Blood Urea Nitrogen in the Early Assessment of Acute Pancreatitis

An International Validation Study

Bechien U. Wu, MD, MPH; Olaf J. Bakker, MD; Georgios I. Papachristou, MD; Marc G. Besselink, MD; Kathryn Repas, BA; Hjalmar C. van Santvoort, MD; Venkata Muddana, MD; Vikesh K. Singh, MD; David C. Whitcomb, MD, PhD; Hein G. Gooszen, MD; Peter A. Banks, MD

Background: Objective assessment of acute pancreatitis (AP) is critical to help guide resuscitation efforts. Herein we (1) validate serial blood urea nitrogen (BUN) measurement for early prediction of mortality and (2) develop an objective BUN-based approach to early assessment in AP.

Methods: We performed a secondary analysis of 3 prospective AP cohort studies: Brigham and Women's Hospital (BWH), June 2005 through May 2009; the Dutch Pancreatitis Study Group (DPSG), March 2004 through March 2007; and the University of Pittsburgh Medical Center (UPMC), June 2003 through September 2007. Meta-analysis and stratified multivariate logistic regression adjusted for age, sex, and creatinine levels were calculated to determine risk of mortality associated with elevated BUN level at admission and rise in BUN level at 24 hours. The accuracy of the BUN measurements was determined by area under the receiver operating characteristic curve (AUC) analysis compared with serum creatinine measurement and APACHE II score. A BUN-based assessment algorithm was derived on BWH data and validated on the DPSG and UPMC cohorts.

Results: A total of 1043 AP cases were included in analysis. In pooled analysis, a BUN level of 20 mg/dL or higher was associated with an odds ratio (OR) of 4.6 (95% confidence interval [CI], 2.5-8.3) for mortality. Any rise in BUN level at 24 hours was associated with an OR of 4.3 (95% CI, 2.3-7.9) for death. Accuracy of serial BUN measurement (AUC, 0.82-0.91) was comparable to that of the APACHE II score (AUC, 0.72-0.92) in each of the cohorts. A BUN-based assessment algorithm identified patients at increased risk for mortality during the initial 24 hours of hospitalization.

Conclusions: We have confirmed the accuracy of BUN measurement for early prediction of mortality in AP and developed an algorithm that may assist physicians in their early resuscitation efforts.

Arch Intern Med. 2011;171(7):669-676

Author Affiliations: Center for Pancreatic Disease, Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Drs Wu, Singh, and Banks and Ms Repas); Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands (Drs Bakker, Besselink, van Santvoort, and Gooszen); Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Drs Papachristou, Muddana, and Whitcomb); and Division of Gastroenterology, The Johns Hopkins Hospital, Baltimore, Maryland (Dr Singh).

ACUTE PANCREATITIS IS A common cause for hospitalization worldwide. Each year, there are over 200 000 hospitalizations for acute pancreatitis in the United States, at a direct cost exceeding $2 billion.[1,2] Although most patients experience only mild, self-limited disease, up to 20% experience a more severe form of illness that can be life-threatening.[3-6] Most patients who ultimately require treatment in an intensive care setting are transferred from the general medical ward during the first 24 to 48 hours of hospitalization.[7] Therefore, management during the initial 24 hours of hospitalization is an important phase of treatment for patients with acute pancreatitis.

See Invited Commentary at end of article

Since the publication of the Ranson criteria nearly 40 years ago,[8] an objective approach to the early assessment of acute pancreatitis has been the focus of a great deal of clinical investigation. Although numerous clinical scoring systems[9-12] and candidate biomarkers[13,14] have been proposed, none of these approaches has become incorporated into routine clinical practice. Despite its limitations, the APACHE II score (Acute Physiology and Chronic Health Enquiry II[10]) remains the assessment scale most often recommended for evaluation of patients with acute pancreatitis.[3,5,15]

Practice guidelines in acute pancreatitis also call for vigorous fluid resuscitation in the early treatment of acute pancreatitis.[16] To evaluate the effectiveness of initial resuscitation efforts, physicians rely on physical examination findings and results of laboratory tests. In this regard, sur-

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013

rogate markers of intravascular volume status such as hematocrit or blood urea nitrogen (BUN) levels can provide valuable feedback regarding a patient's response to initial resuscitation efforts. To help determine which routine laboratory test might be the most useful in the early assessment of patients with acute pancreatitis, members of our group recently conducted a retrospective cohort study from 69 US hospitals.[17] In that study, we determined that serial measurement of BUN was more accurate than hematocrit measurement for the early prediction of mortality in patients with acute pancreatitis.

The purpose of the present study was to develop an objective approach to early clinical assessment of acute pancreatitis based on serial BUN measurements. Our first aim was to validate early changes in BUN level as an early risk factor for mortality using prospectively collected data from the United States and the Netherlands. Our secondary aim was to develop an algorithm based on early changes in BUN to help guide clinicians in their early resuscitation efforts.

METHODS

PATIENT POPULATION AND DATA COLLECTION

We collected data from 3 concurrently conducted prospective cohort studies of acute pancreatitis. All centers used the same criteria for diagnosis of acute pancreatitis. Specifically, patients were required to satisfy at least 2 of the following 3 criteria to confirm the diagnosis: (1) typical epigastric abdominal pain; (2) elevation in amylase and/or lipase levels to at least 3 times the upper limit of normal; and (3) confirmatory findings on cross-sectional abdominal imaging. In addition, each of the studies calculated the APACHE II score based on the worst (most extreme) laboratory and vital sign measurement obtained during the initial 24 hours of hospitalization. All patients were managed with initial fasting (*nil per os*) at the time of hospitalization. Specific resuscitation parameters including frequency of laboratory monitoring were determined by individual treating clinicians according to standards of practice within each institution. Within each study cohort, patients were enrolled at the time of admission and observed until hospital discharge. Ethical approval was obtained from the appropriate institutional review board for each of the individual cohort studies as well as from the partners health care institutional review board for the present combined study.

