Published in final edited form as:

Crit Care Med. 2011 February ; 39(2): 305–313. doi:10.1097/CCM.0b013e3181ffe22a.

Elevation of BUN is predictive of long-term mortality in critically ill patients independent of 'normal' creatinine

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Abstract

Objective—We hypothesized that elevated BUN can be associated with all cause mortality independent of creatinine in a heterogeneous critically ill population.

Design—Multicenter observational study of patients treated in medical and surgical intensive care units.

Setting—20 intensive care units in two teaching hospitals in Boston, Massachusetts

Patients—26,288 patients, age 18 years, hospitalized between 1997 and 2007 with creatinine 0.80–1.30 mg/dl.

Measurements—BUN at ICU admission was categorized as 10–20, 20–40 and >40 mg/dl. Logistic regression examined death at days 30, 90 and 365 post-ICU admission as well as in hospital mortality. Adjusted odds ratios were estimated by multivariable logistic regression models.

Interventions—None

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Institution where work was performed: Brigham and Women's Hospital

The authors have no potential conflicts of interest to disclose.

This work was presented in part at the national meeting of the National Kidney Foundation April, 2010

Key Results—BUN at ICU admission is predictive for short term and long term mortality independent of creatinine. 30 days following ICU admission, patients with BUN >40 mg/dl have an Odds Ratio for mortality of 5.12 (95% CI, 4.30–6.09; $P<.0001$) relative to patients with BUN 10–20 mg/dl. BUN remains a significant predictor of mortality at 30 days following ICU admission following multivariable adjustment for confounders, patients with BUN >40 mg/dl have an Odds Ratio for mortality of 2.78 (95% CI, 2.27–3.39; $P<.0001$) relative to patients with BUN 10–20 mg/dl. 30 days following ICU admission, patients with BUN 20–40 mg/dl have an OR of 2.15 (95% CI, 1.98–2.33; $P<.0001$) and a multivariable OR of 1.53 (95% CI, 1.40–1.68; $P<.0001$) relative to patients with BUN 10–20 mg/dl. Results were similar at 90 and 365 days following ICU admission as well as in-hospital mortality. A subanalysis of patients with blood cultures ($n=7,482$), demonstrated that BUN at ICU admission was associated with the risk of blood culture positivity.

Conclusion—Among critically ill patients with Cr 0.8–1.3 mg/dl, an elevated BUN is associated with increased mortality, independent of serum creatinine.

Keywords

Blood Urea Nitrogen; Intensive Care; Mortality; Gastrointestinal Bleed; Creatinine

Introduction

Blood Urea Nitrogen (BUN) levels are determined by the complex balance between urea production, urea metabolism and urea excretion. BUN is modulated by a number of renal and non-renal dependent factors. Contributors to BUN levels include glomerular filtration, tubular reabsorption of urea, dietary protein intake, parenteral hyperalimentation therapy, catabolism of endogenous proteins, exogenous glucocorticoid dependent catabolism, volume status and upper gastrointestinal bleeding.

BUN is not a direct factor in the pathway of system dysfunction, but rather a surrogate marker associated with increased severity of renal and or systemic illness. BUN is considered to be relatively non toxic, functioning more as a marker for other low molecular weight uremic toxins (1) and is not considered a uremic toxin.(2)

Elevated BUN level is correlated with increased mortality in patients with acute heart failure,(3–9) chronic heart failure,(10) coronary artery bypass graft (CABG)(3) and is predictive for intensive care unit (ICU) stay and survival in acute necrotizing pancreatitis. (11) BUN has been incorporated into risk prediction models in myocardial infarction(12) and pneumonia.(13) In patients with severe Acute Kidney Injury who require dialysis, pre-dialysis BUN is predictive of 60 day mortality.(14) BUN also predicts short term mortality following bone marrow transplant(15) and esophagectomy.(16) Finally, elevated BUN is associated with adverse outcomes in patients with acute coronary syndromes who have glomerular filtration rates > 40 ml/min(17).

Because these observations suggest that BUN may have value as a marker for increased mortality in critically ill patients, we performed a multicenter observational study of critically ill patients among whom BUN was measured in 26,387 critically ill patients hospitalized between 1997 and 2007. The aim of this study is to determine the relationship between elevation of BUN independent of creatinine at ICU admission in patients with Cr 0.8–1.3 mg/dl and long-term mortality.

Materials and Methods

Source Population

We extracted administrative and laboratory data from individuals admitted to 2 academic teaching hospitals in Boston, Massachusetts. Brigham and Women's Hospital (BWH) is a 777-bed teaching hospital with 100 ICU beds. Massachusetts General Hospital (MGH) is a 902-bed teaching hospital with 109 ICU beds. The two hospitals provide primary as well as tertiary care to an ethnically and socioeconomically diverse population within eastern Massachusetts and the surrounding region.

Data Sources

Data on all patients admitted to BWH or MGH between November 2, 1997 and December 31, 2007 were obtained through a computerized registry which serves as a central clinical data warehouse for all inpatients and outpatients seen at these hospitals. The database contains information on demographics, medications, laboratory values, microbiology data, procedures and the records of inpatient and outpatients. Approval for the study was granted by the Institutional Review Board of BWH.

