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ORIGINAL ARTICLE – OPEN ACCESS

The effect of Blood Urea Nitrogen/Albumin Ratio in the Short-Term Prognosis of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: There is no definite laboratory parameter in predicting short-term prognosis in patients with chronic obstructive pulmonary disease (COPD). Our aim was to evaluate the prognostic effect of serum blood urea nitrogen (BUN)/albumin ratio in COPD patients.

Materials and Methods: A retrospective study comprising of 264 COPD patients who were in exacerbation period and selected from 4 centers was carried out. Data on demographic characteristics, disease characteristics, comorbid conditions and short-term prognosis of patients were obtained. and analyzed.

Results: The BUN/Albumin ratio was higher in patients with oxygen saturation <90% (p=0.004). There was no difference between global obstructive lung disease (GOLD) stages means of BUN/Albumin ratio but this rate was higher in those with infective exacerbations (p=0.019). The BUN/albumin ratio of patients who were discharged (5.3±2.2) was significantly higher than the patients who were transferred to the intensive care unit [ICU] (11.7±6.0) (p<0.0001). The cut-off level of BUN/albumin ratio in prediction of the need for ICU was7.2 (sensitivity 80%, specificity 85.4%) and the area under the receiver operating characteristic (ROC) curve was 0.911 (95% CI: 0.861–0.961) (p<0.001). The cut-off level of BUN/albumin ratio in prediction of mortality was 8.1 (sensitivity 88.2%, specificity 85.4%) and the area under the ROC curve was 0.963 (95% CI: 0.930–0.995) (p<0.001).

Conclusion: BUN/albumin ratio can be used as an affordable, inexpensive and practical method for determining the short-term prognosis in hospitalized COPD patients. Prospective studies involving more patients are needed.

Keywords: COPD, biomarker, BUN/albumin ratio, prognosis, mortality

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INTRODUCTION

COPD affects 9–10% of individuals over the age of 40 and its frequency increases with age (1, 2). It has been predicted that COPD will be the 3rd leading cause of death by 2030 (3). COPD is a disease in which chronic systemic inflammation is predominant and many organs and systems are adversely affected because of the effect of both inflammation and hypoxemia (3). It is important to be able to predict the prognosis of the disease because if we can predict the course of the disease, we can take appropriate measures. Some studies have evaluated the short-term prognosis in COPD exacerbation (4–7). We are however unaware of any previous study that investigated the role of BUN/Albumin ratio.

Serum albumin is an indicator of nutritional status (8). Hypoalbuminemia is related to poor outcome in several clinical conditions (8–10). On the other hand, serum BUN level is an important indicator of renal hypoperfusion, which is associated with poor prognosis in patients with COPD (11, 12). In recent years, more and more studies have shown that renal perfusion is decreasing in patients with COPD (11, 12). Previously, BUN/Albumin ratio has been used to determine prognosis in community acquired pneumonia (CAP) (13). To date, the BUN/Albumin ratio has never been used to assess prognosis in COPD.

The ideal parameter for assessing prognosis in COPD should be accessible, practical, cost effective, and simple. BUN and albumin are parameters that may be routinely studied in the laboratory, are cost effective compared to other tests and their serum levels vary when the catabolic process is accelerated in the body. These practical parameters may be considered for use in the prediction of prognosis of COPD. So, we hypothesized that it may be practical to use BUN/Albumin ratio to predict short-term prognosis of COPD exacerbation. Our aim was to evaluate the prognostic effect of BUN/Albumin ratio in COPD patients.

MATERIALS and METHODS

The present study was approved by the Ufuk University Faculty of Medicine Ethics Committee (26052017-5). A retrospective review of 337 hospitalized patients with COPD exacerbations from 4 centers (Gazi University Faculty of Medicine, Hitit University Faculty of Medicine, Ufuk University Faculty of Medicine and Ankara Atatürk Training and Research Hospital) was conducted between 1st of January 2014 and 1st of January 2016. Data registration form was created for the collection of data.

The study's inclusion criteria were (I) forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) <70 in spirometry in stable period of COPD, (II) Have been receiving COPD treatment for at least 1 year, (III) being over 40 years old and (IV) Patients hospitalized from the emergency department or outpatient clinic with a diagnosis of COPD exacerbation. Exclusion criteria were (I) presence of pneumonia, (II) New diagnosis of COPD at the current hospitalization, (III) Presence of chronic kidney disease and (IV) Patients transferred to the ward from intensive care.