The Markers of Severity in Acute Pancreatitis study[18] was conducted at Brigham and Women's Hospital (BWH) from June 2005 through May 2009 for the purpose of evaluation of prognostic markers in acute pancreatitis. Details of the data collection methods used in this study have been previously published.[18] All patients directly admitted or transferred to BWH with a diagnosis of acute pancreatitis during the study period were eligible for participation. Patients were identified prospectively based on lipase level elevation and/or admission diagnosis codes. Demographic data were obtained through patient interviews. Specific clinical parameters that were prospectively collected included vital signs, laboratory test results, and fluid resuscitation parameters. Medical records were obtained for all transferred patients admitted during the study period.

The Dutch Pancreatitis Study Group (DPSG)[18,19] cohort consisted of data collected from 15 Dutch hospitals from March 2004 through March 2007. The hospitals included 8 Dutch university medical centers and 7 major teaching hospitals. The ethics review board of each participating hospital approved the protocol of the cohort study. The study cohort consisted of patients with a first attack of acute pancreatitis potentially eligible for participation in a prospective randomized controlled trial on the use of probiotics in severe acute pancreatitis (the Probiotic Prophylaxis in Predicted Severe Acute Pancreatitis [PROPATRIA]) trial[19]; registration No. ISRCTN38327949). The cohort for the present study was restricted to patients randomized to the placebo arm of the PROPATRIA trial and to patients who could not be randomized due to exclusion criteria (eg, predicted mild disease).[20] Patients not randomized in the context of the PROPATRIA trial continued to have prospective data collected regarding clinical parameters and laboratory tests for the duration of their hospitalization.

The Severity of Acute Pancreatitis Study (SAPS)[21] was conducted at 2 tertiary care hospitals of the University of Pittsburgh Medical Center (UPMC) from June 2003 through September 2007 for the purpose of evaluation of early prognostic markers in acute pancreatitis. All patients directly admitted or transferred to UPMC with a diagnosis of acute pancreatitis during the study period were eligible for participation. Patients had demographic, radiographic, and laboratory data prospectively collected. Details of the collection methods used in the SAPS study have been reported previously.[21]

To evaluate the role of serial BUN measurement as an early prognostic marker, we limited our analysis to patients who had at least 2 BUN measurements collected within 24 hours of hospitalization. Specifically, patients were required to have BUN data collected at admission and a repeat value taken at 24 hours (±6 hours) for study inclusion. For purposes of uniform data presentation, units of BUN are presented as milligrams per deciliter. To convert BUN to millimoles per liter, multiply by 0.357.

STATISTICAL ANALYSIS

We conducted 2 sets of analyses: evaluation of serial BUN measurement for the early prediction of mortality in acute pancreatitis and development of an approach to early assessment based on serial BUN measurement. For our evaluation of BUN levels for early prediction of mortality, we conducted a meta-analysis using data from each of the included studies to determine the impact of an elevated BUN level at admission or a rise in BUN level during the initial 24 hours of hospitalization on risk of in-hospital death. A threshold of 20 mg/dL was used for admission BUN based on previously published findings.[17] To evaluate the effect of a rise in BUN level during the initial 24 hours of hospitalization, changes in BUN value were dichotomized as an increase (≥0 mg/dL) vs decrease from admission value. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each parameter for individual studies and then pooled using a random-effects model. The I^2 test was used to evaluate for heterogeneity between studies (Comprehensive Meta-analysis software Version 2; Biostat, Englewood New Jersey).

We then compared mean admission BUN values and mean change in BUN level at 24 hours according to survival status (fatal cases vs survivors) using the Wilcoxon rank-sum test within study cohorts. The Cochrane-Armitage test of trend was used to evaluate the relationship between extent of elevation in admission BUN measurement as well as the extent of the rise in BUN level during the initial 24 hours of hospitalization with subsequent in-hospital mortality.

We used multivariate logistic regression to obtain effect estimates adjusted for age, sex, and serum creatinine level for admission BUN measurement and change in BUN level at 24 hours. Admission serum creatinine value and change in serum creatinine value were included in this model to determine whether the impact of BUN level on risk of mortality was independent

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013

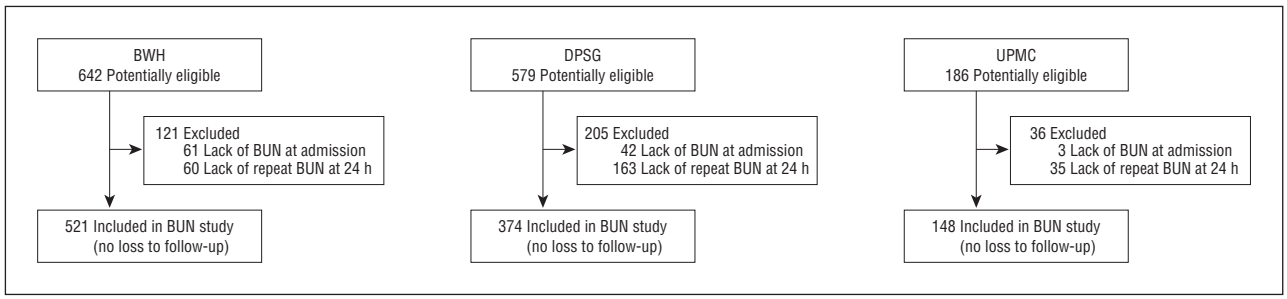

Figure 1. Sources of the study population. Potentially eligible subjects were those originally included in each individual study cohort. Further eligibility for the present study was restricted to patients with serial measurements of blood urea nitrogen (BUN) during the initial 24 hours of hospitalization. BWH indicates Brigham and Women's Hospital cohort; DPSG, Dutch Pancreatitis Study Group cohort; and UPMC, University of Pittsburgh Medical Center cohort.

