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

Jyothi S.¹, Sridevi V.²,*

¹Assistant Professor, ²Professor, Dept. of Biochemistry, Shivamogga Institute of Medical Sciences, Shivamogga, Karnataka, India

*Corresponding Author: Email: srivinny4@gmail.com

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 (R² =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 countries¹,² 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 Association⁵ and the European Society of Cardiology⁶ 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 & measures 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 method13 and BUN was calculated.

The BUN: Creatinine ratio was used for distinguishing between renal and non-renal causes of azotaemia.14,15 Co morbidity 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 (25th; 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 χ2 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% CI (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 X2 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 ≤110 µmol/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 (R²) 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   |
| 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 mm^-3           | 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
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.23 Other studies indicate that uraemia induces expression of osteoblast differentiation factor cbfa1 in the intima and media of arteries, leading to vascular calcification.24

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

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


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 |
|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Refine group +                                      | 1                                                   | 1                                                   | 1                                                   |
| Creatinine>110µmol/L                                | (0.38 to 2.48)                                      | (0.34 to 2.46)                                      | (0.22 to 2.18)                                      |
| BUN >8.6mmol/L                                      | 3.76                                                | 2.48                                                | 2.82                                                |
| Both elevated                                       | (1.76 to 8.08)                                      | (1.14 to 5.46)                                      | (1.02 to 8.10)                                      |
|                                                     | (4.92 to 13.84)                                     | 3.42 to 9.86                                        | (2.16 to 8.12)                                      |

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

**Acknowledgements:** We are indebted to our patients for their cooperation during the study period.

**References**

1. Rusan T Saygito, Marya G Glezer et al. Blood urea nitrogen and Creatinine levels at admission for mortality risk assessment in patients with acute coronary syndromes. Emerg Med J 2010; 27:105-9.
2. Thom T, Haase N, Rosamon W, et al. Heart disease and stroke statistics - 2006 Update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006; 2:85-151.
3. Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet 2008;371(9622):1435-42.
4. Van de Wirt F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909-45.
5. Braunwalde E, Antman EM et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2001;38:294-42.
6. Bertrand ME, Simoons ML et al. Management of Acute Coronary Syndromes without persistent ST segment elevation: recommendations of the Task Force of the European Society of Cardiology. Eur Heart J 2000;21:1406-32.
7. Mak Akanda, KN Choudary et al. Serum Creatinine and Blood urea nitrogen Levels in patients with Coronary Artery Disease. Cardiovasc J 2013;5(2):141-5.
8. Granger CB, Goldberg RJ et al. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 2003;163:2345-53.
9. Shilpak MG, Heidenreich PA et al. Association of renal insufficiency with treatment and outcomes after Myocardial Infarction in elderly patients. Ann Inern Med 2002;137:555-62.
10. Levey AS, Bosch JP et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 1999;130:461-70.
11. Lamb EJ, Price CP. Creatinine, urea and uric acid. In: Burtis A C, Ashwood E R, editors. Teitz Fundamentals of clinical chemistry. 5th ed. Philadelphia: W B Sauders; 2001.p.363, 365, 371.
12. Erba diagnostics Mannheim. Creatinine (CRE) Jaffe’s Method, Initial Rate (Pamplet). Germany: Erba Diagnostics Mannheim:2009.
13. Erba diagnostics Mannheim. Urea GLDH – Urease Method, initial rate (Pamplet). Germany: Erba Diagnostics Mannheim:2008.
14. Stark J. Interpretation of BUN and serum Creatinine. An interactive exercise. Crit Care Nurs Clin North Am, 1998 Dec;10(4):391-6.
15. Aronson D, Mittleman MA et al. Elevated blood urea nitrogen levels as a predictor of mortality in patients admitted for decompensated heart failure. Am J Med 2004;116:466-73.
16. Fehrman-Ekholm I, Skepholom L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. Scand J UrolNephrol 2004;38:73-7.
17. Swedko PJ, Clark HD, Paramsothy K, et al. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med 2003;163:56-60.
18. Kirtane AJ, Leder DM, Waikar SS, et al. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. J Am Coll Cardiol 2005;45:1781-6.
19. Smith GL, Shilpak MG, Havranek EP, et al. Serum urea nitrogen, creatinine, and estimators of renal function: mortality in older patients with cardiovascular disease. Arch Intern Med 2006;166:1134-42.
20. Hartz JA, Kuhn ME, Kayser LK, et al. BUN as a risk factor for mortality after coronary artery bypass grafting. Ann Thorac Surg 1995;60:398-404.
21. Himmelfarb J, Stenvinkel Pet al. The elephant in uremia: Oxidative stress as a unifying concept of cardiovascular disease in uremia. Kidney Int J 1992;62:2524-38.
22. Conte G, Canton A, et al. Renal handling of urea in subjects with persistant azotemia and normal renal function. Kidney Int J 1998;32:721-7.
23. Moe S, Duan D et al. Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. Kidney Int J 2003; 63: 1003-11.