Elevation of blood urea nitrogen is predictive of long-term mortality in critically ill patients independent of "normal" creatinine*

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Objective: **We hypothesized that elevated blood urea nitrogen 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: **Twenty intensive care units in two teaching hospitals in Boston, MA.**

Patients: **A total of 26,288 patients, age ≥18 yrs, hospitalized between 1997 and 2007 with creatinine of 0.80–1.30 mg/dL.**

Interventions: **None.**

Measurements: **Blood urea nitrogen at intensive care unit admission was categorized as 10–20, 20–40, and >40 mg/dL. Logistic regression examined death at days 30, 90, and 365 after intensive care unit admission as well as in-hospital mortality. Adjusted odds ratios were estimated by multivariable logistic regression models.**

Main Results: **Blood urea nitrogen at intensive care unit admission was predictive for short- and long-term mortality independent of creatinine. Thirty days following intensive care unit admission, patients with blood urea nitrogen of >40 mg/dL had an odds ratio for mortality of 5.12 (95% confidence interval, 4.30–6.09; $p < .0001$) relative to patients with blood urea nitrogen of 10–20 mg/dL. Blood urea nitrogen remained a significant predictor of mortality at 30 days after intensive care unit admission following multivariable adjustment for confounders; patients with blood urea nitrogen of >40 mg/dL had an odds ratio for mortality of 2.78 (95% confidence interval, 2.27–3.39; $p < .0001$) relative to patients with blood urea nitrogen of 10–20 mg/dL. Thirty days following intensive care unit admission, patients with blood urea nitrogen of 20–40 mg/dL had an odds ratio of 2.15 (95% confidence interval, 1.98–2.33; <.0001) and a multivariable odds ratio of 1.53 (95% confidence interval, 1.40–1.68; $p < .0001$) relative to patients with blood urea nitrogen of 10–20 mg/dL. Results were similar at 90 and 365 days following intensive care unit admission as well as for in-hospital mortality. A subanalysis of patients with blood cultures (n = 7,482) demonstrated that blood urea nitrogen at intensive care unit admission was associated with the risk of blood culture positivity.**

Conclusion: **Among critically ill patients with creatinine of 0.8–1.3 mg/dL, an elevated blood urea nitrogen was associated with increased mortality, independent of serum creatinine. (Crit Care Med 2011; 39:305–313)**

KEY WORDS: blood urea nitrogen; intensive care; mortality; gastrointestinal bleed; creatinine

Blood urea nitrogen (BUN) levels are determined by the complex balance among 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 nontoxic, 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), and 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 (AKI) who require dialysis, predialysis 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 of >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 was to determine the relationship between elevation of BUN independent of creatinine (Cr) at ICU admission in patients with Cr of 0.8–1.3 mg/dL and long-term mortality.

MATERIALS AND METHODS

Source Population. We extracted administrative and laboratory data from individuals

*See also p. 405.

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admitted to two academic teaching hospitals in Boston, MA. Brigham and Women's Hospital is a 777-bed teaching hospital with 100 ICU beds. Massachusetts General Hospital 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 Brigham and Women's Hospital or Massachusetts General Hospital 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 Brigham and Women's Hospital.

The following data were retrieved: demographics, vital status for up to 10 yrs 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, ninth revision, Clinical Modification (ICD-9-CM) codes, and Current Procedural Terminology (CPT) codes for in-hospital procedures and services.

During the 10-yr study period, there were 26,387 unique patients, age ≥18 yrs, who were assigned the CPT code 99291 (critical care, first 30–74 mins) who also had Cr of 0.8–1.3 mg/dL on the first day of CPT code 99291 assignment. Ninety-nine foreign patients without social security numbers were identified and excluded as mortality was determined via the Social Security Death Index, and 124 patients were excluded for incomplete data. A total of 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) before or on day of ICU admission. Congestive heart failure (CHF) is defined by ICD-9-CM 428.0–428.4 before or on the day of ICU admission (20). 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 before or on the day of ICU admission (22).

Transfusion data were 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 hrs before 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 hrs within 7 days of ICU admission were included.

Records of the administration of total parenteral nutrition (TPN) in the 7 days before 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 was defined as medical or surgical and incorporated the DRG methodology, devised by Centers for Medicare and Medicaid Services (23). The major diagnostic categories are formed by dividing all DRGs into 25 mutually exclusive diagnosis areas (24).