The following data were retrieved: Demographics, Vital status for up to 10 years following ICU admission, Hospital admission and discharge date, laboratory values, blood bank reports, medications, Diagnosis Related Group (DRG) assigned at discharge, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes, and Current Procedural Terminology (CPT) codes for in-hospital procedures and services.

During the 10-year study period there were 26,387 unique patients, age 18 years, who were assigned the CPT code 99291 (critical care, first 30–74 minutes) who also had creatinine (0.8–1.3 mg/dl) on the first day of CPT code 99291 assignment. 99 foreign patients without Social Security Numbers were identified and excluded as mortality is determined via the social security death index. 124 patients were excluded for incomplete data. 26,288 patients constituted the study cohort.

Exposure of Interest and Comorbidities

The exposure of interest was BUN at ICU admission and stratified *a priori* as 10–20 mg/dl, 20–40 mg/dl, and >40 mg/dl.

Sepsis was defined by the presence of any of the following ICD-9-CM codes: 038.0–038.9, 020.0, 790.7, 117.9, 112.5, and 112.81.(18) Acute myocardial infarct is defined by ICD-9-CM 410.0–410.9(19) prior to or on day of ICU admission. Congestive heart failure (CHF) is defined by ICD-9-CM 428.0–428.4 prior to or on the day of ICU admission.(20) Acute kidney injury (AKI) was defined as ICD-9-CM 584.5, 584.6, 584.7, 584.8, or 584.9.(21) Upper gastrointestinal bleed (UGIB) was defined as CPT codes for endoscopy (44.43, 45.13, 45.16, 45.14) with the presence of ICD-9-CM code 531.0–531.9, 532.0–532.9, 533.0–533.9, 534.0–534.9, 578.0, 578.1, or 578.9 prior to or on the day of ICU admission.(22)

Transfusion data was obtained via blood bank reports. Red blood cell transfusion unit amount, date and time were recorded. Only patients who received red blood cell transfusions in the 48 hours prior to ICU admission were included.

Medication records of the administration of the intravenous glucocorticoids Hydrocortisone and Methylprednisolone were obtained. Drug, date of administration and number of doses were recorded. Only patients who received intravenous glucocorticoids for at least 24 hours within 7 days of ICU admission were included.

Records of the administration of total parenteral nutrition (TPN) in the 7 days prior to ICU admission was determined by CPT code 99.15 and confirmed by pharmacy records. Information regarding enteral feeds was not available in this cohort.

Patient Type is defined as Medical or Surgical and incorporates the Diagnostic Related Grouping (DRG) methodology, devised by Centers for Medicare & Medicaid Services (CMS).(23) The Major Diagnostic Categories (MDC) are formed by dividing all DRGs into 25 mutually exclusive diagnosis areas.(24)

The Deyo–Charlson index to assess the burden of chronic illness.(25) The Deyo–Charlson index consists of 17 co-morbidities, which are weighted and summed to produce a score each with an associated weight based on the adjusted risk of one-year mortality. This score ranges from 0 to 33, with higher scores indicating a higher burden. The score does not measure type or severity of acute illness.(25–26) We employed the ICD-9 coding algorithms developed by Quan et al(27) to derive a Deyo–Charlson index for each patient. The validity of the algorithms for ICD-9 coding from administrative data is reported.(27) Due to scant representation, Deyo–Charlson index scores ≥ 7 were combined.

All patients who had blood cultures drawn 48 hours prior or 48 hours subsequent to an ICU admission were identified. Blood cultures were defined as positive if aerobic, anaerobic or fungal blood cultures grew identifiable organisms.

Assessment of Mortality

Information on vital status for the study cohort was obtained from the Social Security Death Index. The Social Security Death Index yields a high sensitivity and specificity for classifying deaths.(28) The censoring date was July 27, 2009.

End Points

The primary end point was 30 day mortality following ICU admission. Other pre-specified end points included 90 day, 365 day and in-hospital mortality, and blood culture positivity.

Statistical Analysis

Categorical covariates were described by frequency distribution, and compared across BUN groups using contingency tables and chi-square testing. Continuous covariates were examined graphically (e.g., histogram, box plot) and in terms of summary statistics (mean, SD, median, inter-quartile range), and compared across exposure groups using one-way ANOVA. Survival analyses considered death by days 30, 90 and 365 post-ICU admission as well as in hospital mortality. In each instance, subjects were excluded if they were censored for incomplete data. 365 day follow-up was present for all 26,288 patients in the cohort.

Unadjusted associations between BUN groups and outcomes were estimated by contingency tables, chi square testing, by bivariable logistic regression analysis. Adjusted odds ratios were estimated by multivariable logistic regression models with inclusion of covariate terms thought to plausibly interact with both BUN levels and mortality. For the primary model (30-day mortality), specification of each continuous covariate (as a linear versus categorical term) was adjudicated by the empiric association with the primary outcome using Akaike's Information Criterion; overall model fit was assessed using the Hosmer Lemeshow test. Models for secondary analyses (90-day, 365-day and in-hospital mortality and blood culture positivity) were specified identically to the primary model in order to bear greatest analogy. We assessed possible effect modification of upper gastrointestinal bleed, acute kidney injury and creatinine on the risk of mortality. We tested the significance of the interaction using the likelihood-ratio test. All p-values presented are two-tailed; values below 0.05 were

considered nominally significant. All analyses are performed using STATA 10.0MP (College Station, TX).

