Admission Hematocrit and Rise in Blood Urea Nitrogen at 24 h Outperform other Laboratory Markers in Predicting Persistent Organ Failure and Pancreatic Necrosis in Acute Pancreatitis: A *Post Hoc* Analysis of Three Large Prospective Databases

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OBJECTIVES: **Predicting severe acute pancreatitis (AP) remains a challenge. The present study compares admission blood urea nitrogen (BUN), hematocrit, and creatinine, as well as changes in their levels over 24 h, aiming to determine the most accurate laboratory test for predicting persistent organ failure and pancreatic necrosis.**

METHODS: **Clinical data of 1,612 AP patients, enrolled prospectively in three independent cohorts (University of Pittsburgh, Brigham and Women's Hospital, Dutch Pancreatitis Study Group), were abstracted. The predictive accuracy of the studied laboratories was measured using area under the receiver-operating characteristic curve (AUC) analysis. A pooled analysis was conducted to determine their impact on the risk for persistent organ failure and pancreatic necrosis. Finally, a classification tree was developed on the basis of the most accurate laboratory parameters.**

RESULTS: **Admission hematocrit ≥44% and rise in BUN at 24 h were the most accurate in predicting persistent organ failure (AUC: 0.67 and 0.71, respectively) and pancreatic necrosis (0.66 and 0.67, respectively), outperforming the other laboratory parameters and the acute physiology and chronic health evaluation-II score. In a pooled analysis, admission hematocrit ≥44% and rise in BUN at 24 h were associated with an odds ratio of 3.54 and 5.84 for persistent organ failure, and 3.11 and 4.07, respectively, for pancreatic necrosis. In addition, the classification tree illustrated that when both admission hematocrit was ≥44% and BUN levels increased at 24 h, the rates of persistent organ failure and pancreatic necrosis reached 53.6% and 60.3%, respectively.**

CONCLUSIONS: **Admission hematocrit ≥44% and rise in BUN at 24 h may be the optimal predictive tools in clinical practice among existing laboratory parameters and scoring systems.**

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INTRODUCTION

Acute pancreatitis (AP) is a common gastrointestinal disease with increasing incidence over the last several decades (1). It currently represents the leading GI-related hospital discharge diagnosis in the United States (2,3). Clinical outcomes vary broadly from an uneventful, mild disease course in the majority of patients to systemic inflammation and a severe course complicated by organ failure in ~20% of patients

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with AP (4). Mortality in these patients can be as high as 30% (4).

Accurate prediction of severe disease early in its course would be of great value in helping clinicians triage patients to the appropriate level of care and guide early management, such as fluid resuscitation during the critical first 24 h (5). Furthermore, it would facilitate comparison of clinical outcomes between different cohorts and evaluation of new therapeutic approaches as they become available.

Accurate prediction mandates clear definitions of severe AP. Recently, two severity classification systems were presented: the Revised Atlanta Classification and the Determinant-Based Classification. Both systems underscore the importance of pancreatic necrosis and/or persistent organ failure as determinants of severe AP (4,6).

The search for an accurate predictor started in 1974, when the first prognostic clinical score, the Ranson criteria, was introduced. Since then, several predictive scoring systems have been developed, including the acute physiology and chronic health evaluation-II (APACHE-II) score, systemic inflammatory response syndrome, and the bedside index for the severity in acute pancreatitis, which are based on a combination of clinical, laboratory, and radiographic findings. A recent large prospective study that compared existing scores showed that they perform with moderate accuracy (around 70–80%) and are all comparable in predicting the development of persistent organ failure (7). One major limitation of the available scoring systems is that they are complex and frequently cumbersome to calculate in clinical practice (8).

