RDW and pro-BNP in predicting short-term mortality in geriatric patients presenting to the emergency department with acute decompensated heart failure

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Abstract

To reveal the ability of Red cell Distribution Width (RDW) to predict short-term mortality in geriatric patients presenting to the emergency department with acute heart failure and compare the results with pro B-type Natriuretic Peptide (pro-BNP). This prospective cohort study was conducted to evaluate the data of patients admitted to the emergency department between August 15th, 2021, and November 15th, 2021. The study population enrolled volunteers aged 65 years and over, who presented with acute heart failure signs and symptoms. Demographics, vital parameters, and laboratory parameters were noted. A total of 424 patients were included in the study. The 30 day-mortality rate of the study cohort was 14.4%. Older age, active malignancy, RDW, C-reactive protein, blood urea nitrogen, and pro-BNP were early independent predictors of short-term mortality. pro-BNP was a better predictor than RDW with a greater area under the curve value (0.841 versus 0.752, p=0.045, DeLong equality test). The created multivariate regression model was able to detect the risk of short-term mortality with high accuracy (area under the curve: 0.943, accuracy: 0.936, sensitivity: 98.1, specificity: 67.2, p<0.001). Initial RDW and pro-BNP were significantly higher in the mortality group among the geriatric patients with acute decompensated heart failure presenting to the emergency department, and pro-BNP was found to be a better predictor of mortality than RDW. RDW presents as a promising hematological marker that aids in the prognosticating short-term mortality in this patient population.

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Informed consent: Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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Introduction

Heart failure is a structural or functional clinical condition with typical symptoms and signs, causing low cardiac output and/or elevated intracardiac pressures due to cardiac abnormalities.[1] Heart failure is a disease with a poor prognosis. Approximately 50% of the diagnosed patients die within five years. Older age, exercise intolerance, elevated plasma norepinephrine and natriuretic peptide levels, anemia, renal dysfunction, hyponatremia, increased troponin levels, and ischemic electrocardiographic findings indicate a poor prognosis. The recognition and early treatment of patients with heart failure and cardiac functional and structural abnormalities may be effective in reducing mortality.[1,2]

Red cell Distribution Width (RDW) is a measure of the range of variation of red blood cell volume reported as part of a standard complete blood count. The prognostic value of RDW has been demonstrated in many diseases and clinical conditions.[3] Many studies have emphasized that RDW can be used to predict short- and long-term mortality in cardiovascular diseases, including stroke and heart failure.[3-5] On the other hand, RDW is a hematological parameter affected by changes in demographic parameters, such as age and gender.[6] In this study, we aimed to reveal the ability of RDW to predict short-term mortality in geriatric patients presenting to the Emergency Department (ED) with acute heart failure and compare the results to pro B-type Natriuretic Peptide (pro-BNP), which has previously been shown to be a strong predictor of mortality in the elderly population with this condition.

Material and Methods

Study design

This prospective, single-center, observational study was carried out at the ED of a 685-bed tertiary education hospital, receiving 1,110 patient admissions per day (annual average). The data of geriatric volunteers who presented to ED between August 15th, 2021, and November 15th, 2021, were documented prospectively.

Study population

Our study population enrolled volunteers aged 65 years and over, who presented to our ED between August 15th, 2021, and November 15th, 2021, with acute heart failure signs and symptoms. The heart failure was defined when the patients stated: a medical history of heart failure, a specific treatment for heart failure (beta blockers, diuretics, ace inhibitors, angiotensin II receptor blockers, and digitalis), signs of heart failure (dyspnea, rales, pretibial oedema), or medical history of clinical or radiographic findings of cardiomegaly or pulmonary oedema or ventricular dilatation and abnormalities of ventricular kinetics assessed by echocardiography. Patients with missing data or unknown mortality status were excluded. Patients who were not tested for RDW or pro-BNP were also excluded. Other exclusion criteria were the presence of diseases or medical history that could affect the RDW level, such as inflammatory bowel disease, pregnancy, and chronic lung diseases, and treated for anemia with erythropoietin and/or iron preparations and/or other anemia treatment modalities. Figure 1 shows the flowchart of the study. Consent was obtained from the patients or the legal guardian if the patient did not have a sufficient level of consciousness to provide consent for participation in the study due to dementia or critical illness.

