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Albumin, pH, $PaCO_2$ and Alveolar-Arterial Gradient Difference Can Predict 30-Day Mortality in COPD Exacerbation

Sema Avci[1]*, Gokhan Perincek[2]

[1]*Department of Emergency Medicine, Usak University Medical Faculty, Usak, Turkey*

[2]*Department of Pulmonology, Kars Harakani State Hospital, Kars, Turkey*

ABSTRACT

Introduction: Early treatment, prognosis and short-term mortality prediction of COPD exacerbation are substantial for physicians in the ED. To compare the A-a O_2 gradient (together with expected A-a O_2 gradient, A-a O2 gradient difference), inflammatory markers (CRP, CAR, procalcitonin, NLR, PLR), and arterial blood gas (pH, pCO2, lactate clearance) in predicting COPD exacerbation patients' 30-day mortality.

Methods: A questionnaire was designed for each patient, including detailed demographic profile, smoking status, comorbidities, vital signs, laboratory results and outcomes (discharge, hospitalization, ICU, 30-day mortality).

Results: 135 (60.3%) of the cases were male and 89 (39.7%) were female. Their ages ranged from 48 to 95 years, with an average of 72.22 ± 10.09. The LOS of cases varied between 1 and 28 days, with an average of 7.00 ± 3.83, ICU admission rate was 8% and the overall mortality rate was 5.4%. Albumin (AUC 0.81) and pH (AUC 0.68) showed the highest 30-day mortality prediction. While A-a O_2 gradient difference (AUC 0.68) showed the highest 30-day mortality prediction, expected A-a O_2 gradient (AUC 0.53) indicated a statistically lower 30-day mortality prediction. While $PaCO_2$ (AUC 0.71) showed the highest 30-day mortality prediction, lactate clearance (AUC 0.54) indicated a statistically lower mortality estimation.

Conclusion: Albumin is a strong predictor of 30-day mortality in COPD exacerbation patients in the ED. In addition, an arterial blood gas sampling measurement including pH, $PaCO_2$ and A-a O_2 gradient difference are simple, precise and practical measurements for estimating 30-day mortality in these patients.

Key words: Albumin, pH, PaCO2, Alveolar-arterial gradient, Chronic obstructive pulmonary disease

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Corresponding author: Sema Avci

e-mail✉: dnzlsema@gmail.com

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory progressive condition which causes serious morbidity and mortality, constitutes approximately 1.5 million emergency department (ED) visits and is the fourth cause of all deaths [1,2]. COPD exacerbation is defined as the acute worsening of respiratory symptoms including dyspnea, cough and purulent sputum, and periods of exacerbation are the most common causes of ED admissions, hospitalization and mortality in COPD patients.3 The increasing number of COPD exacerbations leads to decreased quality of life, increased COPD-related mortality rates and high healthcare costs [2,3]. Obviously, early treatment, prognosis and short-term mortality prediction are essential for physicians in the EDs.

Several laboratory results including well-known inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), c-reactive protein (CRP)/albumin ratio (CAR), procalcitonin and arterial blood gas analysis including (pH, $PaCO_2$, lactate clearance) have been used to predict severity, outcomes and short-long term mortality of patients with COPD exacerbation [4-8]. In addition to these laboratory parameters, the alveolar-arterial oxygen (A-a O2) gradient which is a measure of

difference between the alveolar and arterial concentration of oxygen, has also been used to evaluate the outcomes (mortality, length of stay, severity of the disease) of the patients with pneumonia and pulmonary embolism [9,10].

The aims of the study were to compare the A-a O2 gradient (together with expected A-a O_2 gradient, A-a O_2 gradient difference), inflammatory markers (CRP, CAR, procalcitonin, NLR, PLR) and arterial blood gas (pH, pCO_2, lactate clearance) in predicting COPD exacerbation patients' 30-day mortality in the ED.

