

## Early Changes in Blood Urea Nitrogen Predict Mortality in Acute Pancreatitis

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**BACKGROUND & AIMS:** Routine laboratory tests that reflect intravascular volume status can play an important role in the early assessment of acute pancreatitis (AP). The objective of this study was to evaluate accuracy of serial blood urea nitrogen (BUN) versus serial hemoglobin (Hgb) measurement for prediction of in-hospital mortality in AP. **METHODS:** We performed an observational cohort study on data from 69 US hospitals from January 2003 to December 2006. Repeated measures analysis was used to examine the relationship between early trends in BUN and Hgb with respect to mortality. Multivariate logistic regression was used to evaluate the impact of admission BUN, change in BUN, admission Hgb, and change in Hgb on mortality. Time-specific receiver operating characteristic curves and multivariable logistic regression compared accuracy of BUN, Hgb, and additional routine laboratory tests. **RESULTS:** BUN levels were persistently higher among nonsurvivors than survivors during the first 48 hours of hospitalization (F-test;  $P < .0001$ ). No such relationship existed for Hgb (F-test;  $P = .33$ ). For every 5-mg/dl increase in BUN during the first 24 hours, the age- and gender-adjusted odds ratio for mortality increased by 2.2 (95% confidence limits, 1.8, 2.7). Of the 6 routine laboratory tests examined, BUN yielded the highest area under the concentration-time curve (AUC) for predicting mortality at admission (AUC = 0.79), 24 hours (AUC = 0.89), and 48 hours (AUC = 0.90). Combining admission BUN and change in BUN at 24 hours produced an AUC of 0.91 for mortality. **CONCLUSION:** In a large, hospital-based cohort study, we identified serial BUN measurement as the most valuable single routine laboratory test for predicting mortality in AP.

Acute pancreatitis (AP) has a highly variable disease course. Although the majority of patients have self-limited disease, up to 15% of patients develop a life-threatening illness.<sup>1</sup> Local pancreatic tissue injury can rapidly progress to systemic inflammation and multiorgan dysfunction. Therefore, the ability to track a patient's progress early in the disease course is of considerable clinical importance. Recent critical care data have indicated that the median length of stay for patients with AP before transferring to intensive care was 1 day.<sup>2</sup> Therefore,

the first 24 hours of hospitalization represents a critical "therapeutic window" during which efforts should be made to identify patients at increased risk of severe disease to provide optimal therapy.

Current practice guidelines recommend vigorous fluid resuscitation in the early treatment of AP.<sup>1,3–6</sup> This recommendation is based on reports that improvements in pancreatic microcirculation can ameliorate local tissue injury as well as prevent systemic complications in experimental models of AP.<sup>7–9</sup> The ability to pursue directed fluid resuscitation based on dynamic laboratory testing offers a potentially more effective approach to resuscitation. For example, the early recognition of patients refractory to initial resuscitation may help to identify patients most likely to benefit from vigorous fluid resuscitation with hemodynamic monitoring in an intensive care setting.<sup>10</sup>

Several recent prognostic scoring systems, as well as the original Ranson criteria, incorporate blood urea nitrogen (BUN) for prediction of mortality in AP.<sup>2,11–13</sup> In addition, hemoconcentration using serum hematocrit has also been identified in some studies as an early predictor of necrosis<sup>14,15</sup> and organ failure.<sup>15</sup> Both BUN and hematocrit/hemoglobin (Hgb) are routine laboratory tests that may provide information on changes in intravascular volume status. Therefore, either test could be useful in monitoring early response to initial fluid resuscitation. At present, there is no consensus regarding optimal use of these tests in the early assessment of AP.

The aim of the present study was to determine the prognostic utility of serial measurement of routine laboratory tests in the early assessment of AP. Specifically, we conducted an observational cohort study to evaluate the accuracy of serial BUN versus serial Hgb measurement for the prediction of in-hospital mortality. Our secondary aim was to evaluate the accuracy of time-

*Abbreviations used in this paper:* AP, acute pancreatitis; AUC, area under the ROC curve; BUN, blood urea nitrogen; CL, confidence limit; Hgb, hemoglobin; ICD-9-CM, *International Classification of Diseases, 9th Revision, Clinical Modification*; WBC, white blood cell.

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varying changes in alternative routine laboratory tests for predicting in-hospital mortality in AP.