The Deyo-Charlson Index assesses the burden of chronic illness (25). The Deyo-Charlson Index consists of 17 comorbidities, which are weighted and summed to produce a score each with an associated weight based on the adjusted risk of 1-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 are reported (27). Due to scant representation, Deyo-Charlson Index scores ≥7 were combined.

All patients who had blood cultures drawn 48 hrs prior or 48 hrs 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 prespecified end points included 90-day, 365-day, and in-hospital morality and blood culture positivity.

Statistical Analysis. Categorical covariates were described by frequency distribution and compared across BUN groups by using contingency tables and chi-square testing. Continuous covariates were examined graphically (e.g., histogram and box plot) and in terms of summary statistics (mean, SD, median, and interquartile range) and compared across exposure groups by using one-way analysis of variance. Survival analyses considered death by days 30, 90, and 365 after ICU admission as well as in-hospital mortality. In each instance, subjects were excluded if they were censored for incomplete data. A 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 (ORs) were estimated by multivariable logistic regression models with inclusion of covariate terms thought to interact plausibly with both BUN levels and mortality. For the primary model (30-day mortality), specification of each continuous covariate (as a linear vs. categorical term) was adjudicated by the empirical association with the primary outcome using Akaike's information criterion; overall model fit was assessed by 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, AKI, and Cr on the risk of mortality. We tested the significance of the interaction by using the likelihood ratio test. All p values presented are two-tailed; values below .05 were considered nominally significant. All analyses were performed by using STATA/MP 10.0 (College Station, TX).

RESULTS

Table 1 lists the main relevant characteristics of the 26,288-patient study cohort. Of the patients studied, 36.6% were women and 80.6% were white. The mean age at ICU admission was 61.46 yrs (SD 18.5). The 30-day all-cause mortality was 10.61%, and 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, 9.2% of patients were septic, 13.15% of patients were transfused red blood cells, and 3.7% of patients were treated with intravenous glucocorticoids. A small minority of patients (0.4%) received TPN before ICU admission.

Patient characteristics of the study cohort were stratified according to BUN levels at ICU admission (Table 2). Factors that significantly differed among stratified groups included age, sex, race, Deyo-

Table 1. Patient characteristics of the study population

Characteristic	Value
Total	26,288
Mean age (SD)	61.52 (18.45)
Gender, n (%)	
Female	9,614 (36.57)
Male	16,674 (63.43)
Race, n (%)	
White	21,184 (80.58)
Nonwhite	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, n (%)	
Medical	12,789 (48.65)
Surgical	13,499 (51.35)
Days from hospital admission to intensive care unit care, n (%)	
0	18,624 (70.85)
1	3,120 (11.87)
≥2	4,544 (17.29)
Major diagnostic category, n (%)	
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, n (%)	
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)
Mortality, n (%)	
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)
Red blood cell transfusions, n (%)	
0	22,832 (86.85)
≥1	3,456 (13.15)
Congestive heart failure, n (%)	5,930 (22.56)
Acute myocardial infarction, n (%)	4,593 (17.47)
Sepsis, n (%)	2,429 (9.24)
Coronary artery bypass graft, n (%)	1,680 (6.39)
Glucocorticoids, n (%)	981 (3.73)
Acute kidney injury, n (%)	581 (2.21)
Upper gastrointestinal bleed, n (%)	546 (2.08)
Total parenteral nutrition, n (%)	112 (0.43)
Blood cultures, n (%)	
Negative	6,446 (86.22)
Positive	1,036 (13.78)

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, AKI, HCO_3, hematocrit, TPN, upper gastrointestinal bleed, white blood cells, blood culture positivity, and Cr. Acute myocardial infarction and transfusion did not significantly differ among 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, TPN use was not analyzed further in the patient cohort. AKI was not included in the adjustment analysis, as it is plausibly an intermediate on a causal pathway between BUN and mortality.

In patients with Cr of 0.8–1.3 mg/dL, BUN at ICU admission was associated with increased short- and long-term mortality. Thirty days following ICU admission, patients with BUN of >40 mg/dL had an OR for mortality of 5.12 (95% confidence interval [CI], 4.30–6.09; $p < .0001$) relative to patients with BUN of 10–20 mg/dL. Thirty days following ICU admission, patients with BUN of 20–40 mg/dL had an OR for mortality of 2.15 (95% CI, 1.98–2.33; $p < .0001$) relative to patients with BUN of 10–20 mg/dL (Table 4). After adjustment for age (continuous), sex, race (white and nonwhite), days from hospital admission to ICU care (0–2+), Deyo-Charlson Index (0–7+), type (surgical vs. medical), congestive heart failure, CABG, glucocorticoids, sepsis, hematocrit, upper gastrointestinal bleed, white blood count, HCO_3, and Cr, BUN in the cohort remains a significant predictor of mortality: BUN of >40 mg/dL adjusted OR 2.78; 95% CI, 2.27–3.39; $p < .0001$ and BUN of 20–40 mg/dL adjusted OR 1.53; 95% CI, 1.40–1.68; $p < .0001$ (Table 4). Similar significant robust associations before and after multivariable adjustments were seen with death by days 90 and 365 after ICU admission as well as for in-hospital mortality (Table 4).