Results

Table 1 lists the main relevant characteristics of the 26,288 study cohort. Of the patients studied, 36.6% were women and 80.6% were white. The mean age at ICU Admission was 61.46 years (SD 18.5). 30 day all cause mortality was 10.61%. 48.7% of patients were assigned a Medical DRG at discharge. The most common Major Diagnostic Category in the cohort was the circulatory system. Congestive heart failure was present in 22.6%. 17.5% of patients suffered an acute myocardial infarct. 6.4 % of the cohort underwent CABG and 9.2% of patients were septic. 13.15% of patients were transfused red blood cells. 3.7% of patients were treated with intravenous glucocorticoids. A small minority of patients (0.4%) received total parenteral nutrition prior to ICU admission.

Patient characteristics of the study cohort were stratified according to BUN levels at ICU admission (Table 2). Factors that significantly differed between stratified groups included age, sex, race, Deyo-Charlson Index, DRG type (medical/surgical), and time lag between hospital and ICU admission. Other significant differences in the stratified groups included sepsis, glucocorticoids, CABG, Congestive Heart Failure, acute kidney injury, HCO_3^- , hematocrit, total parenteral nutrition, upper gastrointestinal bleed, white blood cells, blood culture positivity and creatinine. Acute myocardial infarction and transfusion did not significantly differ between stratified groups and were not associated with primary or secondary outcomes. Age, BUN, Deyo-Charlson Index, glucocorticoids, and sepsis are significantly associated with 30-day mortality (Table 3). Due to scant representation, total parenteral nutrition use was not further analyzed in the patient cohort. Acute kidney injury was not included in the adjustment analysis as it is plausibly an intermediate on a causal pathway between BUN and mortality.

In patients with creatinine of 0.8–1.3 mg/dl, BUN at ICU admission was associated with increased short term and long term mortality. 30 days following ICU admission, patients with BUN > 40 have an Odds Ratio for mortality of 5.12 (95% CI, 4.30–6.09; $P < .0001$) relative to patients with BUN 10–20 mg/dl. 30 days following ICU admission, patients with BUN 20–40 mg/dl have an Odds Ratio for mortality of 2.15 (95% CI, 1.98–2.33; $P < .0001$) relative to patients with BUN 10–20 mg/dl (Table 4). After adjustment for age (continuous), sex, race (white, non-white), days from hospital admission to ICU care (0,1,2+), Deyo-Charlson index(0, 1, 2, 3..., 7+), type (surgical vs medical), congestive heart failure, CABG, glucocorticoids, sepsis, hematocrit, upper gastrointestinal bleed, white blood count, HCO_3^- , and creatinine, BUN in the cohort remains a significant predictor of mortality: BUN >40 adjusted OR 2.78; 95% CI, 2.27–3.39; $P < .0001$, BUN 20–40 adjusted OR 1.53; 95% CI, 1.40–1.68; $P < .0001$ (Table 4). Similar significant robust associations pre and post multivariable adjustments are seen with death by days 90 and 365 post-ICU admission as well as in hospital mortality (Table 4).

There is effect modification of the BUN-mortality association on the basis of upper gastrointestinal bleed (Table 5). In all cases, the risk associated with BUN higher than 10–20 mg/dl decreases or is obviated in the presence of upper gastrointestinal bleed. There is no significant effect modification of the BUN-mortality association on the basis of acute kidney injury (P for interaction=0.15 in the primary model, 30-day mortality, adjusted, data not shown).

Following stratification of the data by Creatinine (Cr 0.8–0.9, 1–1.1, 1.2–1.3), a positive association in each stratum is observed which indicates that the BUN-mortality relationship

is not materially confounded by creatinine. The estimates were similar in each creatinine stratum indicating that the effect of BUN on mortality is the same regardless of where a cohort subject is on the creatinine spectrum.(Table 6) Formally, there is no significant effect modification of the BUN-mortality association on the basis of creatinine (P for interaction=0.48 in the primary model, 30-day mortality, adjusted).

In a subanalysis of patients with blood cultures drawn (n= 7482), BUN at ICU admission was associated with blood culture positivity. Patients with BUN > 40 have an Odds Ratio for blood culture positivity of 2.27 (95% CI, 1.76–2.94; P<.0001) relative to patients with BUN 10–20 mg/dl. Patients with BUN 20–40 mg/dl have an Odds Ratio for blood culture positivity of 1.53 (95% CI, 1.33–1.76; P<.0001) relative to patients with BUN 10–20 mg/dl (Table 7). After multivariable adjustment, BUN in the cohort remains a significant predictor of blood culture positivity: BUN >40 adjusted OR of 2.18 (95% CI, 1.65–2.89; P<.0001) and BUN 20–40 adjusted OR of 1.52 (95% CI, 1.31–1.76; P<.0001) both relative to patients with BUN 10–20 mg/dl (Table 7). Thus, cohort patients with BUN>20 mg/dl have a significantly higher risk of bacteremia and or fungemia than patients with BUN 10–20 mg/dl.