Data collection

Data were collected using three sources: study form, computer-based system of hospital, and researcher phone call notes. The study form was completed for each patient providing consent at the time of admission to ED. This form contained information on age, gender, peripheral oxygen saturation, pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature, and comorbidities. Comorbidities were noted as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, immunodeficiency, and malignancy. Initial laboratory parameters of all patients and the 30 day-mortality data of the inpatients were noted from the computer-based system of the hospital. Clinical outcomes within the first 24 hours were recorded as discharge, hospitalization, and intensive care unit admission. The following laboratory parameters were recorded: white blood cell count, neutrophil count, lymphocyte count, hemoglobin, hematocrit, RDW, mean platelet volume, Blood Urea Nitrogen (BUN), C-Reactive Protein (CRP), creatinine, sodium, potassium, troponin I, and neutrophil-to-lymphocyte ratio. The mortality data of the outpatients were obtained through the phone calls made by the researchers. Pro-BNP levels were measured using an Enzyme Linked Immunosorbent Assay (Biosite Diagnostics, San Diego, CA, USA). The cut off recommended by the manufacturer was 125 pg/mL. Complete blood count testing utilized clinical laboratory methods (Coulter LH 780 Hematology Analyzer: Beckman Coulter Inc., Brea, CA).

Statistical analysis

Jamovi (Version 1.6.21.0; The Jamovi Project, 2020; R Core Team, 2019) was used for statistical analyses. The Kolmogorov-Smirnov test was used for the normality analysis of continuous

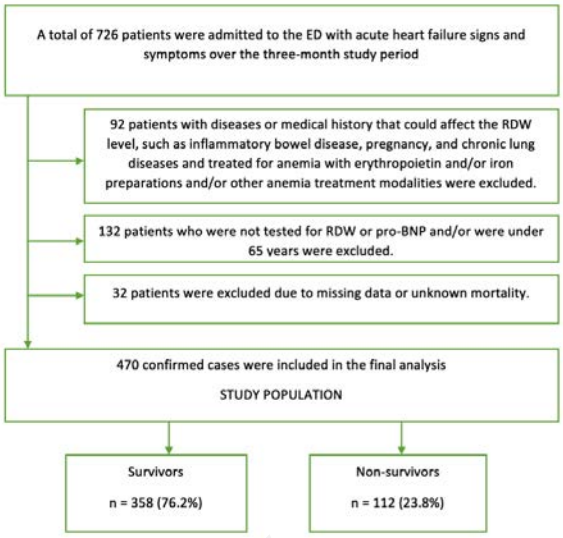

Figure 1. Flowchart of the study.

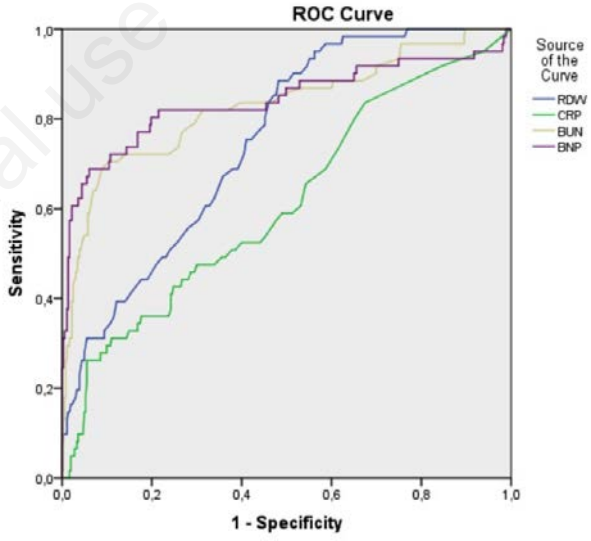

Figure 2. Receiver operating characteristic curves of red blood cell distribution width (RDW), C-reactive protein (CRP), blood urea nitrogen (BUN), and pro-BNP for predicting short-term mortality in geriatric patients with acute decompensated heart failure.

