Prognostic significance of Blood Urea Nitrogen in comparison to Creatinine levels in mortality assessment of patients at admission with Acute Coronary Syndrome in Shivamogga district, Karnataka

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Abstract

Introduction and Objectives: Several studies have hypothesized the relation of Blood Urea Nitrogen (BUN) and serum Creatinine level with the severity of coronary artery disease. The basis of this study is to show the prognostic significance of BUN and serum Creatinine levels at admission for assessing the risk of mortality in patients with acute coronary syndromes (ACS). This study also undertakes the comparative prognostic significance of BUN over serum creatinine as an indicator of risk of mortality in patients with ACS.

Materials and Methods & Results: This was a prospective study of all patients admitted with suspected (n=1019) and retrospectively confirmed (n=65) Myocardial Infarction (MI) or Unstable Angina. The Receiver-operating characteristic curve analysis established that the area under the curve for BUN was higher than that of Creatinine 0.71 (95% CL 0.65 to 0.78) and 0.63 (95% CL 0.59 to 0.66), respectively (*p*=0.005). The threshold level was 8.6mmol/L for BUN and 110µmol/L for Creatinine. Sensitivity was 61% and 56% for threshold levels of BUN and Creatinine, and specificity was 84% and 78%, respectively.

It is seen only an increase of BUN and a combination of increased BUN and Creatinine levels, as risk factors of mortality with ACS. Isolated increase in creatinine levels was not found to be significant. Separate inclusion of BUN and Creatinine as continuous variables in the regression model showed that both were associated with the risk of mortality. Odds Ratio (OR) 1.18 (95% CL 1.12 to 1.25) and 1.08 (95% CL 1.011 to 1.019) per unit increase (R^2 =12.5 and 8.1% respectively). When both were simultaneously included, only the increased BUN level was persistent with the prognosis of ACS: OR after multivariate adjustment 1.14 (95% CL 1.04 to 1.18).

Conclusion: An increased level of BUN is a more significant prognostic marker of mortality assessment at admission in ACS than that of serum Creatinine.

Keywords: Blood Urea Nitrogen, Serum Creatinine, Acute Coronary Syndrome.

Introduction

Acute coronary syndrome (ACS) is a real medical emergency that requires immediate hospital admission. It is the leading cause of death in developed countries[1,2] as well as developing countries like India. Coronary Artery Disease occurs in Indians 5–10 years earlier than in other populations around the world and the major effect of this peculiar phenomenon is on the productive workforce of the country aged 35–65 years. The prevalence of CAD and the incidence of ACS also are very high among Indians.[3] India has the highest burden of ACS in the world.[3] In an uncertain situation, when it can be difficult to establish a patient's true diagnosis for 6-12 hours, it is imperative to determine the risk factors associated with a poor prognosis of ACS.[4] Current guidelines from the American College of Cardiology/ American Heart Association[5] and the European Society of Cardiology[6] recommend that certain interventional strategies are most appropriate for high risk groups. Strategies such as repeat 12 lead ECG recording during symptoms, blood samples for cardiac troponin (troponin T or I) to be taken a minimum of 12 hours after the onset of symptoms. New ischaemic changes on the ECG or elevation of troponin confirm the diagnosis. Adverse cardiovascular outcomes are associated with renal dysfunction.[7] According to Granger et al,[8] an increase in serum creatinine concentration of 1.0mg/dl among patients with ACS raises the risk of mortality by 15-35%. However, supplement information with regard to renal function may be provided by serum blood urea nitrogen, as renal proximal tubule cells may increase BUN re-absorption thus causing increased neuro-hormonal activation.[9] Likewise, higher serum BUN has been associated with adverse outcomes in subjects with acute coronary syndrome.[10] Creatinine tests diagnose impaired renal function & measure the amount of creatinine phosphate in the blood. BUN is an indirect & rough measurement of renal & liver function and measures the amount of urea nitrogen in blood. BUN is directly related to the excretory function of the kidney. The objective of this study was to compare the prognostic significance of BUN verses Creatinine levels in estimating the risk of mortality at admission in patients with ACS.