Discussion

The present study aimed to determine whether serum BUN level at ICU admission was associated with all cause mortality independent of creatinine. This large 10-year multicenter observational study illustrates the all cause mortality risk of BUN elevation at ICU admission. In patients with creatinine 0.8–1.3 mg/dl, BUN at ICU admission is a significant predictor of 30, 90, 365 and in-patient mortality. BUN remains a significant predictor of survival following multivariable adjustments including creatinine, congestive heart failure, sepsis, Deyo-Charlson Index, glucocorticoid use, and time from hospital admission to ICU care. BUN does not take on the same prognostic significance in the setting of an upper gastrointestinal bleed. Finally, BUN at ICU admission is a predictor of risk of blood culture positivity, possibly reflecting immune modulation during catabolism.

Urea ($(\text{NH}_2)_2\text{CO}$) is reabsorbed via active and passive transport in the kidney. Urea excretion increases with increased protein intake and decreased with decreased protein intake.(29) Urea reaches the bowel via the blood and diffuses into the bowel lumen. Products of urea hydrolysis (CO_2 + ammonia) by urease rich microflora in the colon are directly used for glutamine synthesis in enterocytes.(30–31) High incoming concentrations of ammonia from the splanchnic bed are utilized for urea synthesis.(32–34)

Another significant source of ammonia is amino acid catabolism in the course of protein breakdown.(32) The function of the urea cycle and availability of substrates (ammonia and amino acids) in hepatocytes determines the amount of ureagenesis. Long term regulation of the urea cycle occurs during adaptation to chronic increases in enteral or parenteral protein intake or to other protein catabolic states, such as starvation or critical illness.(35)

Variables such as glomerular filtration, tubular reabsorption of urea, protein intake, catabolism, volume status and upper gastrointestinal bleeding can alter BUN. Measured contributors to BUN levels addressed in this study included glucocorticoids, metabolic acidosis, upper gastrointestinal bleeding, renal function and total parenteral nutrition. Glucocorticoids are associated with increased utilization of amino acids for increased ureagenesis.(36) Metabolic acidosis is demonstrated to induce a state of net protein catabolism with sustained negative nitrogen balance, increased protein breakdown and decreased protein synthesis.(37) Total parenteral nutrition is also associated with increased BUN.(38) BUN can also increase independent of a change in serum Creatinine with renal

hypoperfusion from hypovolemia (pre-renal azotemia), sepsis, or reduced cardiac output. (39–40)

Volume status in the critically ill appears to be related to hospital mortality. Positive mean fluid balance is an independent predictor of ICU mortality (41–42). Patients with ARDS achieving goal-directed fluid removal have greater hospital survival(43). Early goal-directed therapy improves mortality in patients with severe sepsis and septic shock.(44) With regards to the BUN-mortality association in our study, an improvement in mortality may be related to early goal-directed resuscitation and, as an effect of increased fluid administration, a reduction in the BUN on day 1 of ICU care.

In this study we focused on patients with Cr 0.8–1.3 mg/dl, values considered to be in the normal range by the institutions under study. These normal creatinine ranges are based on a calibrated determination of serum creatinine that is performed on healthy individuals. This range may have individuals with abnormal renal function as multiple patient variables such as age, gender, race,(45) protein intake,(46) and lean muscle mass can alter creatinine generation. Creatinine at time of ICU admission may be influenced by renal function and fluid balance. We did not include patients with creatinine <0.8 mg/dl in this study as creatinine <0.8 mg/dl in the critically ill is associated with increased mortality.(47)

In our cohort, creatinine significantly differs across BUN strata.(Table 2) In the BUN>40 mg/dl group, 51.4% of the patients had Cr 1.2–1.3. Despite these observations, analysis of cohort data stratified by creatinine demonstrates that the BUN-mortality association is not materially confounded by creatinine.(Table 6) This indicates that the BUN-mortality association in this cohort of patients with Cr 0.8–1.3 mg/dl is independent of creatinine.

The limitations of this study stem from its retrospective observational design with its inherent biases. The patients were selected according to the normal levels of serum creatinine at our institution; these levels are not compared with national references and therefore may not be generalized. Our finding that BUN is a significant predictor of mortality does not include physiologic data. We are unable to adjust for fluid status in our study cohort an important variable that can alter BUN. Also, the study was performed in a tertiary center and the results may not be generalized.

