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Original Article

Efficacy of serum blood urea nitrogen, creatinine and electrolytes in the diagnosis and mortality risk assessment of patients with acute coronary syndrome

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ABSTRACT

Background: Although blood urea nitrogen (BUN), creatinine (Cr) and electrolytes are not the mainstay of diagnosis in acute coronary syndrome (ACS) patients but they may have a role in providing a more detailed view of the complications and mortality rates. The aim of this study was to determine the efficacy of these parameters in the diagnosis and mortality risk-assessment of patients with ACS.
Methodology: A total of 200 patients with ACS were recruited in this prospective study. The relationship of serum BUN, Cr and electrolytes with cardiac enzymes, Global Registry of Acute Coronary Events (GRACE) and mortality was assessed during a 6-months follow-up. Statistical test like multivariate linear regression and binary logistic regression analysis were applied.
Results: On multivariate linear regression analysis, serum potassium (K) (Unstandardized Coefficient B = −3.77; p = 0.04) showed significant negative association with Creatine Kinease and serum BUN (Unstandardized Coefficient B = 0.52; p = 0.001) showed significant positive association with Troponin I. The patients with GRACE > 105 had significantly higher levels of serum BUN and Cr. Receiver operating characteristic curves showed that area under curve (AUC) of BUN (0.7) was higher than AUC of Cr (0.5). Multiple adjusted model showed that patients with BUN > 32.5 mg/dl were almost 20 times more likely to be associated with mortality as compared to reference group.
Conclusion: In addition to cardiac enzymes, K along with BUN and Cr may serve as important aid in diagnosis of ACS. BUN and Cr may also serve as important tools in mortality-risk assessment of ACS patients.

1. Introduction

Acute coronary syndrome (ACS) is one of the major causes of mortality and morbidity worldwide.[1] The severity and type of ACS varies considerably among individuals.[2] Thus, it becomes important to effectively diagnose and determine the prognosis and mortality risk. The use of serum blood urea nitrogen (BUN), creatinine (Cr) and electrolytes' levels for these purposes is a prospective area for exploration. Even though the mainstay of diagnoses remains the cardiac bio-markers such as troponins, Creatine Kinase-MB and electrocardiography (ECG),[3] electrolyte levels along with renal dysfunction markers can aid in providing a better picture of the patient, and identify those patients that are at a greater risk.[4]

BUN is a powerful predictor and is a sensitive marker for hemodynamic changes and kidney perfusion,[5] but the data for the prognostic value of serum BUN in ACS patients independent to rise in glomerular filtration rate (GFR) is scarce. Although serum Cr, being a gold standard test for GFR, has a good prognostic significance among ACS patients,[6] it is not as accurate for normal or mildly reduced kidney function as serum BUN. In such cases, serum BUN may rise independent to changes in GFR under the influence of sympathetic, arginine-vasopressin, and renin-angiotensin-aldosterone systems, which are activated in ACS and

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increase the renal tubular reabsorption of urea,[7] thus making it a better prognosis predictor than Cr in ACS patients.

While criteria such as thrombolysis in myocardial infarction (TIMI) score, Global Registry of Acute Coronary Events (GRACE) score and HEART score are clinically used to work out the prognosis of patients with ACS, the employment of BUN along side in predicting outcome may prove favorable as well.

Even though electrolytes have a significant role in maintaining the integrity of the cardiovascular system, their role in the diagnosis and prognosis of ACS has not been given considerable significance, albeit a few researches on this topic show the relationship of serum levels of sodium (Na) and potassium (K) with long term mortality risk in ACS patients.[8–11] Magnesium (Mg) serves as a beta-adrenoreceptor blocker and also has an anti-platelet action.[11] Calcium (Ca) plays an electrophysiological role in the cardiac muscle and nodal cells,[12] as do sodium (Na) and potassium (K). Therefore, it is highly likely that any derangement in their levels or their relative ratios may hint at an underlying

Table 1
Comparison of baseline demographical, clinical, laboratory and follow-up data between the two groups, A (GRACE score ≤ 105) and B (GRACE score > 105)