Several serum laboratories have been studied individually as predictors of severe disease, including C-reactive protein (CRP), interleukin-1, 6, 8, procalcitonin, polymorphonuclear elastase, tryprinogen activation peptide, and others (9). Among all, CRP is the most promising one, with many studies showing a correlation of its high levels with pancreatic necrosis development and severe AP course (10). However, CRP levels are influenced by liver disease (11), which may be present in many patients with AP who are obese and/or alcoholics. Furthermore, CRP levels peak at 72–96 h after symptom onset, which can limit its prognostic accuracy as patients typically present at variable times after symptom onset (12,13). Finally, CRP is a laboratory marker that is not routinely measured in AP patients throughout the world.

Simple, routine, and widespread laboratory tests, specifically tests for evaluating serum blood urea nitrogen (BUN), hematocrit, and creatinine, have also been proposed as markers of disease severity. Such laboratory parameters have great potential, because they are readily available, inexpensive, and have standardized reference ranges. Multiple studies have reported a significant association between serum levels of BUN, hematocrit, and creatinine on admission and their changes over 24–48 h with severe disease (14–22). However, the majority of these studies are limited by small sample size, retrospective nature, and use of variable outcomes of severity. In 2011, BUN was shown to be an accurate predictor of mortality in a large, prospective study from the United States and The Netherlands, in which an admission BUN ≥20 mg/dl was associated with a 4.6 odds ratio (OR) for mortality (14).

The aim of the present study was to compare admission BUN, hematocrit, and creatinine, as well as changes in their levels over 24 h in order to determine the most accurate predictive laboratory test(s) of persistent organ failure and pancreatic necrosis.

METHODS

Study design and patient population

The present study was based on the retrospective analysis of three concurrent cohorts of prospectively enrolled AP patients from two US centers (University of Pittsburgh Medical Center (UPMC) and Brigham and Women's Hospital (BWH)) and 15 hospitals in The Netherlands, which collectively comprise the Dutch Pancreatitis Study Group (DPSG). The institutional review boards of each center approved the study protocol.

The Severity of Acute Pancreatitis/Pancreatitis-associated Risk Of Organ Failure (SAPS/PROOF) is an ongoing prospective cohort study, which was initiated in 2003 at UPMC (Pittsburgh, PA) (7,23). All patients directly admitted or transferred to UPMC facilities who met criteria for AP were eligible for enrollment. The SAPS/PROOF study aims to assess the risks, biomarkers, and outcomes in AP.

The Markers of Severity in Acute Pancreatitis (MOSAP) cohort was developed at BWH, in Boston, MA (14,24). AP patients directly admitted or transferred to BWH from 2005 through 2009 were prospectively recruited. The aim of the study was to evaluate the prognostic markers of severe AP.

The DPSG cohort consisted of AP patients admitted to any one of the 15 collaborating Dutch hospitals (8 university and 7 major teaching hospitals) from 2004 to 2007 (25–27). Patients with an initial AP episode were initially screened for participation in a randomized controlled trial evaluating the use of probiotics in severe AP (PROPATRIA trial, registration No. ISRCTN38327949). Patients not randomized in the context of the trial were still followed up during their hospitalization, and pertinent laboratory values and clinical outcomes were recorded. Patients who were either randomized to the placebo arm of the trial or those who could not be randomized as they fit one of the exclusion criteria (e.g., predicted mild disease) were included in the cohort of the present study.

All three groups followed uniform diagnostic criteria for AP. Eligible patients were enrolled early on in their disease course and followed up prospectively until hospital discharge. Enrolled patients were managed according to each institution's standards of practice; all patients were initially kept nil per os. Diagnostic and laboratory tests were obtained as deemed necessary by the treating physicians.

For the purposes of the present study, BUN, hematocrit, and creatinine values available at admission and 24 h were abstracted. Our analysis was limited to patients who had both admission and 24-h measurements recorded per laboratory tested. For uniformity of data, BUN and creatinine were appropriately converted and represented as milligrams per deciliter. BUN and hematocrit values were rounded to the tenth decimal and creatinine values to the hundredth decimal. BUN, hematocrit, and creatinine were considered elevated when exceeding thresholds of 20 mg/dl (14), 44% (15,18),

and 1.8 mg/dl (21), respectively, based on thresholds established in prior studies. Twenty-four-hour change in laboratory tests was determined on the basis of difference between the value at 24 h and that on admission for each patient and categorized either as a rise or a decrease (≤0). Transferred patients were included only if all data from their initial presentation were submitted.