Table 1. Demographic and Clinical Characteristics of the 3 Study Cohorts

Characteristic	BWH (n=521)	DPSG (n=374)	UPMC (n=148)	*P* Value[a]
Age, median (IQR), y	52 (41-62)	57 (41.0-70.0)	53 (39-67)	.003
Women, %	51	44	46	.14
Cause, %				
Biliary	43	57	36	<.001
Alcohol	19	18	14	.28
Post-ERCP	12	20	14	<.001
Idiopathic	11	5	27	<.001
Hospital transfer, %	12	13	43	<.001
APACHE II score, median (IQR)	7 (4-11)	6 (4-10)	6 (3-10)	.001
Mortality, %	3.7	7.8	3.4	.04

Abbreviations: ANOVA, analysis of variance; APACHE II, Acute Physiology and Chronic Health Enquiry II[10]; BWH Brigham and Women's Hospital cohort; DPSG, Dutch Pancreatitis Study Group cohort; ERCP, endoscopic retrograde cholangio-pancreatography; IQR, interquartile range; UPMC, University of Pittsburgh Medical Center cohort.

[a] χ^2 Test for categorical variables or ANOVA for continuous variables, as appropriate.

of renal function. We also tested for interaction between change in BUN level and change in serum creatinine level.

To evaluate accuracy of serial BUN measurement for prediction of mortality, we plotted a receiver operating characteristic (ROC) curve based on BUN level at admission and change in BUN level at 24 hours. Accuracy of this model was compared with a similar creatinine-based model and the APACHE II score by comparison of area under the ROC curve (AUC) according to the methods described by DeLong et al.[22]

To develop a BUN-based approach to early assessment (the initial 24 hours), we used recursive partitioning to develop an assessment algorithm that incorporates both the BUN level at admission and a patient's change in BUN level after initial resuscitation for use in the evaluation of patients with acute pancreatitis. Specifically, we applied Classification and Regression Tree analysis (CART, version 6.0; Salford Systems, San Diego, California) to identify specific thresholds for BUN level at admission and change in BUN level at 24 hours that were associated with either increased or reduced risk of in-hospital mortality in the BWH data set. We used a supervised approach to CART analysis in which we prespecified that model development should proceed according to a manner that reflected clinical practice such that admission BUN level was a forced entry as the first split variable followed by change in BUN level at 24 hours. Based on a priori knowledge, we specified an initial threshold of 20 mg/dL for BUN level at admission.[17] All model development was performed exclusively using BWH data with 10-fold cross-validation and the Gini index as split criteria. Following model development, we applied the BUN assessment algorithm to the UPMC and DPSG cohorts for validation purposes.

Unless otherwise noted, all statistical programming was performed in SAS statistical software, version 9.2 (Cary, North Carolina). All reported *P* values are 2-sided, with $\alpha<.05$ threshold used for significance.

RESULTS

STUDY POPULATION

Data from 1407 potentially eligible cases of acute pancreatitis were available from the 3 study cohorts. **Figure 1** illustrates the composition of the study cohorts after application of the study exclusionary criteria. Demographic and clinical characteristics of the cases included from each study are listed in **Table 1**. There were a total of 521 patients with acute pancreatitis included from the BWH cohort (median age, 52 years; 51% women); 374 from the DPSG (median age, 57 years; 44% women); and 148 from UPMC (median age, 53 years; 46% women). The most frequent cause of pancreatitis was biliary in all 3 cohorts. There were differences between study cohorts with respect to age, cause of pancreatitis, proportion of hospital transfers, and mortality.

Demographic and clinical characteristics of the patients excluded based on lack of serial BUN measurements are listed in **Table 2**. A significant proportion of excluded patients were hospital transfers (26% transfers in BWH, 60% transfers in UPMC). Excluded patients also tended to have mild severity of disease as measured by median APACHE II score.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013

BUN LEVELS FOR THE EARLY PREDICTION OF MORTALITY

Admission BUN values were significantly higher among fatal cases compared with survivors in the BWH and DPSG cohorts: BWH mean level, 38.9 mg/dL for nonsurvivors vs 17.7 mg/dL for survivors (Wilcoxon rank sum $P<.001$); DPSG, 27.6 mg/dL vs 18.7 mg/dL ($P<.001$). The BUN values were also higher among fatal cases in the UPMC cohort, but the difference was not significant (22.8 mg/dL vs 17.6 mg/dL) ($P=.11$).

The forest plot for risk of hospital mortality associated with an elevated admission BUN level (≥20 mg/dL) is presented in **Figure 2**A. In pooled analysis, an elevated BUN value at admission was associated with an overall OR of 4.6 (95% CI, 2.5-8.3) for in-hospital mortality ($I^2<0.0001$). The forest plot for the risk of hospital mortality associated with a rise (≥0 mg/dL) in BUN level during the initial 24 hours of hospitalization is presented inFigure 2B. In pooled analysis, a rise in BUN level during the initial 24 hours of hospitalization was associated with an overall OR of 4.3 (95% CI, 2.3-7.9) for mortality ($I^2<0.0001$).

As shown in **Figure 3**A, there was a significant trend toward increased mortality with higher levels of BUN at admission for the BWH and DPSG cohorts (BWH Cochrane-Armitage trend, $P<.001$; DPSG trend, $P<.001$) but not in the UPMC study (UPMC trend, $P=.14$). Change in BUN level at 24 hours differed among fatal cases vs survivors in each of the 3 individual study cohorts (BWH mean change in BUN level, +1.3 mg/dL among nonsurvivors vs −2.5 mg/dL among survivors [$P=.01$]; DPSG, +6.3 mg/dL vs −0.5 mg/dL [$P<.001$]; and UPMC, +12.0 mg/dL vs −1.8 mg/dL [$P=.003$]). Figure 3B displays the relationship between extent of rise in BUN level at 24 hours and subsequent risk for in-hospital mortality. A greater rise in BUN level at 24 hours was associated with increased mortality in all the study cohorts (BWH Cochrane-Armitage trend, $P<.001$; DPSG, $P<.001$; and UPMC, $P=.05$).