Variables	GRACE score ≤ 105 (GROUP A) n = 103	GRACE score > 105 (GROUP B) n = 97	[a]p-value
Age [years]	56.26 ± 10.46	55.59 ± 11.26	0.661
Male, n (%)	69 (67)	72 (74)	0.262
Previous History			
Smoking, n (%)	28 (27)	33 (34)	0.294
Diabetes Mellitus, n (%)	31 (30)	33 (34)	0.552
Hypertension, n (%)	80 (78)	60 (62)	0.015
Family History Of CAD, n (%)	41 (40)	37 (38)	0.810
MI or CAD, n (%)	69 (67)	61 (63)	0.543
PCI, n (%)	12 (12)	11 (11)	0.945
CABG, n (%)	2 (2)	3 (3)	[d]0.675
Admission heart rate [bpm]	83.28 ± 13.57	82.73 ± 16.49	[b]0.797
Admission SBP [mmHg]	139.58 ± 26.83	116.20 ± 26.37	[b]<0.001
Admission DBP [mmHg]	85.94 ± 15.06	74.84 ± 17.21	[b]<0.001
LVEF [%]	48.12 ± 10.69	43.56 ± 12.16	[b]0.005
Killip class on presentation, n (%)			
≤I	77 (75)	47 (48)	<0.001
>I	26 (25)	50 (52)	
NYHA classification, n (%)			
≤I	36 (35)	12 (12)	<0.001
>I	67 (65)	85 (88)	
Number of diseased vessels			
1 vessel, n (%)	39 (38)	26 (27)	0.095
> 1 vessel, n (%)	64 (62)	71 (73)	
Duration of Hospitalization, [days]	7 (5)	7 (5.5)	[c]0.757
CBC profile			
Hemoglobin [g/dl]	12.61 ± 2.03	12.88 ± 2.09	[b]0.360
Platelet count [x10^3/ul]	288.52 ± 87.04	281.54 ± 114.62	[b]0.630
White blood cell count [x10^3/ul]	10.64 ± 3.30	10.74 ± 3.24	[b]0.830
Red blood cell count [x10^6/ul]	4.77 ± 0.75	4.61 ± 0.76	[b]0.126
Hematocrit [%]	38.31 ± 5.99	38.44 ± 5.84	[b]0.874
Cardiac Enzymes			
CK [IU/L]	150 (258)	192 (417.5)	[c]0.150
CK-MB[IU/L]	41 (39)	48 (31.5)	[c]0.122
Troponin-I [ng/ml]	1.0 (3.2)	4.2 (22.9)	[c]<0.001
Follow up			
Rehospitalization, n (%)	17 (17)	21 (22)	0.354
MI, n (%)	16 (16)	20 (21)	0.350
Cardiogenic shock, n (%)	8 (8)	13 (13)	0.194
Stroke, n (%)	5 (5)	7 (7)	0.482
Dialysis, n (%)	0 (0)	3 (3)	[d]0.112
GI Bleeding, n (%)	7 (7)	7 (7)	0.907
Tranfusion, n (%)	8 (8)	12 (12)	0.278
CABG, n (%)	8 (8)	13 (13)	0.194
Acute stent thrombosis, n (%)	35 (34)	24 (25)	0.152
Mortality, n (%)	2 (2)	20 (21)	<0.001
GRACE score	85.59 ± 15.88	134.36 ± 24.48	[b]<0.001

BP: blood pressure; LVEF: left ventricular ejection fraction; CK-MB: creatine kinase MB isoenzyme; MI—myocardial infarction; NYHA—New York Heart Association; CABG: coronary artery bypass grafting GI: gastrointestinal bleeding; PCI: percutaneous coronary intervention; CAD: coronary artery disease: RDW: red distribution width; MPV: mean platelet volume.

[a] p value < 0.05 were considered statistically significant.

[b] Student's *t*-test.

[c] Mann Whitney *U* test was used to compare quantitative data without normal distribution.

[d] Fisher's exact test and x^2 test (Pearson's chi-square test) were used to compare categorical variables.Data presented as mean±standard deviation, median (IQR) and frequency (percentages).

pathology. Our study aims to establish the potential role of these biochemical markers in the diagnosis and mortality risk assessment of ACS patients.

2. Methodology

This prospective study was conducted after approval from the Institutional Review Board (IRB) of Dow University of Health Sciences during the time period of February 2015–2016. We included 200 ACS patients admitted in Cardiac Emergency Department at Civil Hospital Karachi, Pakistan. Two hundred healthy volunteers were also selected as controls for comparison of biochemical markers with those of ACS patients. All the participants gave informed written consent.

Inclusion criteria included patients older than 18 years of age, diagnosed with ACS and those with complete work-up of complete blood count (CBC), serum electrolytes and cardiac enzymes. ACS including NSTEMI (Non-ST segment elevation myocardial infarction), STEMI (ST segment elevation myocardial infarction) and unstable angina (UA) were diagnosed and categorized using the criteria defined by the American Heart Association.[13]

Patients with non-ACS chest pain, severe liver disease, cancer, inflammatory diseases, bleeding disorders, autoimmune diseases, infectious diseases, chronic kidney disease and immunosuppression were excluded from the study. Furthermore, those who were taking drugs such as angiotensin converting enzyme (ACE) inhibitors, diuretics and spironolactone, those who were not available for follow-up and those who died due to any other cause except cardiovascular events during the follow-up were also excluded from the study. All patients were followed for a minimum of six months.