data. Categorical data were presented as number (%) and compared using the chi-squared test. Quantitative variables were presented as median and interquartile range (25^{th}-75^{th} percentile) values, and then compared using the Mann-Whitney test or Student's t-test according to the normality of distribution for the two groups. The study population was determined as 399 with Jamovi program by taking impact size 0.6, α=0.05, power (1-β) =0.95 at a confidence level of 95%. To determine which parameters were the independent predictors of short-term mortality, the parameters were first examined using the univariate logistic regression analysis, and those with a p value of lower than 0.20 were further analyzed with the multivariate logistic regression analysis using the backward stepwise elimination method. The Odds Ratio (OR) and 95% Confidence Interval (CI) values were also calculated for the

parameters included in the regression model.

The Receiver Operating Characteristic (ROC) curves were used to determine the accuracy of RDW, BUN, CRP, and pro-BNP in predicting mortality, and the results were reported as the Area Under the Curve (AUC) values. The optimal cut-off value for the parameters with the highest sensitivity and specificity were determined using Youden's index. The ROC curve was used to determine the accuracy of the regression model in predicting short-term mortality. The DeLong equality test was conducted to evaluate the differences between the AUC values.[7,8] We grouped the patients according to the cut-off values found by using the best Youden's index. We used the chi-square test to evaluate the difference between groups. P values greater than 0.05 were considered statistically significant.

Results

During the study period, a total of 726 patients presented to our ED with acute heart failure signs and symptoms. Using the exclusion criteria, 302 patients were excluded, and finally 424 patients were included in the study (Figure 1). The median age of the patients was 76 (71-84) years, and 235 (55.4%) were male. Sixty-one patients died within 30 days of admission, and the mortality rate of the study cohort was 14.4%. The baseline characteristics of the enrolled patients and comparison of the patient characteristics between the survivor and non-survivor groups are shown in Table 1. In the univariate analysis, older age, active malignancy, low ejection fraction, and certain initial laboratory parameters (RDW, creatinine, CRP, blood urea nitrogen, and pro-BNP) were determined to be associated with mortality. The multivariate analysis revealed that of these potential risk factors, only RDW (OR: 8.29, 95% CI: 3.67-18.7), CRP (OR: 15.59, 95% CI: 2.68-11.68), BUN (OR: 22.87, 95% CI: 11.91-43.89), and pro-BNP (OR: 35.16, 95% CI: 17.47-70.75) were independent predictors of short-term mortality in geriatric patients with acute decompensated heart failure (Table 1).

The ROC curve analysis was performed to determine the pre-

Table 1. Baseline characteristics of the enrolled patients and comparison of the patient characteristics between the survivor and non-survivor groups.