We constructed an age-, sex-, and creatinine-adjusted multivariate logistic regression model to investigate the independent effect of admission and 24-hour change in BUN level on risk of mortality. **Table 3** lists the adjusted effect estimates for each of the 3 study cohorts. Both admission BUN level and change in BUN level at 24 hours were independent predictors of mortality in the BWH and DPSG cohorts. By contrast, only a rise in BUN level during the initial 24 hours was associated with increased risk of mortality in the UPMC cohort. Overall, there was evidence of significant positive interaction between change in BUN level and change in serum creatinine level ($P=.03$) during the initial 24 hours of hospitalization such that patients with a rise in both BUN and creatinine levels had significantly increased mortality compared with either parameter alone.

Table 4 presents the AUC of a 2-variable BUN model (admission value and change at 24 hours) compared with AUC of a similar model using serum creatinine reading as well as the APACHE II score. In each of the study co-

Table 2. Demographic and Clinical Characteristics of Patients Excluded From the Present Study Owing to Lack of Serial BUN Measurements

Characteristic	BWH (n=121)	DPSG (n=205)	UPMC (n=40)
Age, Median (IQR)	52 (41-62)	57 (41.0-70.0)	53 (39-67)
Women, %	60	51	57
Cause, %			
Biliary	41	62	40
Alcohol	15	18	20
Post-ERCP	21	15	15
Idiopathic	11	5	10
Hospital transfer, %	26	10	60
APACHE II Score, Median (IQR)	5 (3-8)	6 (3-8)	5 (3-6)
Mortality, %	2.5	3.9	5.0

Abbreviations: ANOVA, analysis of variance; APACHE II, Acute Physiology and Chronic Health Enquiry II[10]; BUN, blood urea nitrogen; BWH Brigham and Women's Hospital cohort; DPSG, Dutch Pancreatitis Study Group cohort; ERCP, endoscopic retrograde cholangio-pancreatography; IQR, interquartile range; UPMC, University of Pittsburgh Medical Center cohort.

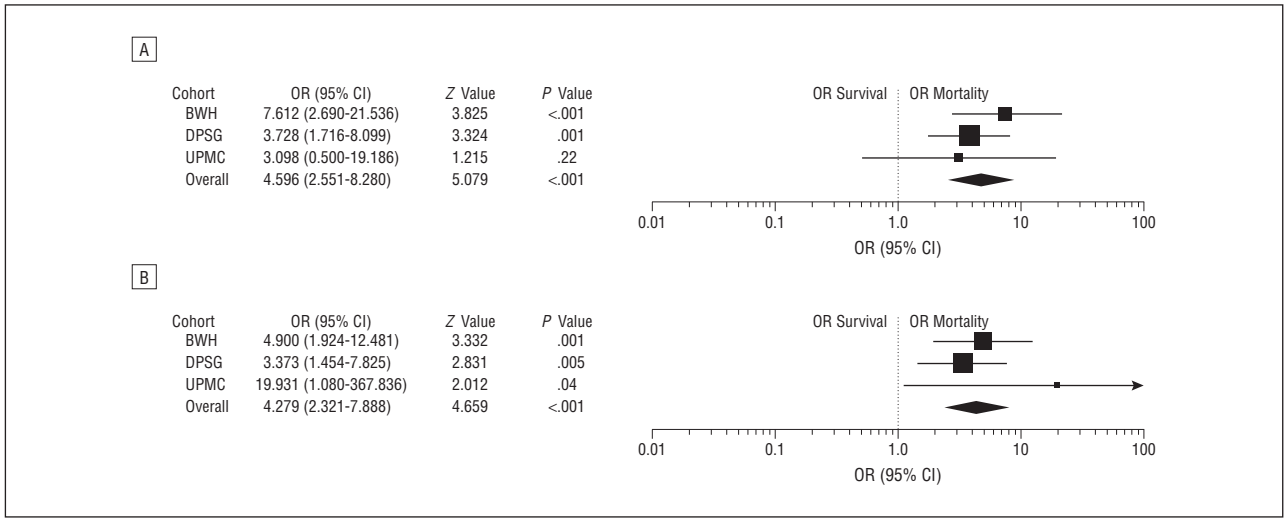

Figure 2. Mortality risk forest plots. A. Risk associated with an elevated blood urea nitrogen (BUN) level (≥20 mg/dL) at admission. Random-effects model was used for pooled analysis. B. Risk associated with a rise in BUN level (of ≥0 mg/dL) at 24 hours. Random-effects model was used for pooled analysis. BWH indicates Brigham and Women's Hospital cohort; DPSG, Dutch Pancreatitis Study Group cohort; and UPMC, University of Pittsburgh Medical Center cohort.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013