MATERIALS AND METHODS

Study design and population

This prospective cross-sectional study was conducted with the approval of Kafkas University Medical Faculty Ethics Commitee between January and April 2020. The study included 224 (89 female, 135 male) patients with COPD exacerbation who admitted to ED, stages I-IV, for all patients. The diagnosis of COPD exacerbation was in accordance with the criteria established by Global Initiative for Chronic Obstructive Lung Disease 2019 [11]. Patients with a diagnosis of COPD, who were admitted to ED due to exacerbation and hospitalized were included in the study. A questionnaire was designed for each patient, including detailed demographic profile, smoking status, comorbidities, vital signs, laboratory results and outcomes (discharge, hospitalization, intensive care unit, 30-day mortality).

The laboratory findings were analyzed within 3 hours after admission to ED including arterial blood gas analysis, serum electrolytes, liver and kidney function tests, complete blood count, NLR, PLR, CRP, CAR, and procalcitonin.

Arterial blood gas samples were drawn from the radial artery in all patients while they were breathing room air to prevent any intervention caused by the maintenance of supplementary oxygen. Atmospheric pressure (mmHg), partial oxygen pressure (PaO2, mmHg), fraction of inspired oxygen (FiO2, 21% for room air), partial carbon dioxide pressure ($PaCO_2$, mmHg) and age (for expected A-a O2 gradient) were recorded for all patients and calculated with https://www.mdcalc.com/a-a-o2-gradient [12]. After calculation process, the A-a O2 gradient and expected A-a O2 gradient for age were obtained. A-a O2 difference was calculated as A-a O2 gradient-expected A-a O2 gradient. Daily atmospheric pressure (mmHg) changes of the region where the study was carried out were obtained from the Turkish State Meteorological Service. Lactate clearance of the patients was calculated as ([initial lactate – second lactate (6 hr later)] /initial lactate) × 100 [13]. After one-month follow up, 30-day mortality after ED admission was evaluated.

Statistical reviews

All statistical calculations were performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY. The continuous variables were expressed as mean ± standard deviation; categoric variables were defined as percentages (%). The normal distribution was determined by histogram and Kolmogorov-Smirnov test. Mean values of continuous variables were compared between the groups using Mann-Whitney U test. Prediction accuracy was assessed using the area under the receiver operating characteristic (ROC) curve. The results were evaluated as 95% confidence interval and p value <0.05, which was considered statistically significant.

RESULTS

Table 1 lists sociodemographic and clinical characteristic of the patients. Accordingly, 135 (60.3%) of the cases were male and 89 (39.7%) were female. Their ages ranged from 48 to 95 years, with an average of 72.22 ± 10.09. 104 (49.3%) of the cases were ex-smoker, 25 (11.8%) were current smoker and 81 (38.4%) were non-smoker. The respiratory rate of the patients ranged between 13 and 29 per minute with an average of 19.99 ± 1.90. The systolic blood pressure of cases varied between 50 and 160 mmHg, with an average of 120.01 ± 11.64. The fever of the cases ranged from 36 to 37.2oC, with an average of 36.41 ± 0.23. The LOS of cases varied between 1 and 28 days, with an average of 7.00 ± 3.83, (intensive care unit) ICU admission rate was 8% and the overall mortality rate was 5.4%. Coexisting diseases were not detected 43 (19.2%) of the patients and anyone was living in nursing home resident. The frequency of comorbidities seen

Table 1: Sociodemographic properties and clinical findings of the cases.

