Evaluation of the Blood Urea Nitrogen-to-Left Ventricular Ejection Fraction Ratio in Predicting Mortality in Patients Presenting to the Emergency Department with Heart Failure Symptoms

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ABSTRACT

Heart failure is a clinical syndrome. In this study, the significance of the blood urea nitrogen-to-left ventricular ejection fraction (BUN-LVEF) ratio in predicting short-term mortality in patients with heart failure symptoms was evaluated. This retrospectively designed study was conducted by evaluating the records of patients with a history of heart failure who presented to the emergency department with heart failure symptoms and signs from 01 January 2018 to 01 January 2020. One hundred and seventy-three patients were included in the sample within the last six months presented to the emergency department with the symptoms of acute heart failure. Blood urea nitrogen (BUN) and the BUNLVEF ratio had a significant relationship with mortality (p=0.004 and <0.010, respectively). In patients with a known history of heart failure presenting to the emergency department with heart failure symptoms, it would be more appropriate to evaluate poor outcomes with the BUNLVEF ratio rather than the LVEF or BUN value alone.

Key Words: *Blood urea nitrogen, Prognosis, Left ventricular dysfunction.*

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Heart failure is a clinical syndrome.[1] In the literature, it has been shown that high blood urea nitrogen (BUN) values and low left ventricular ejection fraction (LVEF) are markers of poor prognosis in patients diagnosed with heart failure due to impaired renal blood flow and neurohormonal effects.[2] The association of BUN with mortality in heart failure patients was known. In addition, the BUN-to-LVEF (BUNLVEF) ratio has previously been reported to predict poor outcomes in patients with a history of coronary artery bypass grafting and acute coronary syndrome.[3]

It was speculated that a combination of LVEF and BUN could be more valuable than each parameter alone in predicting short term mortality in this patient population. Therefore, in the current study, the significance of the BUNLVEF ratio in predicting short-term mortality in patients with heart failure symptoms was evaluated.

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This retrospective study was carried out at the Emergency Department, University of Health Sciences, Umraniye Education and Training Hospital, Istanbul, Turkiye. Ethical approval was obtained from the local ethics committee on March 31, 2022 (No. 120). Four thousands and twenty-nine patients were admitted to the emergency department with symptoms of heart failure, 173 patients were randomly selected and included in the study by G*Power analysis performed with an acceptable margin of error of 5% and a confidence interval of 95%. The records of patients between 01 January 2018 and 01 January 2019, were evaluated from the hospital's computer-based data system. The study included patients with chronic heart failure who presented to the emergency department with complaints such as shortness of breath, chest pain, exertional dyspnea, orthopnea, oedema in the lower extremities, ascites, fatigue, and weakness, and who were diagnosed with heart failure within the last six months and started medical treatment, were included in the study. LVEF was calculated using the following formula: stroke volume / end-diastolic volume × 100. Heart failure was evaluated into three classes according to the LVEF value; reduced ejection fraction for LVEF of 40% or lower, mid-range ejection fraction if LVEF ranging from 41 to 49%, and preserved ejection fraction for LVEF of 50% or greater.[4] Data on 28-day all-cause mortality were obtained from the national death reporting system. The BUNLVEF ratio was calculated by dividing the BUN value by the LVEF value.

Table I: Baseline characteristics of the enrolled patients and their comparison between the survivor and non-survivor groups.