Materials and Methods

The study was conducted prospectively from September 2017 to October 2017 in the Coronary Care Unit (CCU) of the Mc Gann Hospital attached to Shivamogga Institute of Medical Sciences, Shivamogga. The study included all patients admitted with suspected Myocardial Infarction (MI) or Unstable angina (UA), a total of 1019 patients. In addition, the retrospective analysis of medical records revealed 65 more patients with MI and UA who had been transferred to CCU with an initial non-ACS diagnosis. There were no inclusion or exclusion criteria based on age, disease severity, time of admission or duration of hospitalization. The study protocol was approved by the Institutional Ethics Committee, Shivamogga Institute of Medical Sciences, Shivamogga, India. Informed consent was obtained from all the patients.

The data collection, clinical and demographic characteristics, blood test results and ECG changes were assessed on admission at the CCU. Blood was collected within 5-15 min after hospital admission for analysis of BUN and Creatinine levels in plain vacutainer [BD Biosciences] from antecubital vein from each patient. Serum urea and serum creatinine were measured using fully automated analyser – Erba Mannheim (XL -625) and kits supplied by ERBA.

Parameters were estimated by following methods:

a. Estimation of serum creatinine by modified Jaffe's method.[11,12]
b. Estimation of serum urea by GLDH-Urease method[13] and BUN was calculated.

The BUN: Creatinine ratio was used for distinguishing between renal and non-renal causes of azotaemia.[14,15] Co morbid conditions were determined as known before the study (Hypertension, Stable Angina, old MI/ stroke, Congestive Heart Failure) and / or found by the study (diabetes mellitus, kidney, liver disease). The primary outcome of the study was in-hospital mortality. Secondary outcomes included a diagnosis of non-fatal MI or stroke by the treating physician in CCU.

Statistical Analysis

The statistical analysis was performed with SPSS version12.0. The distributions of continuous variables were described using medians (25^{th}; 75th percentiles) and discrete variables were presented as frequencies and percentages. Group differences in baseline characteristics were assessed with the Mann- Whitney U test (for continuous variables) and the χ^2 test (for categorical variables). The results were considered as statistically significant at $p<0.05$. Survival curves were created using the Kaplan-Meier method and compared by the log rank test. The impact of the independent variable on the probability of the primary outcome (in-hospital death) was determined by the OR (Odds ratio) and the 95% CL (confidence limit), which were calculated using the binary logistical regression in both unvaried and multivariate analysis. In multivariate analysis, independent variables were obtained using the step-by step elimination halted at $p<0.05$. The attributive value of independent variables was determined through the X^2 and the Nagelkerke $R.^2$

Receiver – operating characteristics analysis was used to assess the ability of various levels of continuous variables to predict in-hospital mortality. Comparison of two areas under the ROC curve was conducted using Analyse- it for Microsoft Excel (Analyse-it Software Ltd).

Results

Demographic characteristics, medical history and presenting clinical diagnosis are shown in Table 1 for patients with known values of BUN and Creatinine (discharged or in hospital mortality). The median duration of hospitalization was 15 days (13-21). Patients who died at baseline had higher values of all biochemical markers, leukocytes and haemoglobin levels.

The ROC analysis established that the area under the curve for BUN was higher than that of Creatinine, 0.71 (95% CL 0.65 to 0.78) Vs 0.63 (95% CL 0.59 to 0.66), (p=0.005), respectively (Fig 1). The threshold level was 8.6mmol/L as compared to110 µmol/L for Creatinine. The sensitivity (true positive cases) for threshold levels of BUN and creatinine was 61% and 56%, respectively and the specificity (true negative cases) was 84% and 78%, respectively.

An increase in BUN only (Creatinine ≤110µmol/L), Creatinine only (BUN ≤ 8.6 mmol/L) or both was detected in 110 (15%), 59 (8%) and 103 (14%) patients, respectively. In unvaried analysis and after correction for base line characteristics, it was found that an increase in BUN only or in both BUN and Creatinine, but not in Creatinine only was associated with a higher risk of mortality (Table 2).

Evaluation of high risk based only on an increase in creatinine (≥110 µmol/L) therefore led to an overestimate of the risk of mortality in 88 patients (53% patients with abnormal Creatinine levels or 12% of all patients with ACS) and an underestimate of the risk in 54 patients (8% patients with normal creatinine levels or 7% of all patients with ACS). With an increase in BUN only (> 8.6 mmol/L) including 6 patients who died (14% of all deaths or 28% of patients with normal creatinine levels). In a separate regression analysis, both BUN [OR. 1.88 (95% CL 1.10 to 1.22)] and creatinine levels [OR 1.012 (95% CL 1.008 to 1.018)] as continuous variables were associated with an increased risk of death.