Chest x-ray result revealed that 73 of the patients had pneumonia and were therefore excluded. These patients were excluded because previous studies showed that pneumonia patients who have higher BUN/Albumin ratio are under greater risk of needing ICU treatment (13, 14). Following this exclusion, 264 patients were included this study (Fig. 1).

In all centers participating in the study, spirometry was carried out in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (15). The exacerbation of COPD was defined according to the GOLD guidelines (16). Only spirometry staging was performed because the study was retrospective and dyspnea grades (modified medical research council (mMRC) or COPD assessment test) were not recorded for some of the patients. For this reason, it was not possible to use the GOLD-combined staging method.

According to the working principle of the information management systems used in the hospitals, the examination cannot be performed without the diagnosis of illness (ICD-10 code) and the treatment cannot be regulated. For this reason, it was assumed that the comorbidity information was recorded correctly.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 23. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk's test) to determine whether they are normally distributed or not. Normal distribution parameters were compared using Student's t-test. Variables that were not normally distributed were expressed as median (min-max). Chi-square test was used to compare the independent groups while correlation coefficients and their significance were calculated using the Pearson test. A 5% type-I error level was used to infer statistical significance. A p-value of less than 0.05 was considered statistically significant. The capacity of serum BUN/Albumin ratio values in predicting the need for ICU and mortality was analyzed using ROC curve analysis. When a significant cut-off value was observed, the sensitivity, specificity, positive, and negative predictive values were presented. Youden method was used to determine the optimal cut-off values (J=max(sensitivity+specificity-1)). While evaluating the area under the curve, a 5% type-I error level was used to accept a statistically significant predictive value of the test variables.

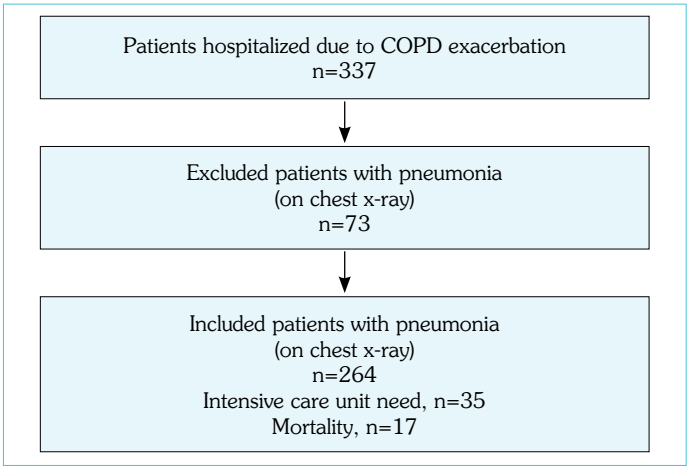

Figure 1. Study design
COPD: Chronic obstructive pulmonary disease

RESULTS

Majority (76.9%) of the patients were males while23.1% were females. The patients' median age was 70 (min: 40, max: 87) years. Forty-seven of the patients (17.8%) were never smokers, 149 (56.4%) of them were ex-smokers, 66 (25%) were active smokers and 2 (0.8%) had missing data. The median smoking history was 40 (min: 0, max: 200) pack-years. Numbers and ratios of GOLD stages (I to IV) of study population were respectively as follows: 2 (0.7%), 94 (35.9%), 111 (42.4%) and 55 (21%). Seventy-eight (29.5%) patients had long time oxygen therapy while 183 (69.3%) did not. One hundred and twenty-four (47%) had biomass exposure. The comorbidities of the patients are shown on Table 1.

The result of the patients' laboratory investigations are as follows: BUN: 20 mg/dL (min: 4, max: 58), creatinine: 0.81 mg/dL (min: 0.43, max: 5.42), albumin: 3.6 g/dL (min: 2.2, max: 4.7), sodium: 139 mmol/L (min: 127, max: 150), potassium: 4.4±0.6 mmol/L, aspartate aminotransferase (AST): 18 U/L (min: 7.6, max: 71), alanine aminotransferase (ALT): 18 U/L (min: 6, max: 99), hemoglobin: 13.5±2.2 g/d/L, white blood cell (WBC): 8.75 10^3/µL (min: 1.4, max: 40.4), platelet: 219.5 10^3/µL (min: 91, max: 446), CRP: 25.6 mg/L (min: 1, max: 394), sedimentation: 31.5 (mm/h (min: 2, max: 120).