		n	%
Gender	Female	89	39.7
	Male	135	60.3
Monthly income	0-150 USD	99	45.8
	151-450 USD	102	47.2
	451-750 USD	13	6
	751-1100 USD	2	0.9
Oxygen concentrator	(+)	80	36.7
	(-)	138	63.3
Home nebulizer	(+)	122	56
	(-)	96	44
BiPAP machine	(+)	20	9.2
	(-)	198	90.8
Education status	Illiterate	113	52.3
	Primary School	82	38
	Middle School	9	4.2
	High School	6	2.8
	University	2	0.9
	Literate	4	1.9
Marital Status	Single	6	2.8
	Married	148	68.5
	Divorced	3	1.4
	Death of partner	59	27.3
Social condition	Living with family	197	93.4
	Alone	12	5.7
	Support of distant relative or neighbour	1	0.5
	Support of civil society organization	1	0.5
Place of residence	Village	137	64.3
	County	18	8.5
	City	58	27.2
Smoking status	Ex-smoker	104	49.3
	Current smoker	25	11.8
	Never smoker	81	38.4
	Passive smoker	1	0.5
COPD drugs	Short-acting beta agonists	1	0.6
	Inhaled corticosteroids	49	29.9
	Combination inhalers	114	69.5
Result of hospitalization	Discharge	215	96
	Death	9	4
Hospitalization unit	Respiratory medicine unit	206	92
	ICU	18	8

among the patients were: Hypertension (n=53), diabetes mellitus (n=31), congestive heart failure (n=19), asthma (n=8), hyperlipidemia (n=3), chronic liver disease (n=1), coronary artery disease (n=4), chronic renal disease (n=4).

Table 2 lists comparisons of vital signs and age with Mann Whitney U test between survivors and non-survivors. The mean age of the non-survivors was significantly higher than the survivors (z=-2.153; p=0.031). Oxygen saturation, respiratory rate and systolic blood pressure did not show significantly difference between two groups) (p>0.05).

Table 3 lists analysis of blood parameters with Mann Whitney U test between survivors and non-survivors. Blood urea nitrogen (BUN) (p=0.009) and creatinine (p=0.028) were significantly lower and hemoglobine (p=0.048) was higher in non-survivors.

Table 2: Comparison of oxygen saturation, respiration, fever, systolic blood pressure and age values by groups.

	Groups	Xsıra	Σ sira	U	z	p
Oxygen saturation	Deaths	68	680	625	-1.412	0.158
	Survivors	91.82	15610			
Respiratory rate	Deaths	117.14	1288.5	801.5	-1.192	0.233
	Survivors	96.86	17821.5			
Temperature	Deaths	100.59	1106.5	1016.5	-0.066	0.948
	Survivors	99.44	18594.5			
Systolic blood pressure	Deaths	109.09	1200	923	-0.599	0.549
	Survivors	98.94	18501			
Age	Deaths	145.54	1746.5	767.5	-2.153	0.031*
	Survivors	105.78	21473.5			

Table 3: Comparison of blood parameters between survivors and non-survivors.