There was effect modification of the BUN-mortality association on the basis of upper gastrointestinal bleed (Table 5). In all cases, the risk associated with a BUN of >10–20 mg/dL decreased or was obviated in the presence of upper gastrointestinal bleed. There was no significant effect modification of the BUN-mortality association on the basis of AKI (p for interaction = .15 in the primary model, 30-day mortality, adjusted, data not shown).

Following stratification of the data by Cr (Cr 0.8–0.9, 1–1.1, and 1.2–1.3), a positive association in each stratum was observed, which indicated that the BUN-mortality relationship was not materially confounded by Cr. The estimates were similar in each Cr stratum, indicating that the effect of BUN on mortality was the same regardless of where a cohort subject was on the Cr spectrum (Table 6). Formally, there was no significant effect modification of the BUN-mortality asso-

Table 2. Associations between covariates and exposure

Covariate	Blood Urea Nitrogen on Intensive Care Unit Admission (mg/dL) 10–20	>20–40	>40	p
n	17,685	7,932	671	
Mean age (SD)	57.61 (18.59)	69.41 (15.34)	71.41 (14.53)	<.0001
Gender, n (%)				
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)	
Nonwhite	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	1,272 (7.19)	545 (6.87)	48 (7.15)	
Deyo-Charlson Index, n (%)				<.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 intensive care unit admission, n (%)				<.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)	
Acute kidney injury, n (%)	286 (1.62)	251 (3.17)	44 (6.52)	<.0001
Coronary artery bypass graft, n (%)	1,084 (6.13)	557 (7.02)	39 (5.81)	<.0001
Congestive heart failure, n (%)	3,150 (17.81)	2,524 (31.82)	256 (38.15)	<.0001
Glucocorticoids, n (%)	596 (3.37)	344 (4.34)	41 (6.11)	<.0001
Sepsis, n (%)	1,238 (7.00)	994 (12.53)	197 (29.36)	<.0001
Total parenteral nutrition, n (%)	53 (0.30)	44 (0.55)	15 (2.24)	<.0001
Upper gastrointestinal bleed, n (%)	154 (0.87)	256 (3.23)	136 (20.27)	<.0001
Patient type, n (%)				<.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, n (%)				<.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 mg/dL	3,820 (21.60)	1,490 (18.78)	101 (15.05)	
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)	
HCO_3, n (%)				<.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)	
Hematocrit, n (%)				<.0001
≤30%	2,630 (14.87)	1,598 (20.15)	291 (43.37)	
30% to 33%	1,719 (9.72)	1,043 (13.15)	124 (18.48)	
33% to 36%	2,136 (12.08)	1,170 (14.75)	98 (14.61)	
36% to 39%	2,990 (16.91)	1,384 (17.45)	64 (9.54)	
39% to 42%	3,469 (19.62)	1,336 (16.84)	35 (5.22)	
>42%	4,741 (26.81)	1,401 (17.66)	59 (8.79)	
White blood cells, n (%)				<.0001
≤4,000/μL	359 (2.03)	250 (3.15)	39 (5.81)	
4,000–10,000/μL	7,715 (43.62)	3,481 (43.89)	209 (31.15)	
>10,000/μL	9,611 (54.35)	4,201 (52.96)	423 (63.04)	
Blood culture, n (%)				<.0001
Negative	3,922 (88.59)	2,230 (83.55)	294 (77.37)	
Positive	505 (11.41)	439 (16.45)	86 (22.63)	

The means are shown in the table unless it is noted as a percentage, in which case the percentage is shown.

ciation on the basis of Cr (p for interaction = .48 in the primary model, 30-day mortality, adjusted).