The attributive value (R^2) of each variable was 13.6% and 7.4%, respectively. With the simultaneous inclusion of both variables in the regression model, only increased BUN levels were pertinent to the prognosis of ACS [OR 1.18 (95% CL 1.06 to 1.18)]. No

statistically significant effect of Creatinine levels on the prognosis of ACS was recorded [OR 1.02 (95% CL 0.96 to 1.04)]. After multiple adjustments (Table 2) the high risk of in-hospital death was associated with only BUN levels [OR 1.14 (95% CL 1.04 to 1.22)] and not with Creatinine levels. In addition prognostic preference of BUN levels as continuous variables was also observed after excluding from the analysis the values of isolated increase in BUN and Creatinine. Thus, we feel that BUN levels have a distinct prognostic significance in assessing the mortality of ACS. Thus, for each unit of BUN elevation, the odds of death increased 1.12 (95% CL 1.06 to 1.20) times after multiple adjustments. As in previous comparisons, Creatinine did not affect the prognosis of ACS.

Table 1: Patients Base line characteristics

Variables	Discharged (n=730)	In-hospital mortality (n=84)	p-value
Female,n (%)	319(44)	31(37)	0.003
Age, years	59(51;68)	63(61;74)	0.001
Medical history, n(%):			
History of hypertension	541(74)	72(85)	0.164
Stable angina	610(84)	63(75)	0.674
Myocardial infarction	340(47)	39(46)	0.759
Congestive cardiac failure	95(13)	9(11)	0.483
Stroke	83(11)	12(14)	0.189
Diabetes mellitus	132(18)	16(19)	0.256
Chronic kidney disease	167(23)	14(17)	0.242
Chronic liver disease	22(3)	------	0.514
At admission:			
ST elevation (>/= 0.5mm) n(%)	88 (12)	49 (58)	0.001
ST depression (>/= 1.0mm) n(%)	240 (33)	58(69)	0.001
Elevated cardiac markers,n(%)	160 (22)	46(55)	0.001
SBP, mmHg	140 (130;160)	120(90;140)	0.001
Heart rate, beats/min	75(64;90)	96(76;118)	0.001
BUN,mmol/L	6.1(4.6;7.8)	10.2 (7.2;16.2)	0.001
Creatinine,µmol/L	94 (80;108)	118(98;160)	0.001
Potassium, mmol/L	4.12(4.01;4.44)	4.36 (4.05;5.02)	0.011
Glucose, mmol/L	5.2 (4.4;6.5)	7.9(6.4;11.4)	0.001
Leucocytes, x 10^{3} $mm3$	8.4(6.4;10.6)	12.2 (9.2;14.4)	0.001
Haemoglobin, g/L	140 (128;152)	132 (116;148)	0.001

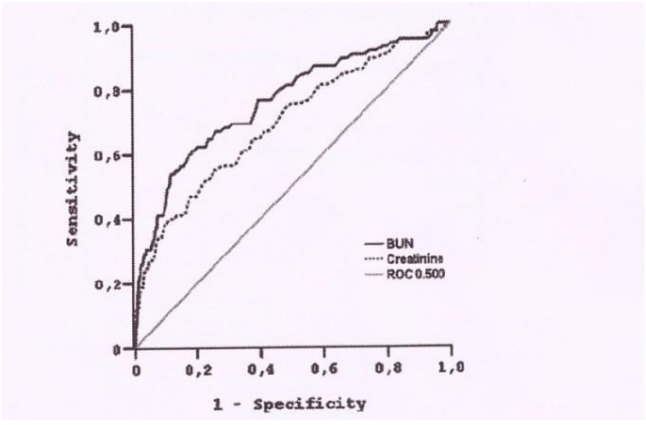

Fig. 1: Receiver-operating characteristic curves for predicting in hospital mortality

Table 2: Unadjusted and multiple adjusted risk of death in patients with elevated blood urea nitrogen (BUN) and / or Creatinine levels

Shivamogga Institute of Medical Sciences, Shivamogga	Shivamogga Institute of Medical Sciences, Shivamogga		
	Shivamogga Institute of Medical Sciences, Shivamogga	Shivamogga Institute of Medical Sciences, Shivamogga	Shivamogga Institute of Medical Sciences, Shivamogga
Refine group +	1	1	1
Creatinine>110µmol/L	1.01 (0.38 to 2.48)	0.90 (0.34 to 2.46)	0.72 (0.22 to 2.18)
BUN >8.6mmol/L	3.76 (1.76 to 8.08)	2.48 (1.14 to 5.46)	2.82 (1.02 to 8.10)
Both elevated	8.84 (4.92 to 13.84)	5.92 3.42 to 9.86)	4.28 (2.16 to 8.12)