In the examination of the arterial blood gases, average pH was 7.39±0.12, partial oxygen pressure (PO_2) was 47.1±21.1 mmHg and partial carbon dioxide pressure (PCO_2) was 39.9±17.9 mmHg. In addition, oxygen saturation (SO_2) was 83.1±11.4 while HCO_3 was 22.6±6.7 mEq/L. Mean values of oxygenation, spirometry GOLD stages and the BUN/Albumin ratio according to type of COPD exacerbation are shown on Table 1. The BUN/Albumin ratio was higher in patients with oxygen saturation <90% (p=0.004).

Table 1. Comorbid conditions of the patients and BUN/albumin averages according to oxygenation, GOLD stages, type of COPD exacerbation and body mass index (BMI)

	n	%
Comorbidity		
Yes	203	76.9
No	61	23.1
Types of comorbidities		
Lung cancer	9	3.4
Hypertension	127	48.1
Atrial fibrillation	20	7.6
CAD	61	23.1
CHF	36	13.6
DM	64	24.2
Osteoporosis	20	7.6
Anxiety-Depression	22	8.3

Parameters	**n**	**BUN/Albumin±SD**	**p**
BMI (kg/m^2)			
<20	23	6.49±3.68	0.895
20–24.9	66	6.37±3.48	
25–29.9	60	6.77±3.91	
≥30	61	7.00±5.29	
Oxygen saturation			
<90	173	6.9±4.4	**0.015**
≥90	91	5.8±3.1	
GOLD stage			
1	2	7.9±7.1	0.710
2	94	6.9±4.9	
3	111	6.5±3.5	
4	55	5.8±2.9	
Type of exacerbation			
Infective exacerbation	166	6.8±3.6	**0.019**
Non-infective exacerbation	98	6.1±4.1	

GOLD: Global obstructive lung disease; HT: Hypertension; AF: Atrial fibrillation; CAD: Coronary artery disease; CHF: Congestive heart failure; DM: Diabetes mellitus; BUN: Blood urea nitrogen

There was no difference between GOLD stages means of BUN/Albumin ratio but this rate was higher in patients with infective exacerbations (p=0.019) (Table 1).

The mean length of stay in hospital was 10.37±7.1 days and the median was 9 days (as to 50% percentile). The BUN (p=0.168), albumin (p=0.247) and BUN/Albumin ratio (p=0.167) had no effect on the length of stay in hospital. Two hundred and twelve (80.3%) of the patients were discharged, 35 (13.3%) were transferred to ICU, and 17 (6.4%) died. The BUN/albumin ratio of patients who were discharged (5.3±2.2) was significantly lower than the patients who were transferred to the ICU (11.7±6.0) (p<0.0001). Moreover, this ratio of patients who were transferred to ICU (11.7±6.0) was similar to those who died (12.2±3.9) (p=1.000).

The cut-off level of BUN/albumin ratio in prediction of the need for ICU was found to be 7.2 (sensitivity 80%, specificity 85.4%). The area under the ROC curve for the prediction of the need for ICU was found to be 0.891 (95% CI: 0.840–0.943) (p<0.001) for BUN, 0.722 (95% CI: 0.628–0.817) (p<0.001) for Albumin and 0.911 (95% CI: 0.861–0.961) for BUN/Albumin (p<0.001). More details on this can be found in Figures 2a, b, and c respectively. The cut-off level of BUN/albumin ratio in prediction of mortality was found to be 8.1 (sensitivity 88.2%, specificity 85.4%). The area under the ROC curve for prediction of mortality was found to be 0.942 (95% CI: 0.899–0.985) (p<0.001) for BUN (Fig. 3a), 0.786 (95% CI: 0.669–0.902) (p<0.001) for Albumin (Fig. 3b) and 0.963 (95% CI: 0.930–0.995) (p<0.001) for BUN/Albumin (Fig. 3c).

DISCUSSION

To our knowledge, this is the first study to investigate the effect of BUN/Albumin ratio on short-term prognosis in COPD. In this study, we found that the BUN/Albumin ratio was higher in patients with oxygen saturation <90% and infective exacerbations. Moreover, this study showed that COPD patients who had higher BUN/Albumin ratio were at increased risk for ICU treatment and higher risk of mortality. The cut-off level of BUN/Albumin in prediction of ICU need was 7.2 (sensitivity 80%, specificity 85.4%) while that of mortality was 8.1 (sensitivity 88.2%, specificity 85.4%).