In a subanalysis of patients with blood cultures drawn (n = 7,482), BUN at ICU admission was associated with blood culture positivity. Patients with BUN of >40 mg/dL had an OR for blood culture positivity of 2.27 (95% CI, 1.76–2.94; $p <$ .0001) relative to patients with BUN of 10–20 mg/dL. Patients with BUN of 20–40 mg/dL had an OR for blood culture positivity of 1.53 (95% CI, 1.33–1.76; $p <$ .0001) relative to patients with BUN of 10–20 mg/dL (Table 7). After multivariable adjustment, BUN in the cohort remains a significant predictor of blood culture positivity: BUN of >40 mg/dL adjusted OR of 2.18 (95% CI, 1.65–2.89; $p <$ .0001) and BUN of 20–40 mg/dL adjusted OR of 1.52 (95% CI, 1.31–1.76; $p <$ .0001) both relative to patients with BUN of 10–20 mg/dL (Table 7). Thus, cohort patients with BUN of >20 mg/dL had a significantly higher risk of bacteremia and or fungemia than patients with BUN of 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 Cr. This large, 10-yr multicenter observational study illustrates the all-cause mortality risk of BUN elevation at ICU admission. In patients with Cr of 0.8–1.3 mg/dL, BUN at ICU admission was a significant predictor of 30-day, 90-day, 365-day and inpatient mortality. BUN remains a significant predictor of survival following multivariable adjustments including Cr, 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 was a predictor of risk of blood culture positivity, possibly reflecting immune modulation during catabolism.

Urea, $(NH_2)_2CO$, 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

Table 3. Adjusted odds ratios for 30-day mortality

Characteristic	Odds Ratio	95% Confidence Interval	*p*
Age	1.02	1.02–1.02	<.0001
Gender			
Male	1.0	1.0–1.0	
Female	1.09	0.99–1.19	.059
Race			
White	1.0	1.0–1.0	
Nonwhite	1.07	0.96–1.20	.235
Blood urea nitrogen			
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
Creatinine			
0.8 mg/dL	1.0	1.0–1.0	
0.9 mg/dL	0.91	0.80–1.04	.182
1 mg/dL	0.92	0.80–1.05	.212
1.1 mg/dL	0.85	0.73–0.98	.025
1.2 mg/dL	0.92	0.79–1.07	.288
1.3 mg/dL	0.89	0.76–1.05	.176
Deyo-Charlson index			
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
Patient type			
Medical	1.0	1.0–1.0	
Surgical	0.63	0.59–0.70	<.0001
Congestive heart failure	0.87	0.79–0.96	.007
Coronary artery bypass graft	0.23	0.17–0.29	<.0001
Glucocorticoids	3.03	2.59–3.55	<.0001
Sepsis	1.85	1.65–2.08	<.0001
Upper gastrointestinal bleed	0.41	0.30–0.56	<.0001

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 blood urea nitrogen and outcomes

	Unadjusted			Adjusted		
Association	Odds Ratio	95% Confidence Interval	*p*	Odds Ratio	95% Confidence Interval	*p*
30-day mortality						
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
90-day mortality						
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
365-day mortality						
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
In-hospital mortality						
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

BUN, blood urea nitrogen.

The referent in each case was a BUN of 10–20 mg/dL. Estimates were adjusted for age (continuous), sex, race (white, nonwhite), days from hospital admission to intensive care unit care (0–2+), Deyo-Charlson Index (0–7+), type (surgical vs. medical), congestive heart failure, coronary artery bypass graft, glucocorticoids, sepsis, hematocrit, upper gastrointestinal bleed, white blood count, HCO_3, and creatinine.

(30, 31). High incoming concentrations of ammonia from the splanchic 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 resorption 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 TPN. 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). TPN is also associated with increased BUN (38). BUN can also increase independent of a change in serum Cr with renal hypoperfusion from hypovolemia (prerenal 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 of 0.8–1.3 mg/dL, values considered to be in the normal range by the institutions under study. These normal Cr ranges are based on a calibrated determination of serum Cr 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

Table 5. Associations between blood urea nitrogen and mortality stratified on upper gastrointestinal bleed