***ST- Implies the PQRST points in ECG. There is no full form for ST.

Discussion

This study shows an increase in BUN and Creatinine levels in patients with ACS. Increase in BUN and Creatinine levels was associated with high risk of in-hospital mortality. Increase in BUN and Creatinine are highly prevalent in patients with ACS. According to Mak Akanda et al, each 1 mg/dl increase in BUN was associated with a raised burden of Coronary Artery Disease.[7] Comparison of the prognostic significance of these factors showed that BUN is a more valuable predictor of ACS prognosis than Creatinine. This fact was substantiated when evaluating the prognostic significance of BUN as a continuous or discrete variable in unadjusted or multiple adjusted analyses. As a result, the calculation of the risk in the patient based on the BUN level would be more accurate.

There are many causes for the higher prognostic significance of BUN levels. Thus, BUN helps to assess kidney function more accurately, acting as an integral indicator of filtration and excretory capability. This advantage of BUN increases with age,[16] while the role of Creatinine substantially decreases.[17] Moreover, it is probable that BUN also characterises prerenal causes of azotaemia as a result of renal hypo perfusion. Unlike hyper creatinaemia, increased BUN levels are associated with an adverse prognosis irrespective of the age, Systolic Blood Pressure (SBP), heart rate and ST segment changes in patients with acute heart disease.[18] According to a study by Smith et al, an increased risk of death within 1 year after MI was seen in association with BUN levels >6.1mmol/L, and this marker was more important in the prognosis of adverse altered outcomes than Creatinine or Creatinine clearance.[19]

According to a study by Hartz et al, he states that there is some other explanation for the risk of death in patients with raised BUN levels and is not explained only by renal function- either initially impaired or reduced as a result of hyperfusion.[20] One can assume that the high intensity of catabolic processes can only accelerate with age and is another source of increased BUN in elderly patients. As shown in a number of studies, as well as in our study, it is the level of BUN- not of Creatinine that increases with age in healthy individuals, whereas the level of protein especially serum albumin decreases.[16]

Blood urea nitrogen may have pro-atherosclerotic effects, as uraemia increases burden of oxidative stress.[21] BUN may also both promote macrophage proliferation and inhibit nitric oxide synthesis.[22] Specially, *in vivo* studies demonstrate that increasing levels of urea inhibit nitric oxide synthesis in mouse macrophages with concurrent macrophage proliferation. Furthermore, uremia accelerates atherosclerosis in Apo-lipoprotein E-deficient mice.[7] Other studies indicate that uraemia induces expression of osteoblast differentiation factor cbfa1 in the intimae and media of arteries, leading to vascular calcification.[23]

Elevated creatinine and BUN may also serve as a marker of an activated sympathetic nervous system or an up regulated rennin-angiotensin system. It has been stated that these changes promote atherosclerosis.[18] Activation of these neurohormonal systems has been associated with increased BUN reabsorption in the renal tubules.

The majority of studies in patients with ACS have focussed on serum creatinine, creatinine clearance and GFR as the metrics of kidney function in association with adverse outcomes. The current study demonstrates that the prognostic value of elevated BUN is independent of elevated serum creatinine levels. Serum Creatinine estimates of kidney function did not appear to provide additional prognostic value in multivariate analysis after accounting for BUN. Notably, the association between BUN and cardiovascular outcomes remained significant across strata of other biomarkers associated with increased cardiovascular risk. Concurrent reports show that increasing BUN predicts poor outcome in subjects with acute coronary

syndromes despite normal or mildly reduced glomerular filtration rates. In addition, the association between BUN levels and mortality was evident suggesting that even minimal elevations in BUN may be a marker of adverse outcomes in ACS.

Study limitations

The finding of our work is the result of a single centre study which limits their application to a larger population. Analysis was based on a single measurement of Creatinine and BUN; the changes in levels over times are likely to occur. In our study we did not account for possible and unknown effects of the ongoing medications including diuretics.

Conclusion

We conclude that BUN level might provide significant prognostic benefits in terms of mortality associated with ACS. BUN can be used as a continuous variable in patients with ACS and may enable the application of more appropriate treatment during the period of overt symptoms.

Conflict of Interest: None

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