The accuracy of ICD-9-CM coding for the identification of medical conditions remains controversial.(18) Administrative coding data has been evaluated for particular disease states(48–52) and comorbidity profiles.(53–54) The Deyo–Charlson index is well suited for use in administrative datasets and algorithms developed to recode administrative collected and coded ICD-9-CM diagnosis data into a Deyo–Charlson index have been well studied and validated.(55–56) With the addition of age and gender data, the Deyo-Charlson index can be considered an alternative method of risk adjustment in the absence of physiologic data.(57)

The present study has several strengths. As other chronic medical conditions may affect the attributed cause of death, all-cause mortality is considered an unbiased and clinically relevant outcome in long-term observational studies.(58–59) Utilization of the Social Security Death Index allowed for long term follow up of the entire cohort following hospital discharge. Our relatively large, regional, multicenter study has sufficient numbers of patients to ensure the adequate reliability of our mortality estimates (n = 26,288, hospital mortality rate = 9.7%). We employed previous records to define comorbidities which increase prevalence of these conditions, resulting in a better risk adjustment.(50, 60) Finally, the timing of measurement of BUN is uniform relative to the onset of ICU admission.

We believe these observations presented in this study are not an epiphenomenon but an association. The mechanism of the association between mortality and high BUN in this study may be related to the neurohumoral response to arterial underfilling. Such response involves AVP, the renin–angiotensin–aldosterone system and the sympathetic nervous system.(61–63) High plasma AVP concentrations can result in increased urea reabsorption in the collecting duct, resulting in an increased BUN.(64) Angiotensin and adrenergic stimulation increase proximal tubular sodium and water reabsorption, decreasing distal fluid delivery which increases flow-dependent urea reabsorption.(65) Such arterial underfilling states are common in cardiac failure and sepsis(66), conditions that contribute to mortality and are common to our cohort. (Figure1)

Elevations in BUN independent of creatinine may have negative impact on patient survival by reflecting the extent of catabolism. Protein catabolism and net negative nitrogen balance is a common feature of critical illness.(67) Major mediators are increase in catabolic hormones (glucagon, epinephrine, cortisol), cytokines and the reduction of anabolism through decreased growth hormone, insulin, and testosterone.(68–69) Persistent hypercatabolism in critical illness results in decreased immune function.(67) (Figure 1)

Nosocomial bloodstream infections as an endpoint is well studied.(70) Blood stream infection and blood stream infection rates are accepted end-points in critical care studies. (71–73) Following adjustment for measurable factors commonly associated with increases in BUN (except catabolism), we find that high BUN is associated with an increased risk of blood culture positivity 48 hours prior and 48 hours after ICU admission. The increased risk of blood culture positivity in patients with BUN > 20 mg/dl may reflect decreased immune function related to the extent of catabolism across our patient cohort. High BUN thus may be a marker for catabolic patients at risk for decreased immune function. Decreased immune function may be a component of the BUN-mortality association witnessed in this study.

In aggregate, these data demonstrate that in patients with creatinine 0.8–1.3 mg/dl, BUN at ICU admission is strongly associated with the risk of death in critical illness and that this risk is independent of creatinine and other risk factors but not upper gastrointestinal bleeding. In concert with the clinical evidence (3–11, 15–17), we believe the value of our findings is the potential in critically ill patients with creatinine 0.8–1.3 mg/dl for BUN to be a prognostic marker for mortality independent of creatinine. As BUN is not a direct factor in the pathway of system dysfunction the authors do not (in the absence of renal failure) advocate extracorporeal urea removal or decreasing nitrogen intake to lessen BUN.

Acknowledgments

This manuscript is dedicated to the memory of our dear friends and colleagues Keith Alan Landesman, MD and Nathan Hellman, MD, PhD. We express deep appreciation to Yan Liu, M.S and Steven M. Brunelli, MD, MSCE for statistical expertise and analysis.

Financial Support: Dr. Christopher is supported by NIH 5K08AI060881.

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Figure 1.
Schematic diagram of potential mechanism of BUN-mortality association

Table 1**Patient Characteristics of the Study Population**

N	26,288
Age-mean(SD)	61.52 (18.45)
Gender-no.(%)	
Female	9,614 (36.57)
Male	16,674 (63.43)
Race-no.(%)	
White	21,184 (80.58)
Non-White	5,104 (19.42)
African American	1,452 (5.52)
Asian	458 (1.74)
Hispanic	1,329 (5.06)
Other	1,865 (7.09)
Patient Type-no.(%)	
Medical	12,789 (48.65)
Surgical	13,499 (51.35)
Days from hospital admission to ICU care -no.(%)	
0	18,624 (70.85)
1	3,120 (11.87)
2	4,544 (17.29)
Major Diagnostic Category-no.(%)	
Circulatory System	8,898 (33.85)
Nervous System	5,334 (20.29)
Respiratory System	4,164 (15.84)
Digestive System	1,530 (5.82)
Musculoskeletal System	1,454 (5.53)
Multiple Significant Trauma	862 (3.28)
Injuries, Toxic Effect of Drugs	754 (2.87)
Infectious	510 (1.94)
Hepatobiliary System and Pancreas	476 (1.81)
Ear, Nose, Mouth and Throat	268 (1.02)
Endocrine	266 (1.01)
Burns	263 (1.00)
Deyo-Charlson Index-no.(%)	
0	3,493 (13.29)
1	4,608 (17.53)
2	5,568 (21.18)
3	4,706 (17.90)
4	3,494 (13.29)
5	2,201 (8.37)
6	1,157 (4.40)