Association	Patients Without UGIB			Patients With UGIB		
	Odds Ratio	95% Confidence Interval	*p*	Odds Ratio	95% Confidence Interval	*p*
Unadjusted 30-day mortality						
BUN 10–20 mg/dL	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dL	2.17	2–2.36	<.0001	1.44	0.73–2.85	.3
BUN >40 mg/dL	6.66	5.53–8.01	<.0001	0.86	0.36–2.03	.7
Interaction $p < .001$						
Adjusted 30–day mortality						
BUN 10–20 mg/dL	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dL	1.53	1.39–1.68	<.0001	1.33	0.66–2.69	.4
BUN >40 mg/dL	3.18	2.58–3.91	<.0001	0.59	0.25–1.43	.2
Interaction $p < .001$						
Unadjusted 90–day mortality						
BUN 10–20 mg/dL	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dL	2.32	2.16–2.50	<.0001	1.35	0.75–2.43	.3
BUN >40 mg/dL	8.26	6.93–9.86	<.0001	0.88	0.43–1.81	.7
Interaction $p < .001$						
Adjusted 90–day mortality						
BUN 10–20 mg/dL	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dL	1.54	1.42–1.68	<.0001	1.24	0.68–2.28	.5
BUN >40 mg/dL	3.64	2.99–4.44	<.0001	0.60	0.28–1.27	.2
Interaction $p < .001$						
Unadjusted 365-day mortality						
BUN 10–20 mg/dL	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dL	2.25	2.11–2.40	<.0001	1.13	0.70–1.82	.3
BUN >40 mg/dL	8.11	6.79–9.68	<.0001	0.87	0.50–1.54	.3
Interaction $p < .001$						
Adjusted 365-day mortality						
BUN 10–20 mg/dL	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dL	1.45	1.34–1.56	<.0001	1.03	0.62–1.71	.9
BUN >40 mg/dL	3.45	2.83–4.20	<.0001	0.60	0.33–1.09	.09
Interaction $p < .001$						
Unadjusted in-hospital mortality						
BUN 10–20 mg/dL	1.0	1.0–1.0		1.0	1.0–1.0	
BUN 20–40 mg/dL	2.11	1.93–2.30	<.0001	1.28	0.61–2.71	.5
BUN >40 mg/dL	7.18	5.96–8.65	<.0001	0.92	0.37–2.30	.9
Interaction $p < .001$						
Adjusted in-hospital mortality						
BUN 10–20 mg/dL	1.0	1–1.0		1.0	1–1.0	
BUN 20–40 mg/dL	1.48	1.35–1.64	<.0001	1.24	0.57–2.70	.6
BUN >40 mg/dL	3.24	2.62–4.00	<.0001	0.74	0.29–1.90	.5
Interaction $p = .002$						

BUN, blood urea nitrogen.

The referent in each case is a BUN of 10–20 mg/dL. Estimates were adjusted for age (continuous), sex, race (white, nonwhite), days from hospital admission to intensive care unit care (0–2+), Deyo-Charlson Index (0–7+), type (surgical vs. medical), congestive heart failure, coronary artery bypass graft, glucocorticoids, sepsis, hematocrit, upper gastrointestinal bleed, white blood count, HCO_3, and creatinine.

alter Cr generation. Cr at time of ICU admission may be influenced by renal function and fluid balance. We did not include patients with Cr <0.8 mg/dL in this study because Cr <0.8 mg/dL in the critically ill is associated with increased mortality (47).

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

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 Cr 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 arginine vasopressin, the renninangiotensin-aldosterone system, and the sympathetic nervous system (61–63). High plasma arginine vasopressin concentrations can result in increased urea resorption in the collecting duct, resulting in an increased BUN (64). Angiotensin and adrenergic stimulation increase proximal tubular sodium and water resorption, decreasing distal fluid delivery, which increases flow-dependent urea resorption (65). Such arterial underfilling states are common in cardiac failure and

Table 6. Adjusted associations between blood urea nitrogen and mortality stratified on creatinine

Association	Odds Ratio	95% Confidence Interval	p
30-day mortality Cr 0.8–0.9 mg/dL			
BUN 10–20 mg/dL	1.0	1.0–1.0	
BUN 20–40 mg/dL	1.60	1.37–1.86	<.0001
BUN >40 mg/dL	3.48	2.17–5.58	<.0001
30-day mortality Cr 1.0–1.1 mg/dL			
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	2.60	1.82–3.70	<.0001
30-day mortality Cr 1.2–1.3 mg/dL			
BUN 10–20 mg/dL	1.0	1.0–1.0	
BUN 20–40 mg/dL	1.51	1.25–1.83	<.0001
BUN >40 mg/dL	2.85	2.10–3.86	<.0001

BUN, blood urea nitrogen; Cr, creatinine.

Estimates were adjusted for age (continuous), sex, race (white, nonwhite), days from hospital admission to intensive care unit care (0–2+), Deyo-Charlson Index (0–7+), type (surgical vs. medical), congestive heart failure, coronary artery bypass graft, glucocorticoids, sepsis, hematocrit, upper gastrointestinal bleed, white blood count, HCO_3, and creatinine. *p* value for interaction = .48.