The patients were interviewed twice with the help of interviewers using two pilot-tested questionnaires, one used at the time of the admission and the other during follow-up. The data of each patient was categorized under three separate sections; 'history and demographics', 'laboratory values and scores at the time of hospitalization', and 'follow-up data'. GRACE score was used to predict prognosis. GRACE is a risk-assessment score, which estimates 6 months mortality in patients with ACS. These scores were calculated using online GRACE ACS Risk and Mortality Calculator.[14]

In order to determine the role of biochemical markers in prognosis of ACS patients and establish a relationship with GRACE score, the patients were divided into two groups, A (GRACE score < 105) and B (GRACE score > 105), according to the median value of GRACE score in our sample which was 105. The total number of patients in group A and B were 103 and 97, respectively.

2.1. Laboratory analysis

An automated hematology analyzer, SYSMEX XN-1000 was used to measure hematological indices. Electrolyte levels were measured by Roche Cobas c501 chemistry analyzer (Roche Diagnostics). Troponin I was measured by Chemiluminescence Microparticle Immune-Assay (CMIA) (Cobas c601), while other cardiac enzymes were measured by Cobas c501.

2.2. Statistical analysis

Analyses were performed using SPSS Statistics, version 17.0 (IBM SPSS Inc., Chicago, IL). The data was tested for normal distribution by Shapiro-Wilk test. All the continuous variables were expressed as mean + standard devation and median (interquartile range) and were analyzed using the Indepedents *t*-test and Mann Whitney *U* test, respectively. Categorical variables were expressed as frequencies (percentages) and were compared using chi-square test or Fisher exact test. Those variables which had a $p < 0.25$ in univariate analysis were included in multivariate linear

Table 2
Multivariate linear regression models showing association of biochemical markers and cardiac enzymes in acute coronary syndrome patients.

Dependent variable: CK					
Model	Unstandardized Coefficients		[a]p-value	95.0% Confidence Interval for B	
	B	Std. Error		Lower Bound	Upper Bound
(Constant)	9.405	3.596	0.010	2.314	16.497
K [mEq/L]	**−3.768**	**1.834**	**0.041**	**−7.384**	**−0.152**
K/Mg	−0.603	0.613	0.327	−1.813	0.607
Na/K	−3.034	1.679	0.072	−6.345	0.277
Dependent variable: CKMB					
Model	Unstandardized Coefficients		[a]p-value	95.0% Confidence Interval for B	
	B	Std. Error		Lower Bound	Upper Bound
(Constant)	2.212	0.717	0.002	0.798	3.627
Ca [mg/dL]	−0.055	0.030	0.066	−0.114	0.004
Na [mEq/L]	−0.001	0.003	0.674	−0.008	0.005
K/Mg	−0.270	0.344	0.432	−0.948	0.407
Na/K	0.133	0.415	0.749	−0.685	0.951
Dependent variable: Troponin I					
Model	Unstandardized Coefficients		[a]p-value	95.0% Confidence Interval for B	
	B	Std. Error		Lower Bound	Upper Bound
(Constant)	3.974	3.078	0.198	−2.096	10.044
Mg [mg/dl]	−0.820	0.939	0.384	−2.671	1.032
PO4 [mg/dl]	0.391	0.338	0.248	−0.275	1.057
Cl [mEq/L]	−2.080	1.548	0.181	−5.134	0.974
Cr [mg/dl]	0.204	0.385	0.596	−0.556	0.965
BUN [mg/dl]	**0.516**	**0.151**	**0.001**	**0.218**	**0.814**
K/Mg	0.103	0.539	0.849	−0.961	1.166

[a] $p < 0.05$ was considered statistically significant.

regression analysis to determine the independent variables likely to affect the cardiac enzymes. The optimum cut-off points for sensitivity and specificity of Cr and BUN in predicting mortality of ACS patients were estimated by performing a receiver operation characteristics (ROC) curve analysis. The following guide was used for classifying the area under curve (AUC) of ROC curve: (i) 0.90–1 = excellent (ii) 0.80–0.90 = good (iii) 0.70–0.80 = fair (iv) 0.60–0.70 = poor (v) 0.50–0.60 = fail.[15] Survival curves were generated using Kaplan-Meier analysis. Binary logistic regression models were applied in order to determine the association of mortality (dependent variable) with Cr and BUN (independent variable). Unadjusted and adjusted, odds ratio (OR) and 95% confidence interval (CI) were calculated. Model I was adjusted for age while model II was adjusted for following factors: age, gender, co-morbidities, heart rate, systolic BP, diastolic BP, Killip class, New York Heart Association (NYHA) classification, left ventricular ejection fraction (LVEF), number of diseased vessels (NODV) and cardiac enzymes.

3. Results

The average age of the population was 55.94 ± 10.83 years while almost 71% (n = 141) were males. More than half (n = 140, 70%) of the patients were hypertensive while almost one-third (n = 78, 39%) of the patients had positive family history of coronary artery disease (CAD). During the mean follow-up time period of 6.3 months, 22 (11%) patients died due to cardiovascular events. Detailed comparison of the baseline characteristics, clinical features and biochemical markers of the groups are shown in Table 1.