7	1,061 (4.04)
<i>Mortality-no.(%)</i>	
30 days	2,789 (10.61)
90 days	3,702 (14.08)
365 days	5,379 (20.46)
In-hospital death	2,551 (9.70)
<i>Red Blood Cell Transfusions-no.(%)</i>	
0	22,832 (86.85)
1	3,456 (13.15)
<i>CHF-no.(%)</i>	5,930 (22.56)
<i>Acute MI-no.(%)</i>	4,593 (17.47)
<i>Sepsis-no.(%)</i>	2,429 (9.24)
<i>CABG-no.(%)</i>	1,680 (6.39)
<i>Glucocorticoids-no.(%)</i>	981 (3.73)
<i>AKI-no.(%)</i>	581 (2.21)
<i>UGIB-no.(%)</i>	546 (2.08)
<i>TPN-no.(%)</i>	112 (0.43%)
<i>Blood Cultures-no.(%)</i>	
Negative	6446 (86.22)
Positive	1036 (13.78)

Table 2

Associations between covariates and exposure

	BUN on ICU admission			P-value
	10–20 mg/dl	>20–40 mg/dl	>40 mg/dl	
N	17685	7932	671	
Age-mean(<i>SD</i>)	57.61(18.59)	69.41(15.34)	71.41(14.53)	<.0001
Gender-no.(%)				
Female	5,871(33.20)	3,415(43.05)	328(48.88)	<.0001
Race (%)				<.0001
White	13,848 (78.30)	6,756 (85.17)	580 (86.44)	
Non-White	3,837 (21.70)	1,176 (14.83)	91 (13.56)	
African American	1,171 (6.62)	265 (3.34)	16 (2.38)	
Asian	321 (1.82)	121 (1.53)	16 (2.38)	
Hispanic	1,073 (6.07)	245 (3.09)	11 (1.64)	
Other	12,72 (7.19)	545 (6.87)	48 (7.15)	
Deyo-Charlson Index-no.(%)				<.0001
0	2,988 (16.90)	491 (6.19)	14 (2.09)	
1	3,490 (19.73)	1,049 (13.22)	69 (10.28)	
2	3,881 (21.95)	1,588 (20.02)	99 (14.75)	
3	3,003 (16.98)	1,568 (19.77)	135 (20.12)	
4	2,027 (11.46)	1,349 (17.01)	118 (17.59)	
5	1,209 (6.84)	877 (11.06)	115 (17.14)	
6	595 (3.36)	504 (6.35)	58 (8.64)	
7	492 (2.78)	506 (6.38)	63 (9.39)	
Days between hospital and ICU admission-no.(%)				<.0001
0	12,744 (72.06)	5,503 (69.38)	377 (56.18)	
1	2,176 (12.30)	861 (10.85)	83 (12.37)	
2	2,765 (15.63)	1,568 (19.77)	211 (31.45)	
AKI-no.(%)	286(1.62)	251(3.17)	44(6.52)	<.0001
CABG-no.(%)	1,084(6.13)	557(7.02)	39(5.81)	<.0001
CHF-no.(%)	3,150(17.81)	2,524(31.82)	256(38.15)	<.0001
Glucocorticoids-no.(%)	596(3.37)	344(4.34)	41(6.11)	<.0001
Sepsis-no.(%)	1,238(7.00)	994(12.53)	197(29.36)	<.0001
TPN-no.(%)	53(0.30)	44(0.55)	15(2.24)	<.0001
UGIB-no.(%)	154(0.87)	256(3.23)	136(20.27)	<.0001
Patient type-no.(%)				<.0001
Medical	8,236(46.57)	4,133(52.11)	420(62.59)	
Surgical	9,449(53.43)	3,799(47.89)	251(37.41)	
Creatinine-no.(%)				<.0001
0.8 mg/dl	3,916 (22.14)	781 (9.85)	60 (8.94)	
0.9 mg/dl	4,414 (24.96)	1,247 (15.72)	48 (7.15)	
1.0 mg/dl	3,820 (21.60)	1,490 (18.78)	101 (15.05)	

	BUN on ICU admission			P-value
	10–20 mg/dl	>20–40 mg/dl	>40 mg/dl	
1.1 mg/dl	2,768 (15.65)	1,582 (19.94)	117 (17.44)	
1.2 mg/dl	1,758 (9.94)	1,546 (19.49)	167 (24.89)	
1.3 mg/dl	1,009 (5.71)	1,286 (16.21)	178 (26.53)	
<i>HCO₃-no.(%)</i>				<.0001
22 mmol/L	3,545(20.05)	1,461(18.42)	164(24.44)	
22–25 mmol/L	5,524(31.24)	2,187(27.57)	162(24.14)	
25–28 mmol/L	5,667(32.04)	2,442(30.79)	170(25.34)	
>28 mmol/L	2,949(16.68)	1,842(23.22)	175(26.08)	
<i>Hematocrit-no.(%)</i>				<.0001
30 %	2,630 (14.87)	1,598 (20.15)	291 (43.37)	
30–33 %	1,719 (9.72)	1,043 (13.15)	124 (18.48)	
33–36 %	2,136 (12.08)	1,170 (14.75)	98 (14.61)	
36–39 %	2,990 (16.91)	1,384 (17.45)	64 (9.54)	
39–42 %	3,469 (19.62)	1,336 (16.84)	35 (5.22)	
>42 %	4,741 (26.81)	1,401 (17.66)	59 (8.79)	
<i>White blood cells-no.(%)</i>				<.0001
4000 / μ L	359 (2.03)	250 (3.15)	39 (5.81)	
4000–10000/ μ L	7,715 (43.62)	3,481(43.89)	209 (31.15)	
>10000/ μ L	9,611 (54.35)	4,201 (52.96)	423 (63.04)	
<i>Blood culture-no.(%)</i>				<.0001
Negative	3,922 (88.59)	2,230 (83.55)	294 (77.37)	
Positive	505 (11.41)	439 (16.45)	86 (22.63)	