	Total (n = 173)	Survivor (n = 148)	Non-survivor (n = 25)	p-value
Age (years)	78.0 (70.0 to 85.0)	78.0 (69.0 to 84.0)	81.0 (77.0 to 87.0)	0.275*
Female	104 (60.1)	86 (58.1)	18 (72.0)	0.275**
Male	69 (39.9)	62 (41.9)	7 (28.0)	
Comorbidities				
Hypertension (%)	77 (44.5)	65 (43.9)	12 (48.0)	0.871**
Diabetes mellitus (%)	58 (33.5)	49 (33.1)	9 (36.0)	0.957**
Chronic obstructive pulmonary disease (%)	48 (27.7)	45 (30.4)	3 (12.0)	0.097**
Coronary heart disease (%)	33 (19.1)	29 (19.6)	4 (16.0)	0.882**
Chronic kidney disease (%)	48 (27.7)	42 (28.4)	6 (24.0)	0.833**
White blood cell count (10^3/µl)	9.6 (7.1 to 12.4)	9.7 (7.1 to 12.4)	9.0 (7.4 to 12.5)	0.917*
Neutrophil count (10^3/µl)	7.1 (5.1 to 9.5)	7.1 (5.0 to 9.2)	6.7 (5.2 to 9.7)	0.816*
Lymphocyte count (10^3/µl)	1.5 (1.0 to 2.1)	1.5 (1.0 to 2.1)	1.5 (1.1 to 1.8)	0.804*
Haemoglobin (g/dl)	11.1 (9.9 to 12.3)	11.2 (9.9 to 12.4)	10.7 (10.0 to 11.9)	0.272*
Haematocrit (%)	35.5 (31.6 to 39.1)	35.7 (31.8 to 39.2)	34.5 (31.5 to 38.4)	0.422*
Mean corpuscular volume (Fl)	87.3 (82.6 to 91.6)	87.7 (84.1 to 91.6)	83.8 (81.9 to 89.0)	0.170*
Red cell distribution width (%)	27.7 (25.9 to 29.2)	27.9 (25.9 to 29.3)	26.7 (25.1 to 27.8)	0.064*
Neutrophil/lymphocyte ratio	4.7 (3.2 to 7.4)	4.6 (3.2 to 7.3)	5.8 (3.3 to 8.8)	0.329*
C-reactive protein (mg/dl)	2.0 (0.6 to 5.0)	2.0 (0.6 to 4.6)	2.8 (0.8 to 7.3)	0.278*
Blood urea nitrogen (mg/dl)	68.5 (49.2 to 96.3)	64.2 (47.1 to 94.2)	92.0 (64.2 to 130.5)	0.008*
Creatinine (mg/dl)	1.3 (1.0 to 1.9)	1.2 (1.0 to 1.9)	1.9 (1.2 to 2.1)	0.119*
Brain natriuretic peptide (pg/ml)	1210.7 (782.8 to 2042.3)	1102.5 (736.5 to 1866.0)	1972.0 (1301.6 to 2881.5)	<0.001*
High-sensitivity troponin (ng/ml)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.085*
Sodium (mmol/l)	138.0 (135.0 to 140.0)	138.0 (135.0 to 140.0)	136.0 (135.0 to 140.0)	0.330*
Potassium (mmol/l)	4.8 (4.4 to 5.3)	4.9 (4.5 to 5.3)	4.7 (4.3 to 5.0)	0.348*
Systolic blood pressure (mm/hg)	140.0 (125.0 to 165.0)	140.0 (125.0 to 165.0)	135.5 (126.8 to 152.8)	0.404*
Diastolic blood pressure (mm/hg)	78.5 (70.0 to 94.2)	80.0 (70.0 to 95.0)	70.5 (67.8 to 78.8)	0.069*
Left ventricular ejection fraction (%)	45.0 (30.0 to 55.0)	45.0 (30.0 to 55.0)	40.0 (30.0 to 50.0)	0.513*
Left ventricular ejection fraction categories				
Reduced ejection fraction	68 (39)	58 (39)	10 (40)	0.939**
Mildly reduced ejection fraction	27 (16)	22 (15)	5 (20)	0.513**
Preserved ejection fraction	78 (45)	68 (46)	10 (40)	0.581**
BUNLVEF ratio	1.8 (1.1-2.6)	1.6 (1.1-2.5)	2.6 (1.5-3.3)	0.010**
BUNLVEF ratio cut-off (%)				
<2.425	119 (69)	108 (73)	11 (44)	0.004**
≤2.425	54 (31)	40 (27)	14 (56)	

**Mann-Whitney U test, **Chi-square test. BUNLVEF: Blood urea nitrogen-to-left ventricular ejection fraction.*

Table II: BUN, creatinine, chronic kidney disease incidence, and BUNLEVF ratio according to the LVEF groups.