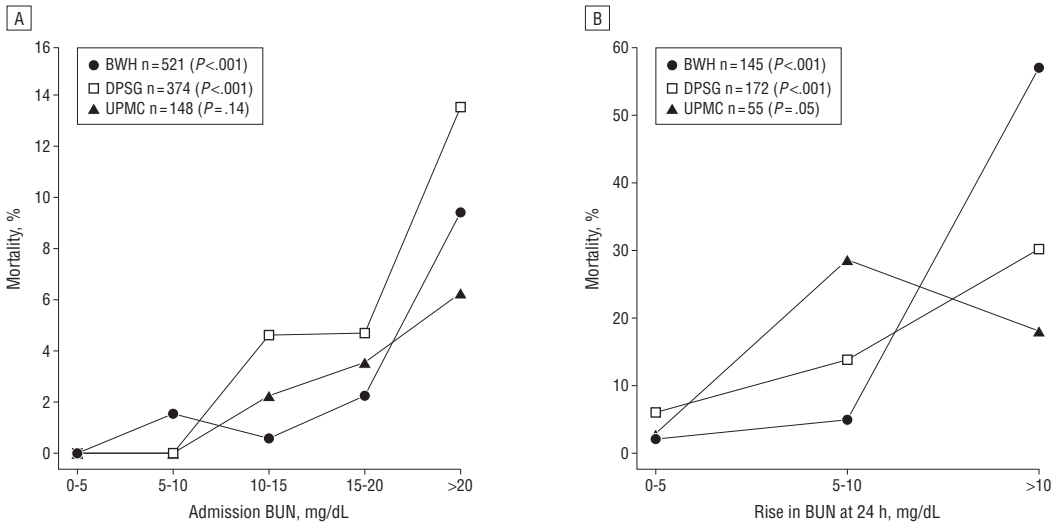

Figure 3. In-hospital mortality. A, Mortality by blood urea nitrogen (BUN) level at admission. B, Mortality by extent of rise in BUN level during initial 24 hours of hospitalization. BWH indicates Brigham and Women's Hospital cohort; DPSG, Dutch Pancreatitis Study Group cohort; and UPMC, University of Pittsburgh Medical Center cohort.

Table 3. Multivariate Logistic Regression Analysis of Risk of In-Hospital Mortality Associated With Elevated BUN Level at Admission and Extent of Rise in BUN at 24 Hours Adjusted for Age, Sex, and Creatinine Level[a]

Cohort	Admission BUN	Rise in BUN at 24 h	Admission Creatinine	Rise in Creatinine at 24 h
BWH	2.0 (1.3-3.0)	2.6 (1.5-4.4)	1.0 (0.7-1.4)	0.8 (0.3-2.4)
DPSG	1.6 (1.1-2.5)	1.8 (1.3-2.5)	0.9 (0.6-1.4)	1.0 (0.7-1.5)
UPMC	1.0 (0.2-4.5)	2.9 (0.5-18.0)	0.5 (0.03-8.1)	6.4 (0.9-47.8)

Abbreviations: BUN, blood urea nitrogen; BWH Brigham and Women's Hospital cohort; DPSG, Dutch Pancreatitis Study Group cohort; UPMC, University of Pittsburgh Medical Center cohort.

[a]All data reported as odds ratios (95% confidence intervals); effect estimates provided are for every increase of 5 mg/dL in BUN or 0.5 mg/dL in creatinine.

horts, the BUN model performed similarly to serum creatinine and the APACHE II models for prediction of mortality (BUN model overall, AUC=0.84; creatinine model, AUC=0.79; and APACHE II score, AUC=0.80).

A BUN-BASED APPROACH TO EARLY ASSESSMENT OF ACUTE PANCREATITIS: CART ANALYSIS

We applied a CART analysis using data from the BWH cohort to develop a quantitative approach to patient assessment that incorporates serial BUN measurement during the initial 24 hours of hospitalization. We specified an initial threshold of ≥20 mg/dL for BUN at admission. Among patients with an elevated BUN level at admission, a decrease in BUN level of at least 5 mg/dL during the first 24 hours of hospitalization was associated with significantly reduced mortality in the BWH cohort (2.9% vs 15%) (χ^2 P=.01). By contrast, a rise of as little as 2 mg/dL or more was associated with increased mortality among patients with a normal BUN level at admission (6.7% vs 0.9% mortality) (χ^2 P=.008).

The algorithm performed similarly when applied to the DPSG and UPMC study cohorts (**Figure 4**). In each study cohort, patients with an elevated BUN level at admission that did not decline by at least 5 mg/dL after 24 hours of hospitalization were at the highest risk for in-hospital mortality (15%-21%). By contrast, patients with an elevated BUN level at admission that declined by 5 mg/dL or more after 24 hours had a substantially reduced mortality risk (0%-3.2%). Among patients with a normal BUN level at admission, those with an increase in BUN level of 2 mg/dL or more at 24 hours experienced significantly increased

Table 4. Accuracy of Serial Measurements of BUN Compared With Serum Creatinine and the APACHE II Score[a]

Cohort	BUN	Creatinine	APACHE II
BWH	0.84 (0.70-0.94)	0.86 (0.78-0.94)	0.89 (0.81-0.98)
DPSG	0.82 (0.74-0.90)	0.74 (0.63-0.84)	0.72 (0.63-0.82)
UPMC	0.91 (0.83-0.99)	0.96 (0.94-0.99)	0.92 (0.85-0.98)
Overall	0.84 (0.79-0.90)	0.79 (0.72-0.86)	0.80 (0.74-0.87)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Enquiry II[10]; AUC, area under the receiver operating characteristic curve; BUN, blood urea nitrogen; BWH Brigham and Women's Hospital cohort; DPSG, Dutch Pancreatitis Study Group cohort; UPMC, University of Pittsburgh Medical Center cohort.