Note: The means are shown in the table unless it is noted as %, then the percentage is shown.

Table 3

Adjusted Odds Ratios for 30-day mortality

	OR	95% CI	P
<i>Age</i>	1.02	1.02–1.02	<.0001
<i>Gender</i>			
Male	1.0	1.0–1.0	
Female	1.09	0.99–1.19	0.059
<i>Race</i>			
White	1.0	1.0–1.0	
Non-white	1.07	0.96–1.20	0.235
<i>BUN</i>			
10–20 mg/dl	1.0	1.0–1.0	
20–40 mg/dl	1.53	1.40–1.68	<.0001
>40 mg/dl	2.78	2.27–3.39	<.0001
<i>Creatinine</i>			
0.8 mg/dl	1.0	1.0–1.0	
0.9 mg/dl	0.91	0.80–1.04	0.182
1.0 mg/dl	0.92	0.80–1.05	0.212
1.1 mg/dl	0.85	0.73–0.98	0.025
1.2 mg/dl	0.92	0.79–1.07	0.288
1.3 mg/dl	0.89	0.76–1.05	0.176
<i>Deyo-Charlson Index</i>			
0	1.0	1.0–1.0	
1	1.95	1.54–2.47	<.0001
2	2.67	2.12–3.35	<.0001
3	2.81	2.23–3.54	<.0001
4	3.17	2.50–4.02	<.0001
5	3.78	2.95–4.84	<.0001
6	3.31	2.52–4.37	<.0001
7+	2.95	2.23–3.91	<.0001
<i>Patient Type</i>			
Medical	1.0	1.0–1.0	
Surgical	0.63	0.59–0.70	<.0001
CHF	0.87	0.79–0.96	0.007
CABG	0.23	0.17–0.29	<.0001
Glucocorticoids	3.03	2.59–3.55	<.0001
Sepsis	1.85	1.65–2.08	<.0001
Upper GI Bleed	0.41	0.30–0.56	<.0001

Note: Each odds ratio is taken from the primary multivariable model, and so is adjusted for all the covariates in that model

Table 4

Unadjusted and Adjusted associations between BUN and outcomes

	Unadjusted			Adjusted		
	OR	95% CI	P	OR	95% CI	P
<i>30 day mortality</i>						
BUN 10–20 mg/dl	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dl	2.15	1.98–2.33	<.0001	1.53	1.40–1.68	<.0001
BUN >40 mg/dl	5.12	4.30–6.09	<.0001	2.78	2.27–3.39	<.0001
<i>90 day mortality</i>						
BUN 10–20 mg/dl	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dl	2.29	2.13–2.47	<.0001	1.55	1.42–1.68	<.0001
BUN >40 mg/dl	6.07	5.17–7.14	<.0001	3.07	2.54–3.71	<.0001
<i>365 day mortality</i>						
BUN 10–20 mg/dl	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dl	2.23	2.09–2.37	<.0001	1.45	1.34–1.56	<.0001
BUN >40 mg/dl	5.82	4.97–6.80	<.0001	2.78	2.31–3.33	<.0001
<i>In-hospital mortality</i>						
BUN 10–20 mg/dl	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dl	2.08	1.91–2.27	<.0001	1.49	1.35–1.64	<.0001
BUN >40 mg/dl	5.50	4.61–6.55	<.0001	2.93	2.38–3.59	<.0001

Note: Referent in each case is BUN 10–20 mg/dl. Estimates adjusted for age (continuous), sex, race (white, non-white), days from hospital admission to ICU care (0, 1, 2+), Deyo-Charlson index (0, 1, 2, 3, ..., 7+), type (surgical vs medical), congestive heart failure, CABG, glucocorticoids, sepsis, hematocrit, upper gastrointestinal bleed, white blood count, HCO₃, and creatinine