## Methods

### Setting and Patient Data

The present study was approved by the Brigham and Women's Institutional Review Board. We obtained patient data from the Cardinal Health Clinical Outcomes Research Database (Cardinal Health, Marlborough, MA). This dataset has supported public reporting of hospital performance in Pennsylvania and elsewhere for 20 years. Details of the data collection and abstraction process for the Cardinal database have been previously described.<sup>16-18</sup> The database contains information on patient demographics, vital signs, laboratory values, comorbidities, and physical examination findings, as well as procedure and diagnosis codes. Data for laboratory values were recorded for the duration of each patient's hospital stay.

### Study Design and Statistical Analysis

We conducted an observational cohort study to compare the prognostic utility of serial measurement of BUN versus Hgb in the early assessment of AP. We identified all adult ( $\geq 18$  years) cases from 69 US hospitals with a principal diagnosis of AP by *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code 577.0 from the Cardinal database between January 2003 and December 2006. **Figure 1** shows the overall study design and data analysis. We conducted 3 separate sets of analyses to evaluate the prognostic utility of early changes in BUN versus Hgb for prediction of in-hospital mortality.

**Repeated measures analysis with mixed model effects.** We performed a repeated measures analysis using mixed model effects for several reasons. First, follow-up laboratory values for an individual patient are correlated with previous values. In addition, there is a significant degree of within-subject heterogeneity in the

covariance of follow-up BUN and Hgb levels. A mixed model is able to account for this within-subject covariability. In addition, because the mixed model is based on maximum likelihood estimates, it does not require the data to be uniform as is the case with the generalized linear model. This feature allows maximum use of available data.

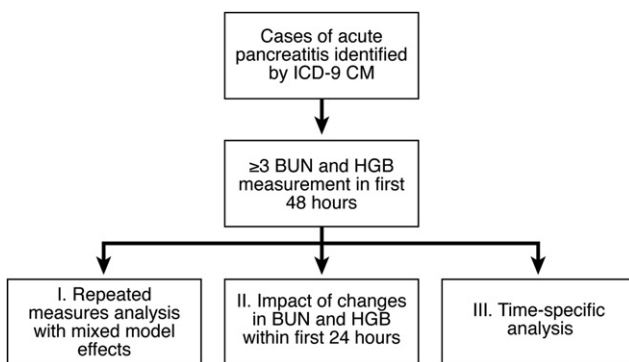
We included all cases of AP with  $\geq 3$  BUN and Hgb measurements within the first 48 hours of hospitalization in a repeated measures analysis (**Figure 1**). We applied a semiparametric, stochastic, mixed model for longitudinal data according to the methods developed by Zhang<sup>19</sup> (SPMM SAS macro). This method uses restricted maximum likelihood to estimate the smoothing parameter and variance components simultaneously. From this analysis we generated mean laboratory levels with 95% confidence limits (CLs) for the first 48 hours among survivors versus nonsurvivors of AP.

In addition, we used multilevel modeling in SAS PROC MIXED to calculate an overall ANOVA F-test statistic for comparison of BUN and Hgb changes over time according to survival status. In the model, we entered survival status as a fixed term; initial BUN and Hgb levels were entered as random terms. Covariance structure was determined based on the Akaike information criteria (AIC) and Schwartz (BIC).

**Impact of change in BUN and Hgb within the first 24 hours.** To characterize how relative changes in BUN and Hgb during the first 24 hours predicted risk of mortality, we identified cases with both BUN and Hgb measured at admission (first value within 6 hours of presentation) and at  $24 \pm 6$  hours (range, 18–30). We then performed multivariable logistic regression (**Figure 1**) to determine the independent effect of admission BUN, 24-hour change in BUN, admission Hgb, and 24-hour change in Hgb on risk of mortality. We further included terms to control for the effects of age and gender in the regression analysis.

**Time-specific multivariable analysis.** The prognostic accuracy of laboratory markers can vary over time. We therefore compared accuracy of serial BUN and Hgb measurement at specific time intervals for predicting mortality (**Figure 1**). Based on previous literature in AP and the routine parameters collected in the Cardinal Health dataset, we included the following additional candidate laboratory markers:

- calcium,<sup>20-22</sup>
- creatinine,<sup>21,23</sup>
- serum glucose,<sup>24,25</sup> and
- white blood cell (WBC) count.<sup>13,24</sup>



**Figure 1.** Study Design. Three sets of analyses for comparison of early changes in BUN and hemoglobin (Hgb) for prediction of mortality in AP. Study cohort was restricted to AP cases with  $\geq 3$  BUN and Hgb measurements within 48 hours of admission.