Variables	Total n = 424 (%, 25th-75th percentile)	Survivor n = 363 (85.6%) (%, 25th-75th percentile)	Non-survivor n = 61 (14.4%) (%, 25th-75th percentile)	Univariate analysis P values	Univariate analysis Odds ratio (95% confidence interval)	Multivariate analysis P values
Age, years	76 (71-84)	76 (71-83)	83 (75-88)	<0.001	3.16 (1.81-5.5)	0.039
Gender	0.244					
Male	235 (55.4)	197 (45.7)	38 (37.7)			
Female	189 (44.6)	166 (54.3)	23 (62.3)			
Emergency department outcomes	<0.001					
Death	3	0	3			
Discharge	244 (27)	217 (30.3)	27			
Hospitalization	116 (68.9)	110 (69.7)	6 (61.5)			
Intensive care unit admission	61 (4.1)	36	25 (38.5)			
Comorbidities						
Chronic obstructive pulmonary disease	100 (13.3)	86 (13.8)	14 (7.7)	0.900		
Hypertension	190 (49.2)	166 (50.5)	24 (38.5)	0.355		
Diabetes mellitus	143 (25.4)	125 (25.7)	18 (23.1)	0.453		
Coronary artery disease	87 (11.5)	75 (11)	12 (15.2)	0.860		
Congestive heart failure	241 (5.7)	207 (3.7)	34 (23.1)	0.851		
Malignancy	20 (0.8)	10 (0.9)	10	<0.001	6.92 (2.75-17.44)	0.003
Vital parameters, median (25th-75th percentile)						
Systolic blood pressure (mmHg)	140 (124-165)	140 (125-170)	140 (112-154)	0.112		
Diastolic blood pressure (mmHg)	80 (68-94)	80 (69-95)	74 (65-92)	0.373		
Oxygen saturation (%)	90 (88-94)	90 (88-95)	90 (88-94)	0.648		
Left ventricular ejection fraction (%)	45 (35-50)	45 (35-55)	40 (35-45)	0.005	0.45 (0.23-0.85)	0.063
Laboratory parameters, median (25th-75th percentile)						
White blood cell count (/µL)	9.65 (7.23-13.1)	9.64 (7.22-13.2)	9.76 (7.43-12.3)	0.959		
Neutrophil count (/µL)	6.87 (4.95-9.17)	6.86 (4.81-9.02)	7.11 (5.22-9.76)	0.108		
Lymphocyte count (/µL)	1.50 (1.03-2.12)	1.49 (1.04-2.11)	1.53 (0.95-2.54)	0.669		
Red cell distribution width (%)	26.8 (23.2-28.4)	26.1 (22.9-28.1)	28.2 (27.1-30.3)	<0.001	8.29 (3.67-18.7)	<0.001
Hemoglobin (g/dL)	11.1 (9.80-12.7)	11.1 (9.80-12.7)	11 (9.8-12.9)	0.909	0.85 (0.49-1.48)	0.823
Hematocrit (%)	35.3 (31.2-40.0)	35.5 (31.2-40.0)	34.3 (30.8-39.9)	0.656		
Mean corpuscular volume (fL)	86.6 (81.3-91.6)	86.6 (81.2-91.5)	86.6 (81.4-91.9)	0.882		
Neutrophil-to-lymphocyte ratio	4.06 (2.63-6.95)	3.76 (2.44-6.75)	11.3 (4.48-13.3)	0.682		
C-reactive protein (mg/L)	1.2 (0.3-4.1)	1.1 (0.3-3.4)	2 (0.5-9.9)	0.002	5.59 (2.68-11.68)	0.022
Blood urea nitrogen (mg/dL)	55.6 (38.5-83.5)	51.4 (38.5-72.8)	124 (70.6-162)	<0.001	22.87 (11.91-43.89)	<0.001
Creatinine (mg/dL)	1.02 (0.8-1.25)	1.05 (0.82-1.29)	0.92 (0.73-1.16)	0.040	0.50 (0.29-1.08)	0.316
Sodium (mEq/L)	138 135-140)	138 (135-140)	137 (134-140)	0.374		
Potassium (mEq/L)	4.8 (4.3-5.3)	4.80 (4.3-5.27)	4.7 (4.3-5.4)	0.116		
Troponin I (µg/L)	0.029 (0.014-0.07)	0.025 (0.013-0.0612)	0.061 (0.025-0.132)	0.761		
Pro-BNP (pg/mL)	787 (560-1173)	739 (537-1004)	2400 (1171-3838)	<0.001	35.16 (17.47-70.75)	<0.001

Table 2. Accuracy of RDW, CRP, BUN, and pro-BNP in predicting short-term mortality in geriatric patients with acute decompensated heart failure

Variables	AUC	95% CI	p	Accuracy	Cut-off value	Sensitivity	Specificity	PPV	NPV
RDW	0.752	0.694-810	<0.001	0.868	26.3	9.84	99.72	85.71	84.81
CRP	0.612	0.532-691	0.003	0.854	9.9	26.23	94.49	44.44	88.4
BUN	0.829	0.763-0.810	<0.001	0.896	94.16	13.11	99.72	88.89	87.23
Pro-BNP	0.841	0.769-0.912	<0.001	0.913	1696.6	31.15	99.72	95	89.6

AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, RDW: Red blood cell distribution width, CRP: C-reactive protein, BUN: blood urea nitrogen.