Table 7. Unadjusted and adjusted associations between blood urea nitrogen and blood culture positivity

Association	Odds Ratio	95% Confidence Interval	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

BUN, blood urea nitrogen.

The referent in each case is a BUN of 10–20 mg/dL. Estimates were adjusted for age (continuous), sex, race (white, nonwhite), days from hospital admission to intensive care unit care (0–2+), Deyo-Charlson Index (0–7+), type (surgical vs. medical), congestive heart failure, coronary artery bypass graft, glucocorticoids, sepsis, hematocrit, upper gastrointestinal bleed, white blood count, HCO_3, and creatinine.

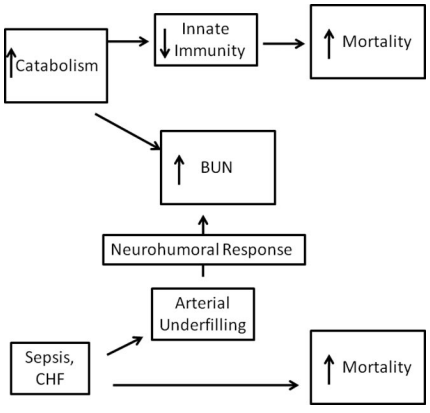

Figure 1. Schematic diagram of potential mechanism of the blood urea nitrogen (*BUN*)-mortality association. *CHF*, congestive heart failure.

sepsis (66), conditions that contribute to mortality and are common to our cohort (Fig. 1).

Elevations in BUN independent of Cr 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, and 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) (Fig. 1).

Nosocomial bloodstream infections as an end point is well studied (70). Bloodstream infection and bloodstream 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 was associated with an increased risk of blood culture positivity 48 hrs prior and 48 hrs after ICU admission. The increased risk of blood culture positivity in patients with BUN of >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 Cr of 0.8–1.3 mg/dL, BUN at ICU admission was strongly associated with the risk of death in critical illness and that this risk was independent of Cr 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 Cr of 0.8–1.3 mg/dL for BUN to be a prognostic marker for mortality independent of Cr. Because BUN was not a direct factor in the pathway of system dysfunction, the authors do not advocate (in the absence of renal failure) extracorporeal urea removal or decreasing nitrogen intake to lessen BUN.

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REFERENCES

1. Johnson WJ, Hagge WW, Wagoner RD, et al: Effects of urea loading in patients with far-advanced renal failure. *Mayo Clin Proc* 1972; 47:21–29
2. Meyer TW, Hostetter TH: Uremia. *N Engl J Med* 2007; 357:1316–1325
3. Hartz AJ, Kuhn EM, Kayser KL, et al: BUN as a risk factor for mortality after coronary artery bypass grafting. *Ann Thorac Surg* 1995; 60:398–404
4. Felker GM, Leimberger JD, Califf RM, et al: Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004; 10:460–466
5. Fonarow GC, Adams KF Jr, Abraham WT, et al: Risk stratification for in-hospital mortality in acutely decompensated heart failure: Classification and regression tree analysis. *JAMA* 2005; 293:572–580
6. Iglesias J, Hom D, Antoniotti M, et al: Predictors of worsening renal function in adult patients with congestive heart failure receiving recombinant human B-type brain natriuretic peptide (nesiritide). *Nephrol Dial Transplant* 2006; 21:3458–3465