Serum lactate dehydrogenase<sup>13</sup> and C-reactive protein levels<sup>26,27</sup> were not available for comparison. Each laboratory marker was considered as a continuous variable. Laboratory collection periods were defined as follows:

**Table 1.** Characteristics of Overall AP Population and Study Cohort

	Overall AP population, <sup>a</sup> Jan 2003 to Dec 2006 (N = 13,384)	Study cohort, <sup>b</sup> Jan 2003 to Dec 2006 (N = 5819)
Hospitals (n)	69	69
Teaching hospitals	47%	47%
Patient demographics		
Age (median, IQR)	54 (42–70)	55 (43–72)
Women	49%	48%
Admission laboratory data (median, IQR)		
BUN, mg/dL	15.0 (10–21)	15.0 (11–22)
Missing (%)	(3.0)	(0)
Hgb, g/dL	14.0 (12.7–15.3)	14.0 (12.6–15.3)
Missing (%)	(2.9)	(0)
Calcium, mg/dL	9.3 (8.8–9.6)	9.2 (8.8–9.6)
Missing (%)	(7.5)	(5.5)
Creatinine mg/dL	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Missing (%)	(4.4)	(2.0)
Glucose, mg/dL	124 (103–160)	127 (106–163)
Missing (%)	(2.9)	(0.9)
WBC count × 10 <sup>3</sup>	10.4 (7.9–13.6)	11.2 (8.4–14.8)
Missing (%)	(3.4)	(0.9)
Outcomes		
Length (d)	4 (3–6)	6.7 (3–7)
ICU admission	5.9%	9.2%
Deaths (%)	146 (1.1)	95 (1.6)

BUN, blood urea nitrogen; Hgb, hemoglobin; ICU, intensive care unit; IQR, interquartile range; WBC, white blood cell.

<sup>a</sup>All AP cases (ICD-9-CM 577.0).

<sup>b</sup>Cases with ≥3 BUN and Hgb measurements in the first 48 hours.

- *Admission*: first measurement within 6 hours of admission;
- *24 hours*: first laboratory measurement obtained within 24 ± 6 hours (range, 18–30) of admission; and
- *48 hours*: first laboratory measurement obtained within 48 ± 6 hours (range, 42–54) of admission.

We used time-specific ROC curves and multivariable logistic regression to evaluate the prognostic utility of each of the 6 individual laboratory tests at serial time points. First, we performed univariate analysis comparing the area under the ROC curve (AUC) for BUN and Hgb, as well as the other routine laboratory tests at all 3 time points for prediction of in-hospital mortality. Compari-

son of AUC was performed using the methods described by DeLong et al.<sup>28</sup>

We then used time-specific multivariable logistic regression to identify the independent contribution of each of the routine laboratory tests in predicting mortality. This also enabled us to control for the effect of serum creatinine on BUN. Specifically, we included terms for each of the 6 laboratory tests in logistic regression models based on the admission and 24- and 48-hour time points.

All reported *P* values are 2 sided with a *P* < .05 level of significance. All statistical analysis was performed using SAS statistical software version 9.1 (SAS Statistical Institute, Cary, NC). The SPMM macro and PROC MIXED procedure with repeated measure ANOVA F-test were used in repeated measure analysis.

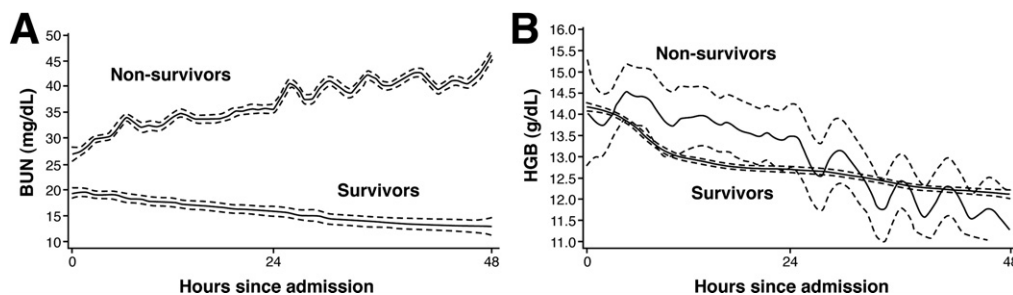
### Results

We identified a total of 13,384 AP cases by ICD-9-CM code (577.0). There were 5819 AP cases with ≥3 BUN and Hgb measurements within 48 hours of admission. Table 1 shows the patient demographics, admission laboratory data, and outcomes of the overall AP population and study cohort. There were no meaningful differences in demographic or admission laboratory data between the study cohort and overall population. However, length of stay (median, 6.7 vs 4 days; *t* test; *P* < .0001), frequency of admission to intensive care (9.2% vs 5.9%;  $\chi^2$ ; *P* < .0001), and mortality (1.6% vs 1.1%;  $\chi^2$ ; *P* < .0001) were increased in the study cohort compared with the overall population.