There was a significant difference between the mean BUN values of patients who died compared with those who did not during the follow-up period (33.2 mg/dl vs 23.0 mg/dl, p = 0.001). On comparison between Group A (GRACE < 105, n = 103) and Group B (GRACE > 105, n = 97), there were no significant differences in hematological indices and cardiac enzymes between the two groups except for Troponin-I which was higher in group B as compared to group A (median 4.2 ng/ml vs 1.0 ng/ml, p < 0.001). Incidence of adverse cardiac events on follow-up such as rehospitalization (p = 0.35), myocardial infarction (MI) (p = 0.35), cardiogenic shock (p = 0.20), stroke (p = 48) and gastrointestinal bleeding (p = 0.91) were similar between the two groups. However, rates of mortality were almost 10-times higher in group B as compared to group A (21% vs 2%, p < 0.001) [Table 1].

On multivariate linear regression analysis, serum K (Unstandardized Coefficient B = −3.77; p = 0.04) showed significant negative association with creatine kinase (CK) and serum BUN (Unstandardized Coefficient B = 0.52; p = 0.01) showed significant positive association with Troponin I. There was no significant association of any biochemical marker with CK-MB in multivariate analysis [Table 2].

Compared with the control group, ACS patients had significantly higher mean levels of Cr (1.53 mg/dl vs 0.90 mg/dl, p < 0.001) and BUN (33.47 mg/dl vs 12.06 mg/dl, p < 0.001). The levels of serum electrolytes and their ratios showed no significant difference between the control group and the ACS group [Table 3].

The patients in group B had significantly higher mean levels of serum Cr (1.71 mg/dl vs 1.36 mg/dl, p < 0.001) and serum BUN (35.41 mg/dl vs 13.56 mg/dl, p < 0.001) as compared with patients in group A. The levels of serum electrolytes and their ratios showed no significant difference between groups A and B [Table 4].

On ROC curve analysis, the AUC of BUN and Cr was 0.7 (95% CI 0.6–0.8) and 0.5(95% CI 0.4–0.7) respectively. BUN was a fair discriminant with a cut-off value of 32.5 mg/dl (sensitivity 68.2% and specificity 71.3%) while Cr was a poor discriminant with a cut-off value of 1.46 mg/dl (sensitivity 54.5% and specificity 46.1%) in predicting mortality [Fig. 1].

Table 3
Comparison of biochemical markers in controls and ACS patients.

Variables	Control (n = 200)	ACS (n = 200)	[a]p-value
Mg[mg/dl]	2.16 ± 0.28	2.12 ± 0.26	0.111
Ca[mg/dl]	9.03 ± 0.55	8.95 ± 0.61	0.162
K[mEq/L]	4.30 ± 0.80	4.35 ± 0.79	0.550
Na[mEq/L]	138.68 ± 4.85	137.74 ± 6.00	0.079
PO_4 [mg/dl]	3.33 ± 0.81	3.22 ± 0.78	0.148
Cl[mEq/L]	97.54 ± 8.30	98.41 ± 5.68	0.217
BUN[mg/dl]	12.06 ± 4.66	33.47 ± 13.27	<0.001
Cr[mg/dl]	0.90 ± 0.31	1.53 ± 0.37	<0.001
Na/K	33.19 ± 5.41	32.57 ± 5.40	0.246
K/Mg	2.02 ± 0.45	2.08 ± 0.45	0.153
Ca/Mg	4.24 ± 0.58	4.27 ± 0.56	0.589
Na/Mg	65.23 ± 8.87	65.79 ± 8.40	0.513

Data presented as mean ± standard deviation. Analysis of data was done using Student's *t*-test.
Na: Sodium; K: Potassium Mg: Magnesium; Cl: Chloride; PO_4: Phosphate; Ca; Calcium Cr: Creatinine; BUN: Blood urea nitrogen Na/K: sodium to potassium ratio; Na/Mg: sodium to magnesium ratio; K/Mg: potassium to magnesium; Na/Mg: sodium to magnesium ratio
[a] p value < 0.05 were considered statistically significant.

Table 4
Comparison of biochemical markers between the two groups, A (GRACE score ≤ 105) and B (GRACE score > 105).

Variables	GRACE score ≤ 105 (GROUP A) n = 103	GRACE score > 105 (GROUP B) n = 97	[a]p-value
Mg[mg/dl]	2.12 ± 0.27	2.12 ± 0.26	0.867
Ca[mg/dl]	9.01 ± 0.61	8.87 ± 0.60	0.096
K[mEq/L]	4.32 ± 0.85	4.39 ± 0.72	0.543
Na[mEq/L]	138.3 ± 6.56	137.11 ± 5.30	0.155
PO_4[mg/dl]	3.26 ± 0.71	3.17 ± 0.85	0.426
Cl[mEq/L]	98.68 ± 5.31	98.11 ± 6.07	0.638
BUN[mg/dl]	13.56 ± 5.62	35.41 ± 11.41	<0.001
Cr[mg/dl]	1.36 ± 0.30	1.71 ± 0.36	<0.001
Na/K	33.05 ± 5.74	32.05 ± 4.99	0.187
K/Mg	2.06 ± 0.43	2.11 ± 0.48	0.507
Ca/Mg	4.32 ± 0.59	4.21 ± 0.52	0.175
Na/Mg	66.32 ± 8.63	65.22 ± 8.15	0.356