7. Yancy CW, Lopatin M, Stevenson LW, et al: Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: A report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; 47:76–84
8. Shenkman HJ, Zareba W, Bisognano JD: Comparison of prognostic significance of amino-terminal pro-brain natriuretic peptide versus blood urea nitrogen for predicting events in patients hospitalized for heart failure. *Am J Cardiol* 2007; 99:1143–1145
9. Cauthen CA, Lipinski MJ, Abbate A, et al: Relation of blood urea nitrogen to long-term mortality in patients with heart failure. *Am J Cardiol* 2008; 101:1643–1647
10. Filippatos G, Rossi J, Lloyd-Jones DM, et al: Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: Insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *J Card Fail* 2007; 13:360–364
11. Faisst M, Wellner UF, Utzolino S, et al: Elevated blood urea nitrogen is an independent risk factor of prolonged intensive care unit stay due to acute necrotizing pancreatitis. *J Crit Care* 2009; 25:105–111
12. Luria MH, Knoke JD, Margolis RM, et al: Acute myocardial infarction: Prognosis after recovery. *Ann Intern Med* 1976; 85:561–565
13. Fine MJ, Auble TE, Yealy DM, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336:243–250
14. Liu KD, Himmelfarb J, Paganini E, et al: Timing of initiation of dialysis in critically ill patients with acute kidney injury. *Clin J Am Soc Nephrol* 2006; 1:915–919
15. Bacigalupo A, Oneto R, Bruno B, et al: Early predictors of transplant-related mortality (TRM) after allogeneic bone marrow transplants (BMT): Blood urea nitrogen (BUN) and bilirubin. *Bone Marrow Transplant* 1999; 24:653–659
16. Bailey SH, Bull DA, Harpole DH, et al: Outcomes after esophagectomy: A ten-year prospective cohort. *Ann Thorac Surg* 2003; 75: 217–222; discussion 222
17. 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: 1781–1786
18. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
19. Trespalacios FC, Taylor AJ, Agodoa LY, et al: Incident acute coronary syndromes in chronic dialysis patients in the United States. *Kidney Int* 2002; 62:1799–1805
20. Mamdani M, Juurlink DN, Lee DS, et al: Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: A population-based cohort study. *Lancet* 2004; 363:1751–1756
21. Waikar SS, Wald R, Chertow GM, et al: Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. *J Am Soc Nephrol* 2006; 17:1688–1694
22. Abraham NS, Cohen DC, Rivers B, et al: Validation of administrative data used for the diagnosis of upper gastrointestinal events following nonsteroidal anti-inflammatory drug prescription. *Aliment Pharmacol Ther* 2006; 24:299–306
23. Rapoport J, Gehlbach S, Lemeshow S, et al: Resource utilization among intensive care patients. Managed care vs traditional insurance. *Arch Intern Med* 1992; 152:2207–2212
24. Zingmond DS, McGory ML, Ko CY: Hospitalization before and after gastric bypass surgery. *JAMA* 2005; 294:1918–1924
25. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987; 40:373–383
26. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45:613–619
27. Quan H, Sundararajan V, Halfon P, et al: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43:1130–1139
28. Newman TB, Brown AN: Use of commercial record linkage software and vital statistics to identify patient deaths. *J Am Med Inform Assoc* 1997; 4:233–237
29. Bhagavan N: Medical Biochemistry. Fourth Edition. Burlington, MA, Harcourt/Academic Press, 2002
30. Bankir L: Urea and the kidney. *In:* The Kidney. Brenner BM (Ed). Philadelphia, WB Saunders, 1996, pp 571–606
31. Stewart GS, Smith CP: Urea nitrogen salvage mechanisms and their relevance to ruminants, non-ruminants and man. *Nutr Res Rev* 2005; 18:49–62
32. Cynober L: Ureagenesis and ammoniagenesis: An update. *In:* Metabolic and Therapeutic Aspects of Amino Acids in Clinical Nutrition. Second Edition. Cynober L (Ed). Boca Raton, FL, CRC Press, 2004, pp 111–123
33. Folin O, Denis W: The origin and significance of the ammonia in the portal blood. *J Biol Chem* 1912; 11:161–167
34. Schroeder W: Über die bildunsstätte des harnstoffs. *Archiv Exper Pathol Pharmakol* 1882; 15:364–402
35. Walsh PJ, Wright PA (Eds): Nitrogen metabolism and excretion. Boca Raton, FL, CRC Press, 1995
36. Garrod O, Davies SA, Cahill G Jr: The action of cortisone and desoxycorticosterone acetate on glomerular filtration rate and sodium and water exchange in the adrenalectomized dog. *J Clin Invest* 1955; 34 761–776
37. Ballmer PE, McNurlan MA, Hulter HN, et al: Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. *J Clin Invest* 1995; 95: 39–45
38. Chen WJ, Oashi E, Kasai M: Amino acid metabolism in parenteral nutrition: With special reference to the calorie: nitrogen ratio and the blood urea nitrogen level. *Metabolism* 1974; 23:1117–1123
39. Dal Canton A, Fuiano G, Conte G, et al: Mechanism of increased plasma urea after diuretic therapy in uraemic patients. *Clin Sci (Lond)* 1985; 68:255–261
40. Aronson D, Mittleman MA, Burger AJ: Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med* 2004; 116: 466–473
41. Sakr Y, Vincent JL, Reinhart K, et al: High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005; 128:3098–3108
42. Simmons RS, Berdine GG, Seidenfeld JJ, et al: Fluid balance and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1987; 135:924–929
43. Humphrey H, Hall J, Sznajder I, et al: Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest* 1990; 97:1176–1180
44. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
45. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39:S1–S266
46. Preiss DJ, Godber IM, Lamb EJ, et al: The influence of a cooked-meat meal on estimated glomerular filtration rate. *Ann Clin Biochem* 2007; 44:35–42
47. Cartin-Ceba R, Afessa B, Gajic O: Low baseline serum creatinine concentration predicts mortality in critically ill patients independent of body mass index. *Crit Care Med* 2007; 35:2420–2423
48. Goldstein LB: Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: Effect of modifier codes. *Stroke* 1998; 29:1602–1604
49. Iezzoni LI, Burnside S, Sickles L, et al: Coding of acute myocardial infarction. Clinical and policy implications. *Ann Intern Med* 1988; 109:745–751
50. Lee DS, Donovan L, Austin PC, et al: Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Med Care* 2005; 43:182–188
51. Levy AR, Tamblyn RM, Fitchett D, et al: Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. *Can J Cardiol* 1999; 15:1277–1282
52. Winkelmayer WC, Schneeweiss S, Mogun H, et al: Identification of individuals with CKD from Medicare claims data: A validation study. *Am J Kidney Dis* 2005; 46:225–232