	Groups	Xsıra	Σ sira	U	z	p
White blood cell	Non-survivors	107.58	21516.5	983.5	-1.049	0.294
	Survivors	88.46	1061.5			
Monocyte	Non-survivors	105.99	20986	1091	-0.475	0.635
	Survivors	97.42	1169			
Neutrophil	Non-survivors	106.24	21036.5	1040.5	-0.722	0.471
	Survivors	93.21	1118.5			
Lymphocyte	Non-survivors	108.5	21699.5	800.5	-1.936	0.053
	Survivors	73.21	878.5			
Eosinophil	Non-survivors	104.68	20727.5	1026.5	-0.792	0.428
	Survivors	118.96	1427.5			
Basophil	Non-survivors	106.59	21104.5	972.5	-1.072	0.284
	Survivors	87.54	1050.5			
Hemoglobine	Non-survivors	108.54	21707.5	792.5	-1.975	0.048
	Survivors	72.54	870.5			
Hematocrit	Non-survivors	108.04	21608	892	-1.492	0.136
	Survivors	80.83	970			
Platelet	Non-survivors	107.51	21502.5	997.5	-0.981	0.327
	Survivors	89.63	1075.5			
Red cell distribution width	Non-survivors	103.98	20691.5	791.5	-1.96	0.051
	Survivors	139.54	1674.5			
Glucose	Non-survivors	106.54	21308.5	1191.5	-0.041	0.967
	Survivors	105.79	1269.5			
BUN	Non-survivors	104.29	20963	662	-2.623	0.009
	Survivors	152.33	1828			
Creatinine	Non-survivors	105.74	21464.5	758.5	-2.195	0.028
	Survivors	146.29	1755.5			
Uric acid	Non-survivors	86.83	14413.5	552.5	-1.774	0.076
	Survivors	116.25	1162.5			
Phosphor	Non-survivors	83.84	13331	611	-0.187	0.851
	Survivors	87.13	697			
Aspartate amino transferase	Non-survivors	109.89	22307.5	834.5	-1.832	0.067
	Survivors	76.04	912.5			
Alanine aminotransaminase	Non-survivors	108.51	21919	806	-1.533	0.125
	Survivors	79.27	872			
Protein	Non-survivors	106.26	20826	832	-1.7	-0.089
	Survivors	75.83	910			
Calcium	Non-survivors	106.42	21178.5	910.5	-0.94	0.347
	Survivors	88.77	976.5			
Sodium	Non-survivors	105.38	21076	976	-1.09	0.276
	Survivors	125.17	1502			
Magnesium	Non-survivors	85.49	13763.5	565.5	-0.581	0.561
	Survivors	75.19	601.5			
Bicarbonate	Non-survivors	106.72	21451.5	1150.5	-0.268	0.789
	Survivors	111.63	1339.5			

Lactate (initial)	Non-survivors	107.27	21453	1047	-0.743	0.458
	Survivors	93.75	1125			
Lactate (second)	Non-survivors	106.64	21115	962	-1.107	0.268
	Survivors	86.67	1040			

Table 4: Investigation of measurements effective in estimating 30-day mortality.

	AUC	SE	95% CI
pH	0.684	0.1	0.487 to 0.881
$PaCO_2$	0.25	0.08	0.094 to 0.407
NLR	0.415	0.087	0.244 to 0.586
PLR	0.36	0.089	0.186 to 0.535
CRP	0.506	0.084	0.342 to 0.670
Albumin	0.811	0.061	0.692 to 0.929
CAR	0.484	0.085	0.317 to 0.652
Procalcitonin	0.37	0.087	0.199 to 0.541
A-a O2 gradient	0.364	0.109	0.149 to 0.578
A-a O2 gradient-expected	0.288	0.086	0.120 to 0.456
A-a O2 gradient difference	0.456	0.105	0.250 to 0.662
Lactate clearance	0.425	0.099	0.232 to 0.619

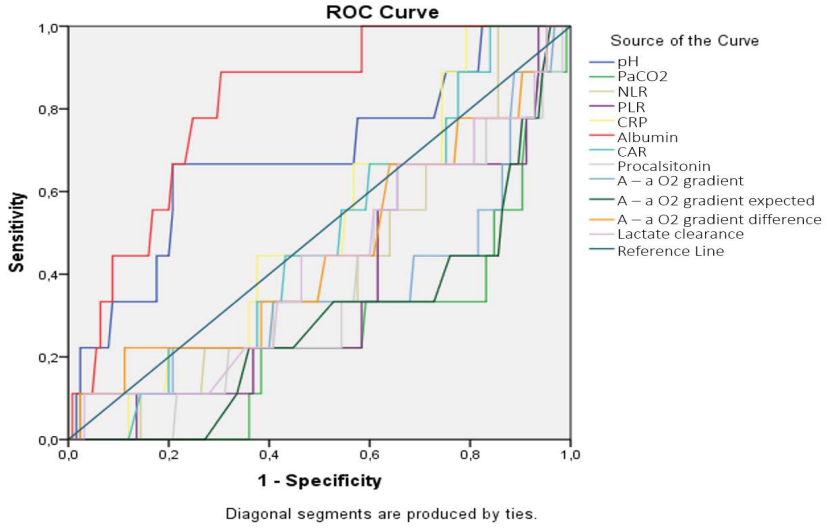

Figure 1: The ROC curves for prediction of 30-day mortality for pH, $PaCO_2$, NLR, PLR, CRP, albumin, CAR, procalcitonin, A-a O2 gradient, A-a O2 gradient-expected, A-a O2 gradient difference and lactate clearance.