Table 3. Frequency of survivor and non-survivor patients according to cut-off values for RDW, CRP, BUN, and Pro-BNP

Variables		Survivor n = 363 (85.6%) (%)	Non-survivor n = 61 (14.4%) (%)	P
RDW	<26.3 %	188 (52)	7 (11)	<0.001
	≥26.3 %	175 (48)	54 (89)	
CRP	<9.9 mg/L	343 (94)	45 (74)	<0.001
	≥9.9 mg/L	20 (5.5)	16 (26)	
BUN	<94.16 mg/dL	325 (90)	18 (30)	<0.001
	≥94.16 mg/dL	38 (10)	43 (70)	
Pro-BNP	<1696.6 pg/mL	343 (94)	20 (33)	<0.001
	≥1696.6 pg/mL	20 (5.5)	41 (67)	

RDW: Red blood cell distribution width, CRP: C-reactive protein;, BUN: blood urea nitrogen.

dictive ability of RDW, CRP, BUN, and pro-BNP for short-term mortality. Table 2 and Figure 2 show the cut-off values of these parameters according to the best Youden's index, as well as their sensitivity, specificity, AUC and 95% CI values. Significant differences were observed between the AUC values of RDW and CRP (0.752 versus 0.612, p = 0.006), RDW and pro-BNP (0.752 versus 0.841, p = 0.045), BUN and CRP (0.829 versus 0.612, p < 0.001), and pro-BNP and CRP (0.841 versus 0.612, p < 0.001; DeLong equality test). However, no significant difference was observed between the AUC values of RDW and BUN (0.752 versus 0.729, p = 0.088) and BUN and pro-BNP (0.829 versus 0.841, p = 0.808; DeLong equality test). Frequency of survivor and non-survivor patients according to cut-off values found by using the best Youden's index for RDW, CRP, BUN and Pro-BNP are presented in Table 3. There was a statistically significant difference in mortality between the groups based on cut-off values (all p values < 0.001, chi-square test).

The created multivariate regression model predicts short-term mortality, the AUC value was calculated as 0.943 (accuracy: 0.936, sensitivity: 98.1, specificity 67.2, p < 0.001; Figure 3).

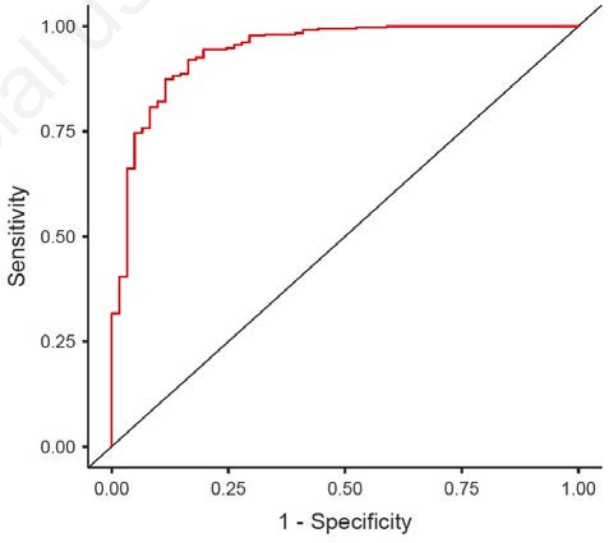

Figure 3. Receiver operating characteristic curve of the multivariate logistic regression model for predicting short-term mortality in geriatric patients with acute decompensated heart failure.

Discussion

In this study, we evaluated 424 geriatric cases of acute decompensated heart failure to investigate the ability of RDW and pro-BNP to predict short-term mortality in ED. We also found that older age, active malignancy, RDW, CRP, BUN, and pro-BNP were early independent predictors of short-term mortality. Pro-BNP was a better predictor than RDW with a greater AUC value (0.841 versus 0.752).[7,8] Additionally, there was a statistically significant difference in mortality between the groups based on cut-off values of RDW, CRP, BUN, and Pro-BNP. More importantly, the created multivariate regression model was able to detect the risk of short-term mortality with high accuracy (AUC: 0.943).