[a]Accuracy determined and reported as AUC (95% confidence interval); accuracy of BUN and creatinine measurement determined by logistic regression model including admission value and change in 24 hours.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013

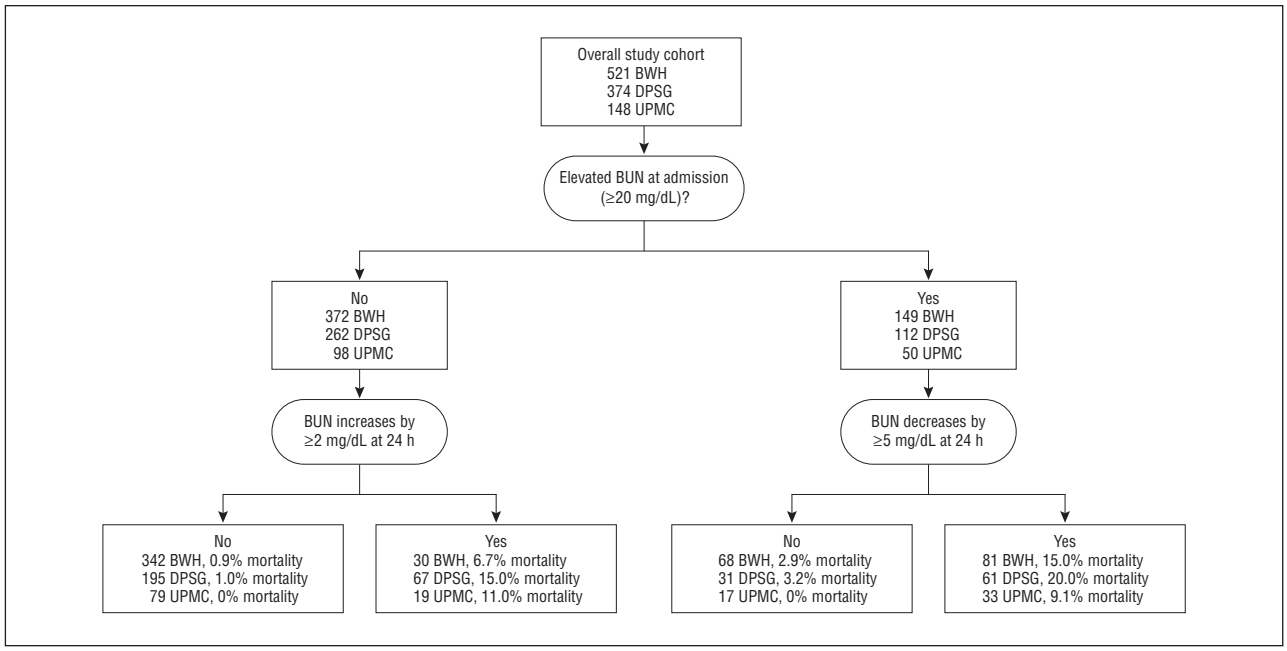

Figure 4. Algorithm for serial blood urea nitrogen (BUN) measurements in the early assessment of acute pancreatitis. Results are based on CART analysis (Salford Systems, San Diego, California) developed using BWH data with subsequent application to DPSG and UPMC study cohorts. BWH indicates Brigham and Women's Hospital cohort (0.9% vs 6.7% [P=.008] and 2.9% vs 15.0% [P=.01], respectively); DPSG, Dutch Pancreatitis Study Group cohort (1.0% vs 15.0% [P<.001] and 3.2% vs 20.0% [P=.03], respectively); and UPMC, University of Pittsburgh Medical Center cohort (0% vs 11.0% [P=.004] and 0% vs 9.1% [P=.21], respectively).

mortality (6%-11%) compared with those whose BUN level did not rise by this amount (0%-1%).

COMMENT

We have confirmed that both an elevated BUN level at admission and an increase in BUN level during the initial 24 hours of hospitalization are independent risk factors for mortality in acute pancreatitis. Using data from 3 concurrent prospective cohort studies conducted in the United States and Netherlands, we have also demonstrated that serial BUN measurement provided accuracy comparable to the more complex APACHE II score for early prediction of in-hospital mortality. We have incorporated these findings into an assessment algorithm based on early changes in BUN level that may provide useful information to physicians during their initial management of patients with acute pancreatitis.

A great deal of research has focused on development of approaches to early risk stratification in acute pancreatitis. Various approaches have included clinical scoring systems such as the Ranson criteria,[8] modified Glasgow,[23] APACHE II score,[10] and others,[9] including our group's recently developed simplified BISAP score (Bedside Index of Severity in Acute Pancreatitis).[12] Additional approaches have included use of inflammatory markers such as C-reactive protein[14] or interleukin (IL)-6 and IL-8.[24] Prior studies have also evaluated the potential role of specific routine laboratory tests in predicting outcome in acute pancreatitis.[25,26] However, none of these approaches has gained widespread acceptance in clinical practice. Because there is no specific pharmacologic treatment for acute pancreatitis, an ideal prognostic marker should help guide physicians in their approach to accepted interventions such as fluid resuscitation.

The potential importance of BUN level in the early assessment of acute pancreatitis has been noted previously. A rise in BUN level of 5 mg/dL or more at 48 hours was 1 of 11 criteria originally established as part of the Ranson score.[8] The BUN level has also been featured in several multifactor clinical scoring systems in acute pancreatitis.[9,12,25] However, many additional routine laboratory tests have also been suggested for early assessment in acute pancreatitis, most notably hemoconcentration (serum hematocrit).[27,28] Unfortunately, attempts to validate the role of hemoconcentration have failed to confirm the accuracy of this test as a prognostic marker in acute pancreatitis,[29-31] likely owing to the heterogeneity of patient populations studied.[31,32]

Early changes in BUN level may reflect several important physiologic processes in acute pancreatitis. In addition to intravascular volume depletion, a rise in BUN level may be secondary to impairment in renal function or potentially concurrent upper gastrointestinal hemorrhage. Renal failure is a relatively common form of organ dysfunction among patients with acute pancreatitis.[33] Nevertheless, an elevated BUN reading at admission or rise in BUN level during the initial 24 hours of hospitalization was an independent risk factor for mortality even after adjusting for changes in serum creatinine level. The incidence of clinically significant gastrointestinal hemorrhage (>500 mL of blood loss) was tracked in the BWH cohort and found to be less than 2%, making this an unlikely explanation for the impact of increasing BUN level on risk of mortality.