### Repeated Measures Analysis

Figure 2A depicts the mean BUN level versus time (BUN trend) with 95% CIs, and Figure 2B depicts the results of a similar analysis for Hgb trend determined by the mixed model analysis. There was a significant difference in the BUN trend between survivors versus nonsurvivors throughout the first 48 hours of hospitalization (repeated measures ANOVA F-test for between-group comparison; *P* < .0001). Specifically, overall BUN levels among nonsurvivors continued to rise whereas overall BUN levels in survivors decreased during the first 48 hours (ANOVA F-test for time-interaction; *P* < .0001). By contrast, no such relationship existed with respect to

**Figure 2.** Repeated measure analysis with mixed effects model. (A) Mean BUN levels among survivors versus nonsurvivors. (B) Mean Hgb levels among survivors versus nonsurvivors. Mean levels along with 95% CIs are depicted. N = 5819 cases. There were 95 (1.6%) deaths.



**Table 2.** Multivariate Logistic Regression Analysis for Prediction of Mortality

Variable	Odds ratio (95% CL)	P
Admission BUN <sup>a</sup>	2.9 (1.8–4.8)	<.0001
Change in BUN <sup>b</sup>	2.2 (1.8–2.7)	<.0001
Admission Hgb <sup>c</sup>	0.9 (0.8–1.1)	.30
Change in Hgb <sup>d</sup>	1.0 (0.8–1.3)	.87

Age- and gender-adjusted effect estimates for admission and change in BUN versus Hgb.

BUN, blood urea nitrogen; CL, confidence limit; Hgb, hemoglobin.

<sup>a</sup>Admission BUN measured in 5-mg/dL increments.

<sup>b</sup>Change in BUN measured in 5-mg/dL increments at 24 hours.

<sup>c</sup>Admission Hgb measured in 1-g/dL increments.

<sup>d</sup>Change in Hgb measured in 1-g/dL increments at 24 hours.

Hgb trend among survivors versus nonsurvivors (repeated measures ANOVA F-test;  $P = .33$ ). Overall Hgb values declined during the first 48 hours among both survivors and nonsurvivors of AP (time effect F-test;  $P < .0001$ ).

**Impact of change in BUN and Hgb within the first 24 hours.** Median admission BUN was 15 mg/dL (interquartile range, 11–22). The median admission Hgb was 14.0 g/dL (12.6–15.3). The median change in BUN at 24 hours was  $-4.0$  mg/dL ( $-7.0$  to  $-1.0$ ). The median change in Hgb at 24 hours was  $-1.1$  g/dL ( $-1.8$  to  $-0.4$ ). Age- and gender-adjusted results from our multivariable logistic regression analysis, including admission BUN, 24-hour change in BUN, admission Hgb, and 24-hour change in Hgb for the prediction of mortality, are presented in Table 2. Both admission BUN and change in BUN were independent predictors of mortality after controlling for the effects of age, gender, admission Hgb, and 24-hour change in Hgb ( $P < .0001$ ). For every 5-mg/dL increase in BUN, the odds ratio for mortality increased by 2.2 (95% CL, 1.9–2.9). The AUC for the logistic regression model combining admission BUN and change in BUN at 24 hours was 0.91 for prediction of in-hospital mortality.