Definitions

The diagnosis of AP was established when patients satisfied at least two out of the three following criteria: (1) characteristic epigastric abdominal pain; (2) elevation of amylase and/or lipase to greater than three times the upper limit of normal at the respective laboratories; and (3) abdominal imaging findings consistent with AP (28). Organ failure included the cardiovascular, pulmonary, and/or renal systems and was defined as systolic blood pressure <90 mm Hg that persisted following fluid resuscitation, arterial PO_2 <60 mm Hg on room air or requirement for mechanical ventilation, and/or a serum creatinine level ≥2 mg/dl after rehydration, or need for hemodialysis in patients without preexisting renal disease (7). Persistent organ failure was defined when lasting more than 48 h. Pancreatic necrosis was diagnosed by lack of pancreatic gland enhancement in patients with available contrast-enhanced imaging of the abdomen (4). If more than one computed tomography scan was available for each patient, and pancreatic necrosis was noted in at least one of them, this patient was included in the pancreatic necrosis group. Isolated peripancreatic necrosis was not included in the analysis of the present study because it is a relatively new term with significant interobserver variation in the way it is diagnosed.

Statistical analysis

Continuous variables are presented as median and interquartile range and categorical variables are presented as proportions. Normality of continuous data was assessed using the Shapiro–Wilk test. Comparisons between groups were performed with the Pearson Chi square test for categorical variables. Continuous variables were compared by the Wilcoxon rank-sum test (two groups) and the Kruskal–Wallis test (three groups).

Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for elevated BUN, hematocrit, and creatinine at admission as well as for their rise at 24 h. Predictive accuracy was measured by the area under the receiver-operating characteristic curve (AUC) and compared between different laboratory tests. The likelihood of developing organ failure and pancreatic necrosis with increasing laboratory values was assessed with the Cochran–Armitage trend test.

A meta-analysis was conducted to determine the impact of the laboratory tests on the risk of organ failure and pancreatic necrosis with ORs and 95% confidence intervals (CI) being calculated by the DerSimonian and Laird random-effects model (29). Heterogeneity between studies was assessed by means of the I^2-test. Finally, a classification tree for predicting severe AP using the most prominent laboratory tests as decision points was developed. Statistical analysis was performed with Stata 13 (StataCorp, College Station, TX).

RESULTS

Patient demographics and clinical outcomes

A total of 1,612 patients with AP were included in the study. Four hundred patients were contributed by UPMC, 633 by BWH, and 579 by the DPSG. The median age of participants was 53 years (interquartile range 40–66); 51% were male; 42.7% of patients had a biliary etiology, 18.4% had an alcoholic etiology, and 15.9% had post-endoscopic retrograde cholangiopancreatography AP. With regard to clinical outcomes, persistent organ failure developed in 18.2% of patients. Of 1,612 AP patients, 1,064 (66%) underwent a contrast-enhanced computerized tomography scan, of whom 270 (25.4%) had findings consistent with pancreatic necrosis. The median length of hospital stay was 7 days (4–14); 4.9% of patients died because of their illness (**Table 1**).

Comparison of BUN, hematocrit, creatinine, and APACHE-II in predicting persistent organ failure and pancreatic necrosis

Table 2a and 2b summarize the performance characteristics of admission BUN ≥20 mg/dl, hematocrit ≥44%, creatinine ≥1.8 mg/dl, and APACHE-II ≥8, as well as rise in BUN, hematocrit, and creatinine at 24 h, in predicting persistent organ failure (**Table 2a**) and pancreatic necrosis (**Table 2b**).