Table 4 and Figure 1 demonstrate the accuracy of pH, pCO_2, NLR, PLR, CRP, albumin, CAR, procalcitonin, A-a O2 gradient, A-a O2 gradient-expected, A-a O2 gradient difference and lactate clearance in predicting 30-day mortality. Albumin (AUC 0.81, 95% CI: 0.69-0.92) and pH (AUC 0.68, 95% CI: 0.49-0.88) showed highest 30-day mortality prediction. pCO_2 (AUC 0.25, 95% CI: 0.09-0.41) and A-a O2 gradient-expected (AUC 0.29, 95% CI: 0.12-0.46) indicated statistically lower 30-day mortality prediction.

Table 5 and Figure 2 demonstrate the accuracy of A-a O2 gradient, expected A-a O_2 and A-a O_2 gradient difference in predicting 30-day mortality. While A-a O2 gradient difference (AUC 0.68, 95% CI: 0.62-0.75) showed highest 30-day mortality prediction, expected A-a O2 gradient (AUC 0.53, 95% CI: 0.46-0.60) indicated statistically lower 30-day mortality prediction.

Table 6 and Figure 3 demonstrate the accuracy of pH, $PaCO_2$ and lactate clearance in predicting 30-day mortality. While $PaCO_2$ (AUC 0.71, 95% CI: 0.64-0.77) showed the highest 30-day mortality prediction, lactate clearance (AUC 0.54, 95% CI: 0.47-0.61) indicated statistically lower mortality estimation.

Table 7 and Figure 4 demonstrate the accuracy of procalcitonine, CRP, CAR, albumin and NLR in predicting 30-day mortality. While albumin (AUC 0.81, 95% CI: 0.73-0.87) showed highest 30-day mortality prediction, CRP (AUC 0.51, 95% CI: 0.42-0.59) and CAR (AUC 0.52, 95% CI: 0.43-0.60) indicated statistically lower mortality estimation.

Table 5: Investigation of measurements effective in estimating 30-day mortality.

	AUC	SE	95% CI
A-a O2 gradient	0.598	0.102	0.528 to 0.664
A-a O2 gradient-expected	0.53	0.0956	0.460 to 0.598
A-a O2 gradient difference	0.684	0.0775	0.617 to 0.746

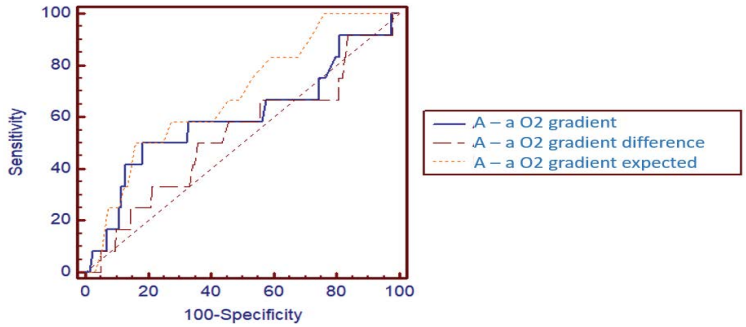

Figure 2: The ROC curves for prediction of 30-day mortality for A-a O_2 gradient, A-a O_2 gradient-expected and A-a O_2 gradient difference.

Table 6:Investigation of measurements effective in estimating 30-day mortality.