In a recent study of 69 US hospitals, our group determined that serial measurement of BUN was the most accurate routine laboratory test for prediction of mortality

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013

when compared with the serum hematocrit, creatinine, calcium, white blood cell count, and glucose assays.[17] That study was limited by use of retrospectively collected administrative data. Since then, Faisst et al[34] have also determined that an elevated admission BUN value was associated with prolonged stay in an intensive care unit among a selected group of patients with severe acute pancreatitis. The present multicenter study has now validated the role of serial BUN measurement for prediction of mortality across 3 independent cohort studies. Although the admission BUN value was not a significant risk factor for mortality in the UPMC study cohort, we attribute this finding to the smaller sample size, as evidenced by the wide confidence intervals for this study cohort depicted in Figure 2A and B. This finding reinforces the importance of the multicenter nature of the present study.

To extend the clinical application of the current study findings, we developed and validated an approach to assessment of patients with acute pancreatitis based on early changes in BUN level. Among patients with an elevated BUN value at admission (>20 mg/dL), a decrease of at least 5 mg/dL at 24 hours was associated with reduced risk of in-hospital death. By contrast, among patients with a normal BUN value at admission, even the slightest rise in BUN level (≥2 mg/dL) was associated with an increased risk of mortality.

There were several potential limitations to the present study. First, there were differences with respect to patient demographics and clinical outcomes among the study cohorts. We therefore used a random-effects model in the meta-analysis and conducted a series of stratified analyses to evaluate the effect of early changes in BUN level on risk of mortality. A second limitation was the exclusion of patients based on lack of serial BUN measurements. This is a potential source of selection bias because all management decisions, including collection of laboratory test results, were left to the discretion of each patient's individual treating physician. To evaluate the extent to which this may have affected our study findings, we have presented a summary of the demographic and clinical characteristics of the patients excluded from the present study (Table 2). In general, patients excluded from the study had milder disease as evidenced by lower APACHE II scores during the initial 24 hours of hospitalization. There were also a high percentage of transferred patients excluded from the BWH and UPMC study owing to an inability to obtain initial hospitalization records. Nevertheless, the mortality rates among the 3 cohorts included in the present study are consistent with other reports of acute pancreatitis.[5,35,36]

In summary, we have confirmed the accuracy of serial BUN measurements for the early prediction of mortality using data from 3 concurrently conducted prospective cohort studies of acute pancreatitis. An elevated BUN value at admission or a subsequent rise in BUN level during the initial 24 hours of hospitalization was an independent risk factor for mortality. We have developed an algorithm based on early changes in BUN level that may help clinicians evaluate a patient's response to early resuscitation efforts in acute pancreatitis.

Accepted for Publication: November 23, 2011.
Correspondence: Bechien U. Wu, MD, MPH, Brigham and Women's Hospital, Division of Gastroenterology, 75 Francis St, Boston, MA 02115 (buwu@partners.org).
Author Contributions: Dr Wu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Wu, Bakker, Papachristou, and van Santvoort. *Acquisition of data:* Wu, Papachristou, Besselink, Repas, van Santvoort, Muddana, Singh, Whitcomb, and Gooszen. *Analysis and interpretation of data:* Wu, Bakker, and Banks. *Drafting of the manuscript:* Wu and Banks. *Critical revision of the manuscript for important intellectual content:* Wu, Bakker, Papachristou, Besselink, Repas, van Santvoort, Muddana, Singh, Whitcomb, Gooszen, and Banks. *Statistical analysis:* Wu. *Obtained funding:* Besselink, Singh, Whitcomb, Gooszen, and Banks. *Administrative, technical, and material support:* Bakker, Repas, van Santvoort, Muddana, Whitcomb, and Banks. *Study supervision:* Repas, Whitcomb, and Banks.
Financial Disclosure: Dr Whitcomb is a consultant for Ambry genetics and serves on the advisory committee of Solvay pharmaceuticals.
Funding/Support: Dr Wu is supported by a 2009 Junior Faculty Career Development Award from the American College of Gastroenterology.
Additional Contributions: The National Pancreas Foundation (NPF), USA, and Senter, an agency of the Dutch Ministry of Economic Affairs, supported the original studies on which this work is based. Funding from the NPF was used for data collection in the BWH study cohort, and Senter funds were used to help support data collection in the DPSG study cohort.

REFERENCES

1. Fagenholz PJ, Castillo CF, Harris NS, Pelletier AJ, Camargo CA Jr. Increasing United States hospital admissions for acute pancreatitis, 1988-2003. *Ann Epidemiol.* 2007;17(7):491-497.
2. Fagenholz PJ, Fernández-del Castillo C, Harris NS, Pelletier AJ, Camargo CA Jr. Direct medical costs of acute pancreatitis hospitalizations in the United States. *Pancreas.* 2007;35(4):302-307.
3. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol.* 2006;101(10):2379-2400.
4. Whitcomb DC. Clinical practice: acute pancreatitis. *N Engl J Med.* 2006;354(20):2142-2150.
5. Forsmark CE, Baillie J; AGA Institute Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. *Gastroenterology.* 2007;132(5):2022-2044.
6. Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. *JAMA.* 2004;291(23):2865-2868.
7. Harrison DA, D'Amico G, Singer M. Case mix, outcome, and activity for admissions to UK critical care units with severe acute pancreatitis: a secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care.* 2007;11(suppl 1):S1.
8. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Localio SA. Objective early identification of severe acute pancreatitis. *Am J Gastroenterol.* 1974;61(6):443-451.
9. Spitzer AL, Barcia AM, Schell MT, et al. Applying Ockham's razor to pancreatitis prognostication: a four-variable predictive model. *Ann Surg.* 2006;243(3):380-388.
10. Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet.* 1989;2(8656):201-205.
11. Osvaldt AB, Viero P, Borges da Costa MS, Wendt LR, Bersch VP, Rohde L. Evaluation of Ranson, Glasgow, APACHE-II, and APACHE-O criteria to predict severity in acute biliary pancreatitis. *Int Surg.* 2001;86(3):158-161.
12. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut.* 2008;57(12):1698-1703.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013

