to be a superior biomarker.

This study results showed a negative correlation (r = -0.41) between serum Cys C and FEV1 a statistically meaningful result was discovered (p = 0.003), while a very significant (p 0.001) negative correlation (r = -0.58) was found between serum Cys C and FEV1/FVC. Our findings are consistent with those of **Chai *et al.*** [16] who performed an extensive search of the literature on the subject of Cys C's function in COPD scouring databases (Data from 15 trials, for a total of 4079 COPD patients and 5949 controls were included in this meta-analysis).

Our investigation was constrained by the small sample size and brief follow-up time. Future research is required to validate the findings.

CONCLUSION

Serum Cystatin C at a cutoff level of > 0.79 is biomarker candidate for AKI prediction in patients with AECOPD. Serum Cystatin C level is negatively correlated with FEV1 and FEV1/FVC. We recommend using of serum Cystatin C for prediction of AKI in COPD patients.

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