Previous studies found that the biomarkers affecting prognosis in stable COPD patients are the ratio of transthyretin, cholesterol level and urinary albumin/creatinine (4–6). The number of biomarkers that affect mortality in COPD exacerbations is even higher. These are urea, proadrenomedullin, procalcitonin and troponin levels (7, 17). These biomarkers are not routine laboratory tests for COPD exacerbation. In addition, these tests require separate equipment, are expensive and difficult to repeat. An ideal biomarker on the other hand must be a parameter that plays a biological role in the pathogenesis of the disease, is easily measurable, achievable, reproducible, changed with treatment, and used clinically. For these reasons, we believe that the BUN/Albumin ratio may be a good prognostic parameter.

Previous studies have revealed the association between impaired renal function and COPD exacerbations (11, 12). These include reduced renal blood flow due to hypoxia, increased inflammation, comorbid conditions and the effects of drugs (11, 12). In our study, those with oxygen saturation <90% had higher BUN/Albumin ratio than those with >90% (p=0.004). We think that hypoxia reduces renal blood flow and consequently increases BUN. Even if the albumin level is normal, due to BUN level increase, the BUN/albumin ratio increases.

Hypoalbuminemia is the result of the combined effects of inflammation and inadequate protein in chronic diseases. Albumin is a negative acute phase reactant and the levels decrease during the acute phase response due to increase in catabolism of albumin (18). Several studies have shown that hypoalbuminemia is associated with poor prognosis in patients with COPD (18, 19).

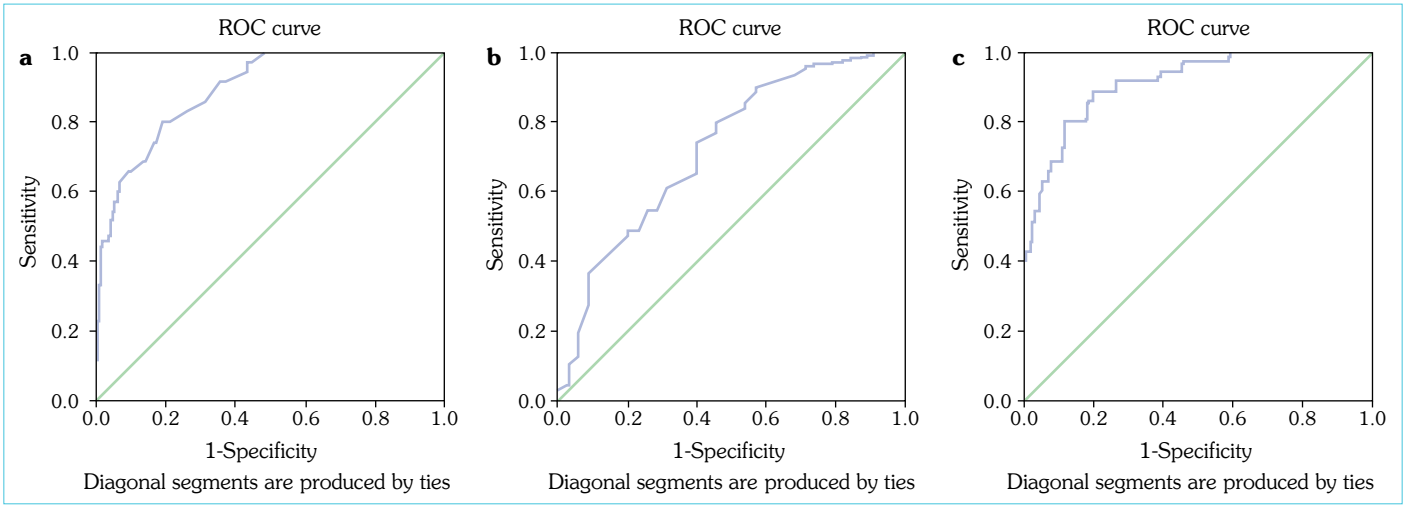

Figure 2. (a) The Receiver Operating Characteristic (ROC) curve constructed from BUN as a predictor of the need for ICU among COPD patients. The area under the ROC curve: 0.891 (95% CI: 0.840–0.943) (p<0.001). (b) ROC curve constructed from Albumin ratio as a predictor of the need for ICU in patients with COPD. The area under the ROC curve: 0.722 (95% CI: 0.628–0.817) (p<0.001). (c) ROC curve constructed from BUN/albumin ratio as a predictor of the need for ICU in COPD patients. The area under the ROC curve: 0.911 (95% CI: 0.861–0.961) (p<0.001)