	AUC	SE	95 % CI
pH	0.658	0.102	0.590 to 0.721
$PaCO_2$	0.71	0.0874	0.644 to 0.770
Lactate clearance	0.54	0.0802	0.470 to 0.608

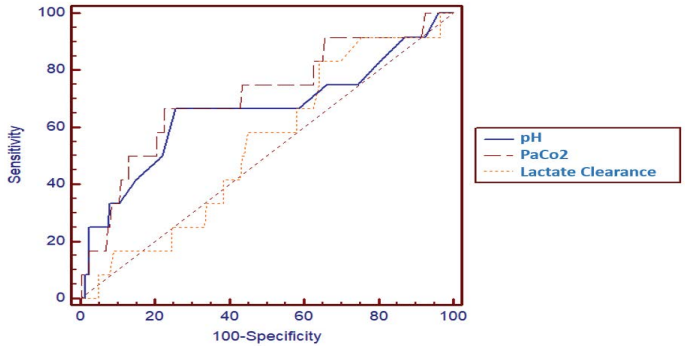

Figure 3. The ROC curves for prediction of 30-day mortality for pH, $PaCO_2$ and lactate clearance.

Table 7: Investigation of measurements effective in estimating 30-day mortality.

	AUC	SE	95% CI
Procalcitonin	0.63	0.0924	0.543 to 0.712
CRP	0.506	0.0876	0.418 to 0.593
CAR	0.516	0.0895	0.428 to 0.603
Albumin	0.811	0.0632	0.734 to 0.873
NLR	0.585	0.0916	0.497 to 0.670

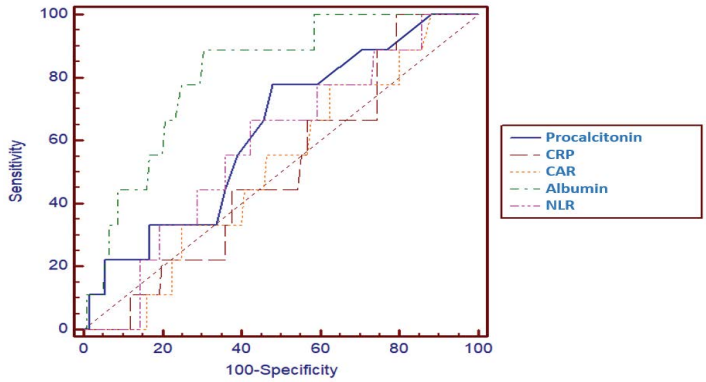

Figure 4: The ROC curves for prediction of 30-day mortality for procalcitonin, CRP, CAR, albumin and NLR.

DISCUSSION

Mortality prediction in patients with COPD exacerbation in the ED is important for patient management. The study aimed to compare arterial blood gas (pH, $PaCO_2$, lactate clearance), A-a O2 gradient and various inflammatory markers (NLR, PLR, CRP, CAR, procalcitonin). In the study, the 30-day mortality rate and ICU admission rate were 5.4% and 8%, respectively. The mean age of the non-survivors was higher than the survivors. The long and short term mortality rates of COPD exacerbation are quite different and the portion of this study is lower compared to these studies [14-17]. Although non-survivors in our study were elderly and the number of comorbidities was high, the lower mortality rate may be due to early admission to the ED and the high rate of hospitalization.

In the study, lower BUN, creatinine and higher hemoglobine were related to 30-day mortality among COPD exacerbation patients. Dehydration due to high fever, acute inflammatory reaction, decreased oral intake in the elderly population, smoking, increased number of comorbidities, hypoperfusion caused by hypoxia and hypercapnia may lead to impaired renal functions in COPD exacerbation patients [18,19]. Moreover, the impairment of renal functions is a factor which increases the severity of COPD and acute renal failure may increase mortality and hospital admissions.20 Serum creatinine level provides indirect information about the total muscle mass in the body [20]. Furthermore, acute serum creatine elevation is an indicator of muscle breakdown, and this increase is not seen patients with body muscle atrophy or wasting such as severe COPD [21,22]. In addition, BUN increases with the catabolism of body mass, low BUN level indicates cessation of catabolism [21]. Low creatinine and BUN levels in non-survivors may be result from severe COPD stage and muscle atrophy. Hemoglobin abnormalities such as anemia and polycythemia are common in patients with COPD and hypoxia-induced erythropoiesis leads to secondary polycythemia in these patients [23]. So, cor pulmonale and pulmonary hypertension are based on polycythemia in COPD [24]. In addition, high hemoglobin level concentration increases mortality rate and leads to poor outcomes as it predisposes to hypertension, stroke, thrombosis and cardiovascular events [23,24].