Figure 3 illustrates mortality according to extent of change in BUN at 24 hours. We stratified these results by admission BUN using a threshold of 22 mg/dL (75th percentile of admission BUN values). Irrespective of admission value, increases in BUN at 24 hours were associated with higher mortality (Figure 3A). By contrast,

**Table 3.** Summary of Time-Specific AUC Estimates for 6 Candidate Routine Laboratory Parameters for Prediction of In-Hospital Mortality

	Admission	24 Hours	48 Hours
BUN	0.79	0.89	0.90
Calcium	0.63	0.85	0.87
Creatinine	0.69	0.81	0.82
WBC count	0.67	0.65	0.62
Hgb	0.50	0.50	0.64
Glucose	0.67	0.56	0.63

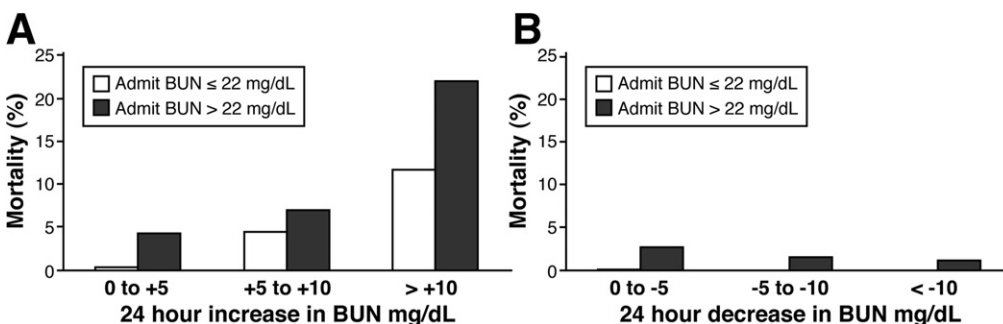
AUC, area under the concentration–time curve; BUN, blood urea nitrogen; Hgb, hemoglobin; WBC, white blood cell.

decreases in BUN were associated with reduced mortality (Figure 3B).

### Time-Specific Analysis

**Time-specific ROC curves.** To evaluate changes in the prognostic value of BUN versus Hgb over time, we calculated time-specific ROC curves utilizing laboratory test results obtained at 3 time points (admission and 24 and 48 hours). Table 3 summarizes the AUC results for serial BUN and Hgb measurement as well as additional routine laboratory tests. BUN was more informative than Hgb at all 3 time points. The greatest increase in predictive accuracy for BUN occurred between admission and 24 hours (AUC at admission 0.79 vs AUC at 24 hours 0.89;  $\chi^2$ ;  $P < .0001$ ). There was no significant difference between the 24- and 48-hour AUC for BUN (24-hour AUC 0.89 vs 48-hour AUC 0.90;  $\chi^2$ ;  $P = .28$ ).

**Time-specific multivariable logistic regression.** We constructed multivariable logistic regression models for prediction of in-hospital mortality for each time point (admission and 24 and 48 hours) incorporating terms for each of the 6 laboratory parameters (BUN, Hgb, calcium, creatinine, WBC count, and glucose). In the admission model, only BUN, calcium, and WBC count were significant with Wald  $\chi^2$  value ( $P < .0001$ ). Creatinine, Hgb, and glucose levels were not significant at the  $P < .05$  level. Overall AUC combining the 3 laboratory tests (BUN, calcium, and WBC) at admission was 0.80. By contrast, in both the 24- and 48-hour logistic regression models, only BUN and calcium were significant on multivariate analysis. Combining the 2 parameters did not



**Figure 3.** Mortality according to change in BUN at 24 hours. Results stratified by admission BUN level (threshold of 22 mg/dL represents 75th percentile). (A) Mortality by extent of BUN increase at 24 hours. (B) Mortality by extent of BUN decrease at 24 hours. Cochran–Armitage trend  $P < .0001$  for mortality according to extent of BUN change at 24 hours for both levels of admission BUN.

yield a significantly higher AUC than use of BUN alone (data not shown).

## Discussion

In a large, hospital-based, observational cohort study, we have compared the accuracy of serial BUN versus serial Hgb measurement for prediction of mortality in AP. First, we demonstrated that mean BUN levels were persistently elevated among nonsurvivors versus survivors of AP during the first 48 hours of hospitalization. Second, an elevated admission BUN and a rise in BUN within the first 24 hours of hospitalization were both independently associated with increased mortality after controlling for the effect of age, gender, and Hgb. Third, serial BUN measurement was the most accurate single prognostic marker for in-hospital mortality compared with serial measurement of alternative routinely collected laboratory tests at admission and 24 and 48 hours. Early changes in BUN predicted mortality after controlling for other routine laboratory tests, including serum creatinine. By contrast, neither admission Hgb nor change in Hgb at 24 hours was independently associated with an increase in mortality.