Table 5

Associations between BUN and mortality stratified on UGIB

	Patients without UGIB			Patients with UGIB		
	OR	95%CI	P	OR	95%CI	P
<i>Unadjusted 30-day mortality</i>						
BUN 10-20	1.0	1.0-1.0		1.0	1.0-1.0	
BUN 20-40	2.17	2.00-2.36	<.0001	1.44	0.73-2.85	0.3
BUN >40	6.66	5.53-8.01	<.0001	0.86	0.36-2.03	0.7
interaction p<0.001						
<i>Adjusted 30-day mortality</i>						
BUN 10-20	1.0	1.0-1.0		1.0	1.0-1.0	
BUN 20-40	1.53	1.39-1.68	<.0001	1.33	0.66-2.69	0.4
BUN >40	3.18	2.58-3.91	<.0001	0.59	0.25-1.43	0.2
interaction p<0.001						
<i>Unadjusted 90-day mortality</i>						
BUN 10-20	1.0	1.0-1.0		1.0	1.0-1.0	
BUN 20-40	2.32	2.16-2.50	<.0001	1.35	0.75-2.43	0.3
BUN >40	8.26	6.93-9.86	<.0001	0.88	0.43-1.81	0.7
interaction p<0.001						
<i>Adjusted 90-day mortality</i>						
BUN 10-20	1.0	1.0-1.0		1.0	1.0-1.0	
BUN 20-40	1.54	1.42-1.68	<.0001	1.24	0.68-2.28	0.5
BUN >40	3.64	2.99-4.44	<.0001	0.60	0.28-1.27	0.2
interaction p<0.001						
<i>Unadjusted 365-day mortality</i>						
BUN 10-20	1.0	1.0-1.0		1.0	1.0-1.0	
BUN 20-40	2.25	2.11-2.40	<.0001	1.13	0.70-1.82	0.3
BUN >40	8.11	6.79-9.68	<.0001	0.87	0.50-1.54	0.3
interaction p<0.001						
<i>Adjusted 365-day mortality</i>						
BUN 10-20	1.0	1.0-1.0		1.0	1.0-1.0	
BUN 20-40	1.45	1.34-1.56	<.0001	1.03	0.62-1.71	0.9

	Patients without UGIB			Patients with UGIB		
	OR	95%CI	P	OR	95%CI	P
BUN >40	3.45	2.83–4.20	<.0001	0.60	0.33–1.09	0.09
interaction p<0.001						
<i>Unadjusted in-hospital mortality</i>						
BUN 10–20	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40	2.11	1.93–2.30	<.0001	1.28	0.61–2.71	0.5
BUN >40	7.18	5.96–8.65	<.0001	0.92	0.37–2.30	0.9
interaction p<0.001						
<i>Adjusted in-hospital mortality</i>						
BUN 10–20	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40	1.48	1.35–1.64	<.0001	1.24	0.57–2.70	0.6
BUN >40	3.24	2.62–4.00	<.0001	0.74	0.29–1.90	0.5
interaction p=0.002						

Note: Referent in each case is BUN 10–20 mg/dl. Estimates adjusted for age (continuous), sex, race (white, non-white), days from hospital admission to ICU care (0, 1, 2+, Deyo-Charlson index(0, 1, 2, 3..., 7+), type (surgical vs medical), congestive heart failure, CABG, glucocorticoids, sepsis, hematocrit, white blood count, HCO₃, and creatinine

Table 6

Adjusted associations between BUN and mortality stratified on Creatinine

	OR	95%CI	P
<i>30-day mortality Cr 0.8–0.9</i>			
BUN 10–20	1.0	1.0–1.0	
BUN 20–40	1.60	1.37–1.86	<.0001
BUN >40	3.48	2.17–5.58	<.0001
<i>30-day mortality Cr 1.0–1.1</i>			
BUN 10–20	1.0	1.0–1.0	
BUN 20–40	1.52	1.31–1.76	<.0001
BUN >40	2.60	1.82–3.70	<.0001
<i>30-day mortality Cr 1.2–1.3</i>			
BUN 10–20	1.0	1.0–1.0	
BUN 20–40	1.51	1.25–1.83	<.0001
BUN >40	2.85	2.10–3.86	<.0001

Note: Referent in each case is BUN 10–20 mg/dl. Estimates adjusted for age (continuous), sex, race (white, non-white), days from hospital admission to ICU care (0, 1, 2+), Deyo-Charlson index(0, 1, 2, 3..., 7+), type (surgical vs medical), congestive heart failure, CABG, glucocorticoids, sepsis, hematocrit, white blood count, and HCO₃. P value for interaction is 0.48.

Table 7

Unadjusted and Adjusted associations between BUN and blood culture positivity

	OR	95% CI	P
Unadjusted			
BUN 10–20 mg/dl	1.0	1.0–1.0	
BUN 20–40 mg/dl	1.53	1.33–1.76	<.0001
BUN>40 mg/dl	2.27	1.76–2.94	<.0001
Adjusted			
BUN 10–20 mg/dl	1.0	1.0–1.0	
BUN 20–40 mg/dl	1.52	1.31–1.76	<.0001
BUN>40 mg/dl	2.18	1.65–2.89	<.0001

Note: Referent in each case is BUN 10–20 mg/dl. Estimates adjusted for age (continuous), sex, race (white, non-white), days from hospital admission to ICU care (0,1, 2+), Deyo-Charlson index(0, 1, 2, 3..., 7+), type (surgical vs medical), congestive heart failure, CABG, glucocorticoids, hematocrit, white blood count, HCO₃, and creatinine