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Role Of Cystatin C In Prediction Acute Kidney Injury Among Patients With Chronic Obstructive Pulmonary Disease

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Abstract

Background: complicated chronic obstructive pulmonary disease patients who had acute exacerbation been in a great risk for developing acute kidney injury (AKI). it ranges between 1.9% and 21.3%. It has been submitted that serum protein cystatin C (Cys C) can be used as a indicator for the initial 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). Materials: The study was conducted on 150 subjects distributed into three groups: Group (1) comprised fifty patients with an AECOPD, group (2) involved fifty patients with stable COPD without exacerbation and group (3) encompassed fifty subjects as control subjects who were employed from the general population and harmonized for age and sex. All participants were exposed to full history taking, clinical assessment and laboratory investigations. Serum creatinine at admission and after 48 hours was assessed. Pulmonary function test (PFT) was implemented 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 acute exacerbation chronic obstructive pulmonary disease (AECOPD) who had serum cystatin C level more than 0.79 are supposed to have a higher risk of developing HA-AKI. Serum Cystatin C level is

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negatively correlated with FEV1 and FEV1/FVC. We recommend using of serum Cystatin C for prediction of AKI among COPD patients.

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

INTRODUCTION

A common, avoidable, and treatable illness brought on by continuous exposure to hazardous particles or gases and influenced by host characteristics such as immature lungs, chronic obstructive pulmonary disease (COPD) is defined as airflow limitation caused by anomalies in the airways and/or lungs. [1].Globally, the prevalence of AKI is increasing, and it often accelerates the development of end-stage renal failure and chronic kidney disease (CKD) [2]. Between 1.9 and 21.3% of individuals with AECOPD also have AKI.

The most important endogenous inhibitor of cysteine protease is cystatin C, or Cys C. Cys C interacts with cathepsins in sick or dying cells to create complexes that control the release or synthesis of proteases from lysosomes [4]. Cys C levels were higher in patients with inflammatory lung illness, chronic renal disease, and emphysema [5]. Serum cystatin C is a marker that holds significant potential for the early identification of AKI [6]. The main goal of our study was to assess the predictive value of cystatin C for acute kidney injury in patients with COPD.

PATIENTS AND METHODS

This research was performed at Chest Diseases Department, Makkah Hospital, Saudi Arabia in theperiod from January 2022 to October 2022 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 define the correlation between Cys C levels and pulmonary function test (PFT). The study was completed 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 worseningof 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, estimatedGFR, serum total bilirubin and international normalized ratio (INR)). Serum creatinine at admission and after 48hours 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 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 utilizedthe 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 decide the correlation between two quantitative factors within the same group, Spearman correlation coefficients were hired. The confidenceinterval 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).

		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
	Female	18	36%	16	32%	20	40%		NS
Age (years)	Median	66.5		60		59		KW =	0.002
	IQR	57 – 72		57 - 64		55 - 66		12.9	S

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

		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%		

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).

		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		

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).

		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 ($x10^3$/ul)	Median	295	300	225	KW =4.15	0.125 NS
	IQR	186.8 - 350	252.3 -350	200 - 316		
TLC ($x10^3$/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		

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).

		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).

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

DISCUSSION

Severe acute kidney injury is associated with a poor prognosis, which includes substantial clinical burden and in-hospital mortality. Previous studies have demonstrated that AKI increases the likelihood of hospital death for those with AECOPD. [9].

Our initial goal was to ascertain whether blood cystatin C (Cys C) levels at admission in COPD patients are a reliable indicator of the severity of AKI. 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 tostable 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). The study's findings concur with those of Wang et al. [9], who assessed 4898 hospitalized patients with acutely worsened COPD. Of thesepeople, 349 (12.0%) had AKI obtained in the hospital, whereas 205 (7.1%) had CA-AKI. Percentage ofoccurrences of CA-

and Hospital acquired-acute kidneyinjury (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.

We were able to analyze a significant amount of population-based data with the assistance of the Healthcare Inpatient Database from seven distinct locations nationally. Hirayama and colleagues [13] have out a retrospective cohort study. Hospitalized AECOPD patients were 356,990. Age at median was 71, and menmade 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 mayaccount for the substantial variances across these studies, or ethnic variations. This may be related to theunderlying causes and comorbidities as CKD, nephrotoxic drugs and DM. A possible explanation forthis might be a lack of adequate interventions and healthcare.