An important finding was the strong association between the extent of BUN increase at 24 hours and the risk of mortality, irrespective of admission BUN. Each increase in BUN of 5 mg/dL was associated with a corresponding increase in risk of mortality (odds ratio, 2.2; 95% CL, 1.8–2.7). By contrast, patients who experienced a decrease in BUN during the first 24 hours of hospitalization had substantially reduced mortality.

We evaluated BUN and Hgb as prognostic markers in AP for several reasons. First, as routine laboratory tests, these measurements are widely available with rapid assay and minimal added cost. Second, both BUN and Hgb are routine laboratory markers that can reflect changes in intravascular volume status. Third, several clinical scoring systems have incorporated BUN for predicting mortality,<sup>2,11,13</sup> although other studies have identified hemoconcentration using serum hematocrit as an important independent prognostic marker in AP.<sup>14,15</sup> However, there remains no consensus regarding an optimal approach to use of routine laboratory tests to monitor disease course in AP. Therefore, the current study represented an opportunity to systematically compare the prognostic accuracy of serial BUN, Hgb (as a surrogate for hematocrit), and other routine laboratory measurements in the early assessment of AP.

Current prognostic markers in AP have important limitations. First, the majority of studies examining routine laboratory markers have focused on intermediate end points, such as necrosis and organ failure,<sup>15,25</sup> rather than mortality. Nonspecific inflammatory markers such as C-reactive protein, procalcitonin, and polymorphonuclear are useful in predicting severity, but are not available in routine clinical practice and can require significant pro-

cessing time.<sup>27,29–33</sup> A specific marker of pancreatic protease activation, urinary trypsinogen activating peptide has shown promise in the early prediction of necrosis and organ dysfunction.<sup>34</sup> However, urinary trypsinogen activating peptide is also not currently available and has not been specifically evaluated with respect to mortality.

There are several possible mechanisms by which changes in BUN may be related to mortality in AP. We hypothesize that the initial and subsequent BUN values may be a reflection of a 2-compartment model system. The admission BUN (compartment 1) may reflect the underlying physiologic state of the patient including intravascular volume depletion and pre-renal azotemia. By contrast, a persistent elevation or subsequent rise in BUN (compartment 2) may reflect either a failure to adequately volume resuscitate patients early in their disease course, deterioration of renal function, or a state of ongoing negative nitrogen balance related to increased protein catabolism induced by AP.<sup>35–37</sup> Irrespective of the specific mechanism, we have clearly shown that patients with an early rise in BUN are at increased risk for in-hospital mortality.

There were several limitations to the current study. First, AP cases were identified by ICD-9-CM code rather than the more stringent Atlanta symposium criteria.<sup>38</sup> Also, to compare the impact of early changes in BUN and Hgb, we limited our analysis to patients with repeat measurements for both tests within the first 48 hours of hospitalization. This restriction introduced an element of selection bias (more severely ill patients are more likely to have repeat laboratory testing performed). Despite similar admission laboratory characteristics, there was increased length of stay (median, 6.7 days), frequency of ICU admission (9.2%), and mortality (1.6%) in the study cohort compared with the overall AP population (Table 1). However, outcomes in the study cohort including mortality remained at a level consistent with prior population-based reports of AP.<sup>39</sup> A final limitation was the inability to compare BUN measurement to alternative clinical scoring systems (APACHE II, Ranson) or inflammatory markers (C-reactive protein) because these data were not available in the Cardinal database, which only collects routine clinical data.

Despite these limitations, the findings of the present study have several direct clinical implications. First, an elevated admission BUN should be a signal to physicians to institute more intensive early resuscitation efforts. Second, serial measurement of BUN during the first 24 hours of hospitalization provides valuable additional clinical information regarding the efficacy of initial resuscitation as well as potential disease progression. Combining serial BUN measurement with physiologic parameters such as urine output and hemodynamic monitoring<sup>10</sup> may provide suitable targets for future, goal-directed resuscitation in AP. It remains to be determined whether intensive resuscitation efforts

such as aggressive fluid resuscitation can improve outcome in patients with early rises in BUN.

In summary, early changes in BUN predict mortality in AP. We identified serial BUN measurement as the most valuable single routine laboratory test for predicting in-hospital mortality during the first 24 hours of hospitalization. There was a strong association between extent of BUN rise and mortality. A reduction in BUN was associated with significantly improved survival. Careful monitoring of BUN levels during the initial 24 hours of AP helps to identify patients at increased risk for mortality and provides important information on the effectiveness of initial therapy.

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*Conflicts of interest*

The authors disclose no conflicts.