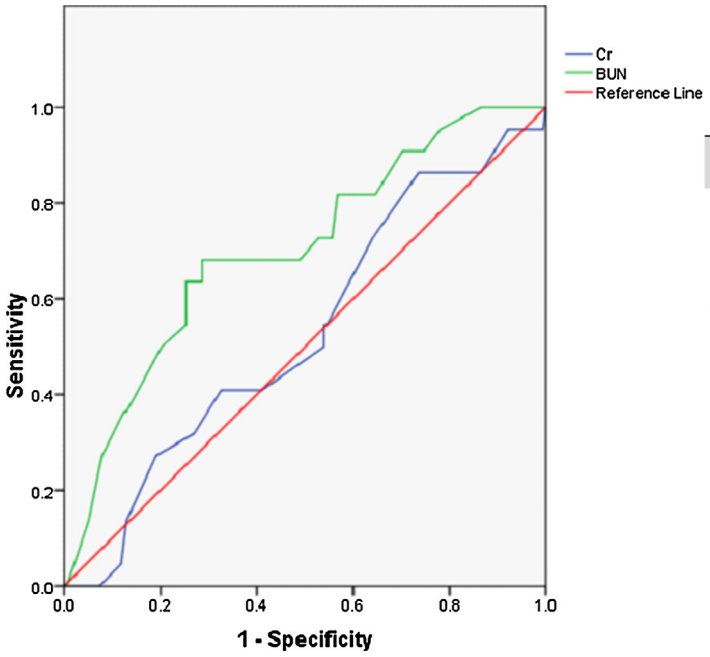
Data presented as mean ± standard deviation.
Student's test was used to compare quantitative data.
Na: Sodium; K: Potassium Mg: Magnsesium; Cl: Chloride; PO_4: Phosphate; Ca; Calcium Cr: Creatinine; BUN: Blood urea nitrogen Na/K: sodium to potassium ratio; Na/Mg: sodium to magnesium ratio; K/Mg: potassium to magnesium; Na/Mg: sodium to magnesium ratio.
[a] p value < 0.05 were considered statistically significant.

3.1. Survival analysis

Kaplan Meier survival analysis showed that patients with BUN > 32.5 mg/dl had lowest probability of survival as compared to patients with Cr > 1.46 mg/dl and/or increase in both Cr and BUN (log rank p < 0.001) [Fig. 2].

3.2. Unadjusted and adjusted binary logistic regression analysis

An increase in BUN only (Cr < 1.46 mg/dl), Cr only (BUN < 32.5 mg/dl) or both was detected in 19 (9.5%), 60 (30%) and 47 (23.5%) patients, respectively. In univariate analysis it was found that patients with BUN > 32.5 mg/dl were almost 10 times (OR = 10.2, 95% CI 2.6–40.3) more likely and patients with both BUN and Cr elevated were almost 4 times (OR = 3.6, 95% CI 1.0–12.7) more likely to be associated with mortality as compared to the reference group (patients with Cr < 1.46 mg/dl and BUN < 32.5 mg/dl). Moreover after adjustment for baseline characteristics (Model II), it was found that an increase in BUN only or Cr only or in both



	Cr	BUN
Sensitivity	54.5%	68.2%
Specificity	46.1%	71.3%
AUC	0.529	0.702
95% CI	0.406-0.652	0.586-0.817
p value	0.655	0.002
Optimum cut-off	1.46	32.5

Fig. 1. Receiver operating characteristic (ROC) curve analysis predicting mortality.