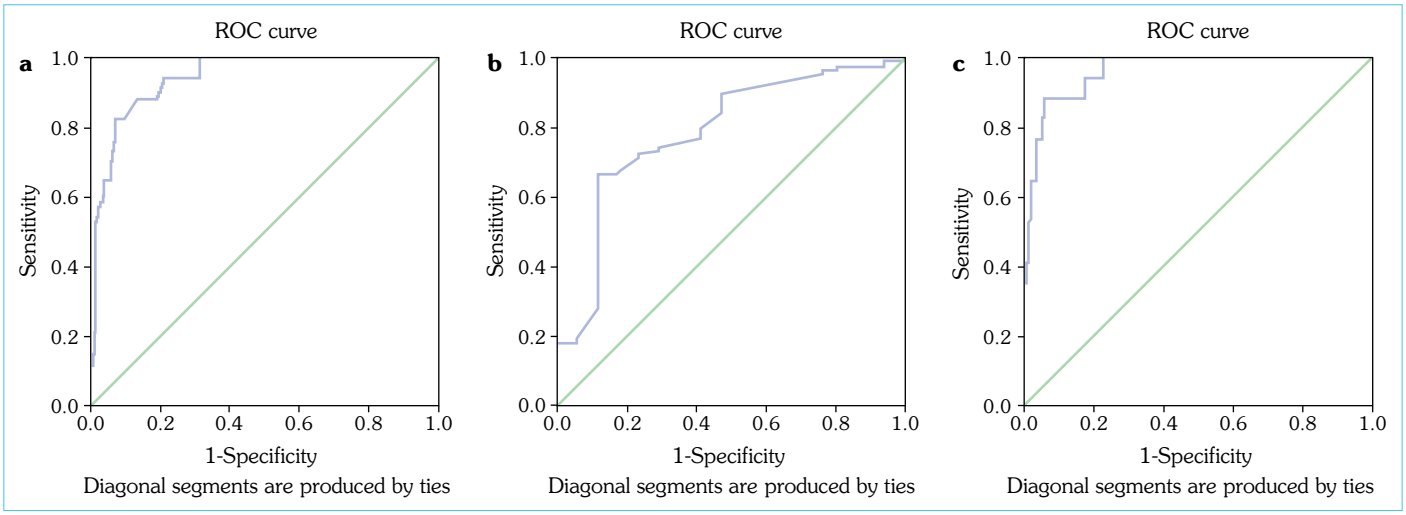

Figure 3. (a) The Receiver Operating Characteristic (ROC) curve constructed from BUN as a predictor of mortality in patients with COPD. The area under the ROC curve: 0.942 (95% CI: 0.899–0.985) (p<0.001). (b) ROC curve constructed from Albumin ratio as a predictor of mortality in patients with COPD. The area under the ROC curve: 0.786 (95% CI: 0.669–0.902) (p<0.001). (c) ROC curve constructed from BUN/albumin ratio as a predictor of mortality in patients with COPD. The area under the ROC curve: 0.963 (95% CI: 0.930–0.995) (p<0.001)

There is intense inflammation in COPD and catabolism increases. Therefore, albumin levels may decrease. Even if the BUN is normal, the BUN/Albumin ratio increases because of the low albumin levels. In our study, those with infective exacerbations had higher BUN/Albumin ratio than those with non-infective exacerbations.

The major limitation of our study is that it was a retrospective study. Nevertheless, information on many parameters were available through regular registrations in the hospital information management systems in the participating centers. Another limitation is that only tertiary hospitals were included in this study. Therefore, the results obtained cannot be generalized and should be interpreted with caution.

In conclusion, BUN/albumin ratio can be used as an affordable, inexpensive, practical method for determining the short-term prognosis in hospitalized COPD exacerbation. According to our findings, the prognosis worsens as the BUN/Albumin ratio increases. If this ratio is above 7.2, the patient may need intensive care and if above 8.2, it may result in fatality. Global medicine focuses on "precision medicine" and the development of the concept of "precision medicine" in COPD will be very valuable. Until new and highly sensitive biomarkers are discovered to determine the prognosis in COPD, existing biomarkers can be used effectively. Howbeit prospective studies are needed but within the framework of existing biomarkers, we think that the BUN/Albumin ratio may be an efficacious alternative parameter.

Ethics Committee Approval: The Ufuk University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 26.05.2017, number: 26052017-5).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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