		Total	Reduced ejection fraction	Mildly reduced ejection fraction	Preserved ejection fraction	p
BUNLEVF ratio	Median (IQR)	2.6 (1.8-3.4)	1.9 (1.3-2.8)	1.2 (0.9-1.9)	1.8 (1.1-2.6)	<0.001*
Blood urea nitrogen (mg/dl)	Median (IQR)	66.3 (47.1-97.9)	62.1 (42.8-89.9)	67.4 (51.4-109.1)	70.6 (47.1-104.9)	0.114*
Creatinine (mg/dl)	Median (IQR)	1.2 (1.0-1.9)	1.2 (1.0-1.7)	1.3 (1.1-2.1)	1.4 (1.0-2.1)	0.325*
Chronic kidney disease (%)	Absent	248 (79.0)	102 (84.3)	47 (81.0)	99 (73.3)	0.091*
	Present	66 (21.0)	19 (15.7)	11 (19.0)	36 (26.7)	

*IQR, Interquartile range. *Kruskal Wallis test.*

Jamovi was used to analyse the data. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test. The Mann-Whitney U test was used for continuous variables. Kruskal Wallis test was used to evaluate more than two groups. The difference between categorical data was evaluated with the chi-square test. A p-value of <0.05 was considered statistically significant. The receiver operating characteristic (ROC) analysis was performed, and the results of this analysis were shown with the area under the curve (AUC). As a result, 173 patients were included in the sample. The median (25^{th}-75^{th} percentile) age was 78.0 (70.0-85.0) years, and 104 (60.1%) of the patients were female. For the whole sample, the median BUN was 68.5 mg/dl (49.2-96.3), the median LVEF was 45.0 (30.0-55.0 %), and the median BUNLVEF ratio was 1.8 (1.1-2.6) (Table I). The BUNLVEF ratio statistically significantly differed according to the LVEF groups (p <0.001, Table II). The highest BUNLVEF ratio was observed in the reduced ejection fraction group, with a value of 2.6 (25-75 percentile: 1.8-3.4). The AUC value of the BUNLVEF ratio was calculated as 0.660 and cut-off value 2.425 according to the ROC analysis.

This study was conducted with patients who presented to the emergency department with heart failure symptoms and a history of heart failure diagnosis within the last six months. There was significant difference in the BUNLVEF values between the survivors and non-survivors groups. Although a high BUNLVEF ratio was associated with mortality in patients with heart failure. There was no significant difference in the LVEF values between the survivors and non-survivors.

Yeh *et al*. found that the change in post-treatment LVEF compared to the baseline LVEF was associated with prognosis compared to the baseline LVEF at admission. Contrary to the studies showing that a decrease in LVEF is associated with a high risk for poor outcomes, in the current study, no significant difference was observed in the mortality rates between the reduced, mid-range, and preserved LVEF groups.

BUN clearance is affected by the glomerular filtration rate and tubular reabsorption of urea. Khoury *et al*. reported that a high BUN value was associated with poor prognosis in patients with heart failure.[5] In this study, there was a significant correlation between high BUN values and mortality, which is consistent with previous studies. However, the increase in LVEF did not cause a decrease in BUN at the same rate. Although renal perfusion can be considered to be normal in patients with preserved LVEF, there was no decrease in the BUN values of the patients with preserved LVEF in this cohort. In addition, the patients with reduced LVEF had no higher BUN than the remaining LVEF groups, suggesting that there are factors other than LVEF that affect renal function or protein degradation. The mean BUN values in the reduced LVEF group being almost the same as in the preserved LVEF group can also be explained by clinicians tending to be more cautious in the medical treatment of patients with reduced LVEF values in the presence of heart failure. At the same time, since this group of patients was followed up more closely, the similarity in the BUN values between the LVEF subgroups may be related to treatment success.

The reason why authors included patients with a history of chronic heart failure at the time of admission was that BUN shows changes due to protein intake, catabolism, renal perfusion, or neurohormonal effects.[6] Renal function may not be impaired and BUN values may not be elevated in the early period in patients with acute heart failure, and these effects are observed later. In addition, acute decompensated heart failure may develop for various reasons ranging from myocardial infarction to infection. Considering that the mechanisms affecting BUN values in this patient group may not be related to heart failure, the authors did not include patients newly diagnosed with heart failure in this study.

The first limitation of the study is that LVEF measurement is a user-dependent parameter, and therefore there may be differences in the results of different operators. The second limitation concerns the single-centric and retrospective nature of the study.

According to these results, BUN, which is affected by renal blood flow and neurohormonal events, can be evaluated together with LEVF in order to predict poor outcomes more accurately in patients with known heart failure who present to the emergency department with clinical worsening.

COMPETING INTEREST:
The authors did not declare any conflict of interest.

AUTHORS' CONTRIBUTION:
AO: HSA, SO, SEE: Design of the work, acquisition, analysis, interpretation of data, drafting the work, final approval, and agreement to be accountable for all of the work.

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