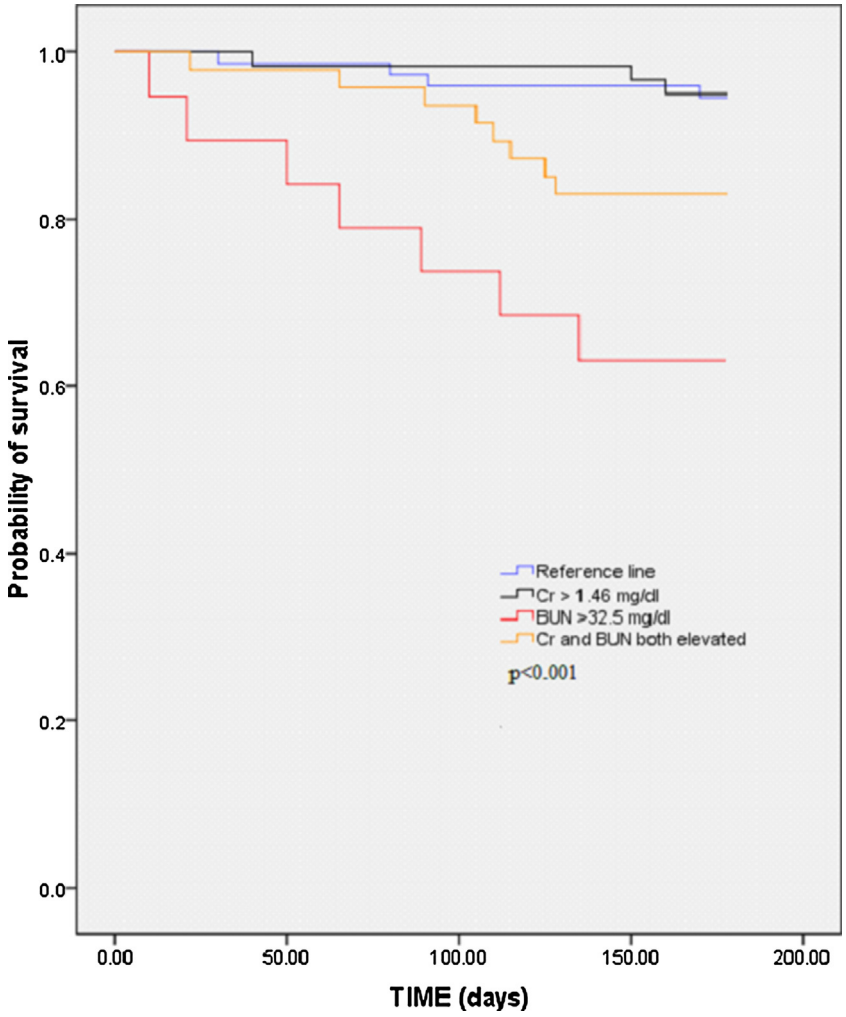


Fig. 2. Kaplan–Meier Survival curve for 6-months mortality in patients with raised BUN and/or Cr levels.

Table 5
Unadjusted and multiple-adjusted risk of death in patients with elevated BUNand/or Cr levels.

At admission	OR (95% CI)		
	Unadjusted (Model I)	Age-adjusted	Multiple-adjusted[a] (Model II)
Reference group[b]	1	1	1
Creatinine > 1.46 mg/dl (only)	0.921 (0.198–4.285)	0.948 (0.201–4.475)	1.483 (0.229–9.617)
BUN > 32.5 mg/dl (only)	10.208 (2.587–40.280)	13.713 (3.212–58.549)	19.943 (2.691–147.785)
Both elevated	3.590 (1.016–12.687)	3.378 (0.931–12.251)	3.849 (0.773–19.170)

[a] Adjusted for age, gender, co-morbids, heart rate, systolic BP, diastolic BP, Killip class, NYHA classification, LVEF, NODV and cardiac enzymes.
[b] Patients with Cr < 1.46 mg/dl and BUN < 32.5 mg/dl at admission.

BUN and Cr, was associated with a high risk of mortality. It should be noted that in multiple-adjusted model (Model II) patients with BUN > 32.5 mg/dl were almost 20 times (OR = 19.9, 95% CI 2.7–147.8) more likely to be associated with mortality as compared to the reference group whereas patients with Cr > 1.46 mg/dl were almost 2 times (OR = 1.5, 95% CI 0.2–9.6) and patients with both BUN and Cr elevated were almost 4 times (OR = 3.8, 95% CI 0.8–19.2) more likely to be associated with mortality as compared to the reference group (Table 5).

4. Discussion

Our study shows that serum K and serum BUN are significantly correlated with cardiac enzymes in patients suffering from ACS. Several previous studies show similar findings.[4,16–18] From among these, K levels showed an inverse relationship with CK levels. One potential explanation for this could be the role of adrenaline in driving K into the cells.[19] In times of stress, including MI, the adrenaline surge due to sympathetic nervous system activation, apart from its various physiological abilities also has the ability to force K into cells, accounting for a decrease in serum K levels.[20,21] A similar discussion was proposed in the study by Solini et al.[22] These findings suggest that potassium along with BUN may serve as adjuvant diagnostic markers for ACS, and in settings where cardiac enzymes cannot be conducted, be used to aid other investigations in diagnosing ACS.

In contrast to the control patients, ACS patients showed significantly elevated levels of serum Cr and BUN. Such findings have been reported in several previous studies.[23] One reason for the increased BUN in ACS patients may be the association of uremia with atherosclerosis due to the oxidative stress exerted on vessel walls, eventually leading to myocardial ischemia or infarction.[24] Secondly, the sympathetic nervous system and the renin-angiotensin system are up regulated during an episode of ACS, both of which are associated with increased reabsorption of BUN from the kidney tubules.[25] Thirdly, increased serum Cr and BUN levels being markers of kidney function may indicate renal disease, and the association of renal disease with coronary artery disease has been well established.[26] Therefore, a reason for the ACS patients having higher Cr and BUN levels than the control group may simply be due to the fact that renal patients are more likely to present with ACS. Increased levels may be a reason, or the result of ACS.