13. Johnson CD, Lempinen M, Imrie CW, et al. Urinary trypsinogen activation peptide as a marker of severe acute pancreatitis. *Br J Surg*. 2004;91(8):1027-1033.
14. Papachristou GI, Whitcomb DC. Inflammatory markers of disease severity in acute pancreatitis. *Clin Lab Med*. 2005;25(1):17-37.
15. Working Party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut*. 2005;54(suppl 3):iii1-iii9.
16. Gardner TB, Vege SS, Pearson RK, Chari ST. Fluid resuscitation in acute pancreatitis. *Clin Gastroenterol Hepatol*. 2008;6(10):1070-1076.
17. Wu BU, Johannes RS, Sun X, Conwell DL, Banks PA. Early changes in blood urea nitrogen predict mortality in acute pancreatitis. *Gastroenterology*. 2009;137(1):129-135.
18. Singh VK, Wu BU, Bollen TL, et al. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. *Am J Gastroenterol*. 2009;104(4):966-971.
19. Besselink MG, van Santvoort HC, Buskens E, et al; Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9613):651-659.
20. Besselink MG, van Santvoort HC, Boermeester MA, et al; Dutch Acute Pancreatitis Study Group. Timing and impact of infections in acute pancreatitis. *Br J Surg*. 2009;96(3):267-273.
21. Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol*. 2010;105(2):435-441, quiz 442.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.
23. Corfield AP, Cooper MJ, Williamson RC, et al. Prediction of severity in acute pancreatitis: prospective comparison of three prognostic indices. *Lancet*. 1985;2(8452):403-407.
24. Pooran N, Indaram A, Singh P, Bank S. Cytokines (IL-6, IL-8, TNF): early and reliable predictors of severe acute pancreatitis. *J Clin Gastroenterol*. 2003;37(3):263-266.
25. Fan ST, Choi TK, Lai EC, Wong J. Prediction of severity of acute pancreatitis: an alternative approach. *Gut*. 1989;30(11):1591-1595.
26. Muddana V, Whitcomb DC, Khalid A, Slivka A, Papachristou GI. Elevated serum creatinine as a marker of pancreatic necrosis in acute pancreatitis. *Am J Gastroenterol*. 2009;104(1):164-170.
27. Baillargeon JD, Orav J, Ramagopal V, Tenner SM, Banks PA. Hemoconcentration as an early risk factor for necrotizing pancreatitis. *Am J Gastroenterol*. 1998;93(11):2130-2134.
28. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas*. 2000;20(4):367-372.
29. Lankisch PG, Mahlke R, Blum T, et al. Hemoconcentration: an early marker of severe and/or necrotizing pancreatitis? a critical appraisal. *Am J Gastroenterol*. 2001;96(7):2081-2085.
30. Remes-Troche JM, Duarte-Rojo A, Morales G, Robles-Díaz G. Hemoconcentration is a poor predictor of severity in acute pancreatitis. *World J Gastroenterol*. 2005;11(44):7018-7023.
31. Gardner TB, Olenec CA, Chertoff JD, Mackenzie TA, Robertson DJ. Hemoconcentration and pancreatic necrosis: further defining the relationship. *Pancreas*. 2006;33(2):169-173.
32. Wu BU, Conwell DL, Singh VK, et al. Early hemoconcentration is associated with pancreatic necrosis only among transferred patients. *Pancreas*. 2010;39(5):572-576.
33. Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br J Surg*. 2006;93(6):738-744.
34. Faisst M, Wellner UF, Utzolino S, Hopt UT, Keck T. Elevated blood urea nitrogen is an independent risk factor of prolonged intensive care unit stay due to acute necrotizing pancreatitis. *J Crit Care*. 2010;25(1):105-111.
35. Bruennler T, Hamer OW, Lang S, et al. Outcome in a large unselected series of patients with acute pancreatitis. *Hepatogastroenterology*. 2009;56(91-92):871-876.
36. Lowenfels AB, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. *Curr Gastroenterol Rep*. 2009;11(2):97-103.

INVITED COMMENTARY

BUN Level as a Marker of Severity in Acute Pancreatitis

Simple, Universal, and Accurate

Acute pancreatitis is a devastating disease, causing over 200 000 hospitalizations in the United States annually. A cause of extensive morbidity, the per-incident mortality rate of acute pancreatitis is approximately 5%. With no pharmacologic intervention that has proven reliable in improving clinical outcomes, it is imperative that clinicians recognize patients with a predicted severe outcome early in their course. Early recognition of severity allows for appropriate triage to the intensive care unit, adequate fluid resuscitation, and initiation of enteral feedings.

For many clinicians, the Ranson criteria remain the gold standard for risk stratification in acute pancreatitis.[1] Developed in the early 1970s as a clinical prediction model, the criteria rely on 5 admission parameters and six 48-hour parameters to determine whether severe pancreatitis is likely or unlikely. In addition, based on the number of parameters present, the risk of mortality can be calculated (eg, presence of 5-6 criteria signals a 40% mortality rate). The advantage to the Ranson model was its ability to accurately calculate mortality risk using fairly simple parameters; the obvious downside was the need to wait 48 hours prior to definitive stratification.

In an effort to improve not only on the Ranson accuracy but also its complexity, multiple subsequent scoring systems have been developed in the last 40 years. It is safe to say that none of these systems has really offered a widely accepted, clinically useful alternative, with the exception of the APACHE II scoring system.[2] Although deemed the gold standard for predicting severity in acute pancreatitis, the APACHE II system is complex (based on 12 physiologic measurements, previous health status, and age) and was not developed specifically for acute pancreatitis. In addition, the score generally requires intensive care unit level evaluation and should only be calculated once at admission, thereby limiting its usefulness over the course of the subsequent hospitalization.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/22/2013