In this study, albumin (0.81) and pH (0.68) were the strongest predictor of 30-day mortality in COPD exacerbation patients among pH, pCO_2, NLR, PLR, CRP, albumin, CAR, procalcitonin, A-a O_2 gradient, A-a O_2 gradient-expected, A-a O_2 gradient difference and lactate clearance. Albumin (0.81) was also superior in predicting mortality compared to the other inflammatory markers. The mortality predictive power of $PaCO_2$ (0.71) was higher than pH and lactate clearance. A-a O2 gradient difference (AUC 0.68) was better than expected A-a O2 gradient and A-a O2 gradient in predicting mortality. Besides albumin, pH, $PaCO_2$ and A-a O_2 gradient difference can also be used mortality prediction for COPD exacerbation in the ED. Trauma, critical conditions such as sepsis, organ failure, chronic inflammatory diseases cause increased vascular permeability and lower serum albumin level [25,26]. Moreover, albumin is an acute plasma protein responsible for microvascular permeability, acid-bas equilibrium and prevention of platelet aggregation. So, decreased serum level of albumin is associated with poor outcomes including morbidity, mortality and ICU admission in particularly critically ill patients [26-29]. COPD is a chronic and inflammatory disease and the worsening of the disease severity during exacerbation may explain the role of albumin as a predictor of mortality. Additionally, albumin is an inflammatory marker which can be obtained more easily and practically than arterial blood gas in the ED. Although the blood gas sampling procedure is difficult, pH, $PaCO_2$ and A-a O2 gradient difference are substantial in terms of showing respiratory acidosis, compensation status and deep hypoxia [30]. The effects of pH and $PaCO_2$ in predicting mortality, hospital admission rate, long-term changes, and non-invasive ventilation duration in COPD patients have been shown in several studies [31-34]. In addition, we could not find any study in the literature on the relationship between A-a O2 gradient difference and COPD exacerbation.

This single-center study had some limitations. To begin with, the patient population was comparatively small and we did not evaluate a coexisting pneumonia for arterial blood gas analysis including A-a O_2 gradient, expected A-a O_2 gradient and A-a O_2 gradient difference. A detailed effect of comordid diseases to mortality was unknown. 30-day follow-up period after

ED admission, merely mortality was evaluated and the treatment protocol was not recorded. Furthermore, local hematoma, aneurysm, air or thrombus embolism, infection, laceration, hemorrhage, needle stick injuries and pain may ocur after arterial blood gas sampling [35,36].

CONCLUSION

Albumin is strong predictor of 30-day mortality in COPD exacerbation patients in the ED. In addition, an arterial blood gas sampling measurement including pH, $PaCO_2$ and A-a O_2 gradient difference are simple, precise and practical measurements for estimating 30-day mortality in these patients.

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AUTHOR CONTRIBUTIONS

S.A. and G.P. helped in the concept analysis, data collection, design, literature search, interpretation of data, preparation of initial and final draft. All the authors read and approved the final draft.

FUNDING

None declared.

AVAILABILITY OF DATA AND MATERIALS

The authors agree to the conditions of publication including the availability of data and materials in our manuscript.

CONFLICT OF INTEREST

None declared.

INFORMED CONSENT

Informed consent was obtained from the participants or their legally authorized representatives.

ETHICAL APPROVAL

This study was approved by the local ethics committee of Kafkas University Medical Faculty.

HUMAN RIGHTS

The principles outlined in the Declaration of Helsinki have been followed.

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