For the prognosis of ACS patients, we used the GRACE score as a comparative marker for several biochemical markers in order to estimate the prognosis. While the GRACE score factors in several variables such as the age, Killip class, electrocardiographic changes, cardiac markers and Cr levels, it does not account for the patient's serum BUN and electrolyte levels at the time of admission. Our study shows that patients who have a higher GRACE score also tend to have significantly higher serum BUN levels. This can be explained by the fact that patients of ACS are in a state of renal hypo-perfusion due to sympathetic vasoconstriction and decreased cardiac output that leads to decreased excretion of Cr and BUN by the kidneys, hence increased serum levels.

GRACE score includes Cr levels in its calculation and Cr levels are directly related to BUN levels. Therefore, with increasing BUN levels, the GRACE score should also be expected to rise. The role of electrolytes in determining prognosis of ACS patients was not found to be significant in our study, likely due to the fact that electrolyte imbalances are acute changes and are less likely to determine long term prognosis.

Since BUN and Cr proved to be useful markers in the diagnosis and prognosis of ACS patients, we performed further analysis to observe association of these markers with mortality in our study. Upon ROC analysis, BUN and Cr had cut off values of 32.5 mg/dl and 1.46 mg/dl respectively in predicting the mortality. Moreover, BUN has a higher sensitivity and specificity than Cr in determining the mortality of ACS patients according to our study. This finding is supported by several other studies that conclude that the significance of Cr in determining the renal function declines with age,[27,28] and that this role is better played by BUN levels.[29,30] Moreover, logistic regression analysis proved that such patients whose BUN levels were greater than our observed cut-off values were almost 20 times more likely to experience adverse cardiovascular events leading to mortality, after effects of other variables (such as age, gender, comorbids, cardiac enzymes etc) on the outcome were excluded. A similar study by Saygitov et al. showed that elevations in serum BUN on admission were associated with a four times greater risk for mortality.[31] Two differences are worth discussing with regard to this study. Firstly, the risk of mortality is far greater in our study. A reason for this could be the post ACS healthcare and lifestyle differences between the two settings. It is very likely that these differences could account for a worse prognosis of patients in our setting. Secondly, the cutoff value observed for BUN during ROC analysis in the aforementioned study was 8.8 mmol/L (24.64 mg/dL) which is considerably less than our value of 32.5 mg/dL. An explanation for this contrast could be the fact that the door-to-hospital time during an emergency in Karachi is much more than that in Moscow, hence on-admission BUN levels recorded will generally be higher as more time has elapsed since the onset of ACS.

Our study has certain limitations. First, this study was conducted in one particular hospital of the city, focusing on a small group of people with more or less similar demographics. Hence, the application of the results of this study over a large population might be limited. Secondly, the time at which blood samples were drawn from the patients to test for electrolytes was not standardized for all patients, even though they were all taken at admission.

5. Conclusion

Our study shows that for diagnosis of ACS, potassium levels along with serum BUN and Cr are useful adjuvant biochemical

markers. Furthermore, BUN and Cr may play a role in the pathogenesis of ACS, or may be an outcome of ACS. Regardless of that, BUN and Cr were found significantly raised in ACS patients in our study, making them useful adjuvant diagnostic markers. For prognosis of ACS patients, BUN and Cr serve as important tools to identify patients who are at a greater risk, as per their comparison with other scales of estimating prognosis (GRACE score). Patients with increased BUN levels on admission were also observed to be several times more likely to experience mortality due to cardiovascular events. BUN being a relatively common test done in routine, can make it efficient to flag high risk ACS patients for close monitoring of any adverse cardiovascular events.

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Disclosure

The Authors declare that there is no conflict of interest.