This study showed highly statistically significant (p-value < 0.001) increase of serum Cys C in AECOPDgroup (median = 0.95, IQR = 0.86 – 1) when comparedto 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 themwere men. Seventy-nine individuals (7.6%), were diagnosed with HA-AKI. They discovered that in thosewith 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 wereincluded 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 ofany aetiology. Furthermore, a study by Zhang et al. [15] that assessed serum and/or urine Cys C for the diagnosis of AKI found that serum Cys C was a better biomarker.

This study results showed a negative correlation (r= -0.41) between serum Cys C and FEV1 a statisticallymeaningful 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 scouringdatabases (Data from 15 trials, for a total of 4079 COPDpatients and 5949 controls were included in this meta- analysis).

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 recommendusing of serum Cystatin C for prediction of AKI in COPD patients.

References

1. Halpin D, Criner G, Papi A et al. (2021): Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD science committee report on COVID-19 and chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine, 203 (1): 24-36.

2. Chen D, Cao C, Jiang L et al. (2020): Serum cystatin C: A potential predictor for hospital-acquired acute kidney injury in patients with acute exacerbation of COPD. Chronic Respiratory Disease, 17: 1479973120940677. doi: 10.1177/1479973120940677.

3. Barakat M, McDonald H, Collier T et al. (2015): Acute kidney injury in stable COPD and at exacerbation. International Journal of Chronic Obstructive Pulmonary Disease, 10: 2067-77.

4. Xiao D, Liu H, Zhang H et al. (2012): Impact of cystatin C levels on infarct size and hemorrhage volume in acute cerebral stroke. Journal of Neurology, 259 (10): 2053-9.

5. Rokadia H, Agarwal S (2012): Serum cystatin C and emphysema: results from the National Health and Nutrition Examination Survey (NHANES). Lung, 190 (3): 283-90.

6. Vestbo J, Hurd S, Agustí A et al. (2013): Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American Journal of Respiratory and Critical Care Medicine, 187 (4): 347-65.

7. Kellum J, Sileanu F, Murugan R et al. (2015): Classifying AKI by urine output versus serum creatinine level. Journal of the American Society of Nephrology, 26 (9): 2231-8.

8. Nici L, Donner C, Wouters E et al. (2006): American thoracic society/European respiratory society statement on pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine, 173 (12): 1390- 413.

9. Wang X, Xie Z, Xiong S et al. (2020): Acute kidney injury in hospitalized patients with nonexacerbated chronic obstructive pulmonary disease. BMC Pulmonary Medicine, 20 (1): 1-8.

10. Zinellu E, Fois A, Sotgiu E et al. (2021): Serum albumin concentrations in stable chronic obstructive pulmonary disease: a systematic review and meta- analysis. Journal of Clinical Medicine, 10 (2): 269. doi: 10.3390/jcm10020269.

11. Wang Y, Stavem K, Dahl F et al. (2014): Factors associated with a prolonged length of stay after acute exacerbation of chronic obstructive pulmonary disease (AECOPD). International Journal of Chronic Obstructive Pulmonary Disease, 9: 99-105.

12. Cao C, Chen D, Li J et al. (2018): Community- acquired versus hospital-acquired acute kidney injury in patients with acute exacerbation of COPD requiring hospitalization in China. International Journal of Chronic Obstructive Pulmonary Disease, 13: 2183-90.

13. Hirayama A, Goto T, Hasegawa K (2020): Association of acute kidney injury with readmissions after hospitalization for acute exacerbation of chronic obstructive pulmonary disease: a population-based study. BMC Nephrology, 21 (1): 1-9.

14. Yong Z, Pei X, Zhu B et al. (2017): Predictive value of serum cystatin C for acute kidney injury in adults: a meta-analysis of prospective cohort trials. Scientific Reports, 7: 41012. doi: 10.1038/srep41012

15. Zhang Z, Lu B, Sheng X et al. (2011): Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. American Journal of Kidney Diseases, 58 (3): 356-65.

16. Chai L, Feng W, Zhai C et al. (2020): The association between cystatin C and COPD: a meta-analysis and systematic review. BMC Pulmonary Medicine, 20 (1): 182. doi: 10.1186/s12890-020-01208-5.