53. Humphries KH, Rankin JM, Carere RG, et al: Co-morbidity data in outcomes research: Are clinical data derived from administrative databases a reliable alternative to chart review? *J Clin Epidemiol* 2000; 53:343–349
54. Kieszak SM, Flanders WD, Kosinski AS, et al: A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *J Clin Epidemiol* 1999; 52:137–142
55. Moreno RP, Metnitz PG, Almeida E, et al: SAPS 3–From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005; 31:1345–1355
56. Sibbald W: Evaluating critical care-using health services research to improve quality. *In:* Update in Intensive Care Medicine. Vincent JL (Ed). Heidelberg, Germany, Springer-Verlag, 2001
57. Quach S, Hennessy DA, Faris P, et al: A comparison between the APACHE II and Charlson Index Score for predicting hospital mortality in critically ill patients. *BMC Health Serv Res* 2009; 9:129
58. Gottlieb SS: Dead is dead–artificial definitions are no substitute. *Lancet* 1997; 349: 662–663
59. Lauer MS, Blackstone EH, Young JB, et al: Cause of death in clinical research: Time for a reassessment? *J Am Coll Cardiol* 1999; 34: 618–620
60. Preen DB, Holman CD, Spilsbury K, et al: Length of comorbidity lookback period affected regression model performance of administrative health data. *J Clin Epidemiol* 2006; 59:940–946
61. Schrier RW, Berl T, Anderson RJ: Osmotic and nonosmotic control of vasopressin release. *Am J Physiol* 1979; 236:F321–F332
62. Schrier RW: Body fluid volume regulation in health and disease: A unifying hypothesis. *Ann Intern Med* 1990; 113:155–159
63. Schrier RW, Abraham WT: Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; 341:577–585
64. 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
65. Schrier RW: Blood urea nitrogen and serum creatinine: Not married in heart failure. *Circ Heart Fail* 2008; 1:2–5
66. Schrier RW, Wang W: Acute renal failure and sepsis. *N Engl J Med* 2004; 351:159–169
67. Casaer MP, Mesotten D, Schetz MR: Bench-to-bedside review: Metabolism and nutrition. *Crit Care* 2008; 12:222
68. Wolfe RR: Sepsis as a modulator of adaptation to low and high carbohydrate and low and high fat intakes. *Eur J Clin Nutr* 1999; 53(Suppl 1):S136–S142
69. Biolo G, Grimble G, Preiser JC, et al: Position paper of the ESICM Working Group on Nutrition and Metabolism. Metabolic basis of nutrition in intensive care unit patients: Ten critical questions. *Intensive Care Med* 2002; 28:1512–1520
70. Wenzel RP, Edmond MB: The impact of hospital-acquired bloodstream infections. *Emerg Infect Dis* 2001; 7:174–177
71. Shorr AF, Jackson WL, Kelly KM, et al: Transfusion practice and blood stream infections in critically ill patients. *Chest* 2005; 127:1722–1728
72. Blaine KP, Tuohy MJ, Wilson D, et al: Progression to bacteremia in critical care patients colonized with methicillin-resistant *Staphylococcus aureus* expressing Panton-Valentine leukocidin. *Diagn Microbiol Infect Dis* 2010; 68:28–33
73. Miller RS, Norris PR, Jenkins JM, et al: Systems initiatives reduce healthcare-associated infections: A study of 22,928 device days in a single trauma unit. *J Trauma* 2010; 68:23–31