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References

1. Hung CL, Chien DK, Shih SC, et al. The feasibility and diagnostic accuracy by multiple cardiac biomarkers in emergency chest pain patients: a clinical analysis to compare 290 suspected acute coronary syndrome cases stratified by age and gender in Taiwan. *BMC Cardiovasc Disord*. 2016;16:191–192.
2. Uren N. Acute coronary syndromes: assessing risk and choosing optimal pharmacological regimens for a superior outcome. *Eur Heart J Suppl*. 2010;12 (suppl D):D4–13.
3. Pearson DA, Wares CM, Mayer KA, et al. Troponin Marker for acute coronary occlusion and patient outcome following cardiac arrest. *West J Emerg Med*. 2015;16:1007–1013.
4. Ramasamy R, Murugaiyan SB, Gopal N, et al. The prospect of serum magnesium and an electrolyte panel as an adjuvant cardiac biomarker in the management of acute myocardial infarction. *J Clin Diagn Res*. 2013;7:817–820.
5. Aronson D, Hammerman H, Beyar R, et al. Serum blood urea nitrogen and long-term mortality in acute ST-elevation myocardial infarction. *Int J Cardiol*. 2008;127(3):380–385.
6. 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(11):1781–1786.
7. Klein L, Massie BM, Leimberger JD, et al. Admission or changes in renal function during hospitalization for worsening heart failure predict post discharge survival: results from the outcomes of a prospective trial of intravenous milrinione for exacerbation of chronic heart failure (OPTIME-CHF). *Circ Heart Fail*. 2008;1:25–33.
8. Keskin M, Kaya A, Tatlısu MA, et al. The effect of serum potassium level on in-hospital and long-term mortality in ST elevation myocardial infarction. *Int J Cardiol*. 2016;221:505–510.
9. Shlomai G, Berkovitch A, Pinchevski-Kadir S, et al. The association between normal-range admission potassium levels in Israeli patients with acute coronary syndrome and early and late outcomes. *Medicine (Baltimore)*. 2016;95:3778.
10. Burkhardt K, Kirchberger I, Heier M, et al. Hyponatraemia on admission to hospital is associated with increased long-term risk of mortality in survivors of myocardial infarction. *Eur J Prev Cardiol*. 2015;22:1419–1426.
11. Myoishi M, Kitakaze M. A role of magnesium: magnesium in the therapy for cardiovascular diseases. *Clin Calcium*. 2005;15:265–270.
12. Eisner D, Bode E, Venetucci L, et al. Calcium flux balance in the heart. *J Mol Cell Cardiol*. 2018;58:110–117.
13. Acute Coronary Syndrome [Internet]. Heart.org. 2017 [cited 11 February 2017]. Available from: http://www.heart.org/HEARTORG/Conditions/HeartAttack/AboutHeartAttacks/Acute-Coronary-Syndrome_UCM_428752_Article.jsp#.WJ-IYzt97IU.
14. GRACE ACS Risk and Mortality Calculator - MDCalc [Internet]. Mdcalc.com. 2017 [cited 12 February 2017]. Available from: http://www.mdcalc.com/grace-acs-risk-and-mortality-calculator/.
15. The Area Under an ROC Curve [Internet]. Gim.unmc.edu. 2017 [cited 25 February 2017]. Available from: http://gim.unmc.edu/dxtests/roc3.htm.
16. Solini A, Zamboni P, Passaro A, et al. Acute vascular events and electrolytes variations in elderly patients. *Horm Metab Res*. 2006;38:197–202.
17. Ising H, Günther T, Bertschat F, et al. Alterations of electrolytes in serum and erythrocytes after myocardial infarction. *Magnesium Res*. 1987;6:192–200.
18. Aalbers TG, Houtman JPW. Relationships between trace elements and atherosclerosis. *Sci Total Environ*. 1985;43:255–283.
19. DeFronzo RA, Bia M, Birkhead G. Epinephrine and potassium homeostasis. *Kidney Int*. 1981;20:83–91.
20. Jewitt DE, Reid D, Thomas M, et al. Free noradrenaline and adrenaline excretion in relation to the development of cardiac arrhythmias and heart-failure in patients with acute myocardial infarction. *Lancet*. 1969;293:635–641.
21. Karlsberg RP, Cryer PE, Roberts R. Serial plasma catecholamine response early in the course of clinical acute myocardial infarction: relationship to infarct extent and mortality. *Am Heart J*. 1981;102:24–29.
22. Solini A, Zamboni P, Passaro A, et al. Acute vascular events and electrolytes variations in elderly patients. *Horm Metab Res*. 2006;38:197–202.
23. Akanda MA, Choudhury KN, Ali MZ, et al. Serum creatinine and blood urea nitrogen levels in patients with coronary artery disease. *Cardiovasc J*. 2013;.
24. Himmelfarb J, Stenvinkel P, Ikizler TA, et al. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int*. 2002;62:1524–1538.
25. Conte G, Dal Canton A, Terribile M, et al. Renal handling of urea in subjects with persistent azotemia and normal renal function. *Kidney Int*. 1987;32:721–727.
26. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295.
27. Duncan L, Heathcote J, Djurdjev O, et al. Screening for renal disease using serum creatinine: who are we missing? *Nephrol Dial Transplant*. 2001;16:1042–1046.
28. 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;163:356–360.
29. Aono T, Matsubayashi K, Kawamoto A, et al. Normal ranges of blood urea nitrogen and serum creatinine levels in the community-dwelling elderly subjects aged 70 years or over–correlation between age and renal function. *Nihon Ronen Igakkaizasshi. Jpn J Geriatr*. 1994;31:232–236.
30. Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scand J Urol Nephro*. 2004;38:73–77.
31. Saygitov RT, Glezer MG, Semakina SV. Blood urea nitrogen and creatinine levels at admission for mortality risk assessment in patients with acute coronary syndromes. *Emerg Med J*. 2010;27:105–109.