In analysis of study, firstly, nonparametric tests were used to determine the relationship between biomarkers and mortality. Significantly difference was observed between survivor and non-survivor groups in the terms of RDW, CRP, BUN, pro-BNP, and creatinine. Secondly, multivariant analysis were performed to determine independent predictors. Multivariant analysis determined RDW, CRP, BUN, and pro-BNP were independent predictors. A further analysis was performed based on ROC curve to show the biomarkers' ability to distinguish whether a patient died or survived. ROC analysis showed pro-BNP has highest AUC value, and CRP has the lowest. According to DeLong's test results pro-BNP and BUN best predictors with no significant different AUC values. [7,8]

RDW is a parameter included in the complete blood count, has

a low cost, and is used in the differential diagnosis of blood diseases, such as anemia and thalassemia.[3] It refers to the variability in mean corpuscular volume values of circulating erythrocytes. RDW has also been evaluated as a predictor of mortality in patients with cardiovascular disease, cancer, chronic lung diseases, symptomatic chronic congestive heart failure, and acute heart failure. In the current literature, it has also been demonstrated that RDW is associated with poor outcomes in thromboembolic events, such as acute myocardial infarction, stroke, and heart failure.[3-5]

There are several plausible explanations for the role of RDW in the pathogenesis of heart failure. Oxygen delivery in the myocardium is vital in heart failure. RDW is one of the most important parameters showing the quality of circulating erythrocytes. Elevated RDW is commonly seen in the presence of infective erythrocytes in the circulation, which is mostly associated with nutritional disorders and irregular erythropoietin secretion. On the other hand, RDW is also affected in clinical conditions in which erythrocyte function is impaired, such as hemolysis and post blood transfusion.[9,10] Another logical explanation for the role of RDW in heart failure is anemia of chronic disease, in which the reticuloendothelial block plays a role in pathogenesis. This is accompanied by impaired iron use and ineffective erythropoiesis. This whole pathological process results in high RDW.[11]

In 2010, van Kimmenade *et al.* reported a significant relationship between one-year mortality and RDW, and suggested RDW as a prognostic factor in acute heart failure.[12] Oh *et al.* investigated the relationship between RDW and echocardiographic parameters in acute heart failure and revealed the relationship between left ventricular ejection fraction and RDW.[13] In another study with a methodology similar to that of the current study, He *et al.* compared the ability of pro-BNP and RDW to predict 30- and 90-day mortality in acute heart failure. The authors suggested that RDW was a better predictor than pro-BNP in predicting 30-day mortality.[14] The difference between our study and that of He *et al.* is that we evaluated a geriatric population. Nishizaki *et al.* retrospectively evaluated the diagnoses of patients who died in a geriatric health center and showed that RDW was a predictor of fatal heart failure.[15] The strengths of the present study, compared to that of Nishizaki *et al.*, include the prospective design and the data being obtained from the follow-up of geriatric patients presenting to ED with acute decompensated heart failure.

In the current study, BUN values were found to be significantly higher in the mortality group. The clinical utility and clinical significance of high BUN values are still unclear.[16-19] On the other hand, three hypotheses have been proposed regarding the cause of elevated BUN in patients with acute heart failure: i) increased concentration dependent urea reabsorption in proximal tubules due to increased renin angiotensin aldosterone system activity;[16,17] ii) increased flow dependent urea reabsorption in distal tubules due to systemic nervous system hyperactivity;[17,18] iii) upregulation of urea transporters in inner medullary collecting duct due to increased arginine vasopressin release.[19]

Limitations

Our study has several limitations. The observational design of the study can be considered as the most important limitation. In addition, parameters such as iron, iron-binding capacity, erythropoietin, and ferritin, which may contribute to the explanation of the pathogenesis of acute heart failure, were not evaluated because these parameters are not routinely tested in ED. Frailty is a clinical condition in which an individual is more vulnerable to developing addiction or death when exposed to a stressor. All geriatric patients do not have the same frailty and risk of mortality due to heart failure.[20] In the light of this information, it should be considered that fragility is a confounding factor for current study. Thus, comprehensive geriatric assessment and frailty identification could not be done due to the intensity of ED and the observational design of the study is another important limitation of current study. Furthermore, the single-center nature and the relatively small cohort were factors that reduced the generalizability of the findings. We consider that multicenter studies should be conducted to validate our results in larger patient populations.

Conclusions

In conclusion, according to our results, initial RDW was significantly higher in the mortality group among the geriatric patients presenting to ED with acute decompensated heart failure, and pro-BNP was a better predictor of mortality than RDW. RDW presents as a promising hematological marker that assists in prognosticating short-term mortality in this patient population.

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