With regard to admission values, hematocrit ≥44% performed with the highest accuracy in predicting persistent organ failure, with an AUC of 0.67. At 24 h, rise in BUN revealed the highest predictive accuracy (AUC 0.71) and was the only marker that surpassed the 0.7 threshold. It performed better than the majority of laboratory values and was only similar to admission hematocrit (AUC 0.66) and APACHE-II (AUC 0.66; **Table 2a**). With regard to pancreatic necrosis, admission hematocrit (AUC 0.66) and rise in BUN at 24 h (0.67) significantly outperformed the remaining laboratory parameters and APACHE-II (**Table 2b**).

Admission hematocrit and rise in BUN at 24 h as early predictors of persistent organ failure and pancreatic necrosis

The forest plot displaying the association between admission hematocrit and persistent organ failure risk is presented in **Figure 1a**. In the pooled analysis, admission hematocrit ≥44% was associated with an overall OR of 3.54 (95% CI, 2.12–5.91) for persistent organ failure. Similarly, the association between rise in BUN at 24 h and persistent organ failure is shown in **Figure 1b**. Rise in BUN was associated with an OR of 5.84 (95% CI, 2.64–12.93) for persistent organ failure. The forest plots for risk for pancreatic necrosis associated with admission hematocrit ≥44% and rise in BUN are shown in **Figures 2a and b**, respectively. Admission hematocrit ≥44% was correlated with an overall OR of 3.11 (95% CI, 1.84, 5.26) and rise in BUN at 24 h with an OR of 4.07 (95% CI, 2.04–8.12) for development of pancreatic necrosis in the pooled analysis.

As illustrated in **Figure 3a**, higher levels of admission hematocrit were associated with increased rates of persistent organ failure and pancreatic necrosis (Cochran–Armitage trend, both $P<0.001$). Similarly, greater rise in BUN at 24 h was correlated with higher rates of persistent organ failure and pancreatic necrosis (Cochran–Armitage trend, both $P<0.001$; **Figure 3b**).

Early prediction classification tree based on admission hematocrit >44% and rise in BUN

Subsequently, we evaluated how admission hematocrit ≥ vs. <44% followed by changes in BUN at 24 h related to the development of persistent organ failure and pancreatic necrosis. A total of 974 patients had available data on admission hematocrit levels and on admission and 24-h BUN levels and organ failure development. Of 974 AP patients, 326 had admission hematocrit ≥44%. Of those 326 patients, 151 developed a rise in BUN at 24 h, of which 81 (53.6%) developed persistent organ failure. An overall 175 patients had elevated admission hematocrit without a rise in BUN; among them 28 (16%) developed persistent organ failure. A total of 648 patients had admission hematocrit <44%. Of them, 130 were noted to have a rise in BUN at 24 h, of which 38 (29.2%) developed persistent organ failure. Five hundred eighteen patients had both admission hematocrit <44% and no rise in BUN. The persistent organ failure rate among those patients was 7.9% (*n*=41; **Figure 4a**).

The same analysis was performed for pancreatic necrosis and revealed similar results. Pancreatic necrosis developed in 60.3% of patients with both admission hematocrit ≥44% and rise in BUN at 24 h, and in 11.7% when admission hematocrit was <44% and BUN did not increase at 24 h (**Figure 2b**).

DISCUSSION

This is a *post hoc* analysis of three large prospective databases from the U.S. and Netherlands, evaluating simple laboratory parameters as predictors of severe AP. We found that admission hematocrit ≥44% and rise in BUN at 24 h revealed the highest accuracy and outperformed the remaining laboratory tests. In the pooled analysis, admission hematocrit ≥44% and rise in BUN at 24 h showed

Table 1. Demographics and clinical outcomes of 1,612 AP patients from the 3 study cohorts

	TOTAL *n*=1,612	UPMC *n*=400	BWH *n*=633	DPSG *n*=579	*P* value
Age, median (IQR)	53 (40–66)	51 (36–66)	52 (41–62)	57 (41–70)	0.002
Gender, male, %	51.0	51.5	48.5	53.2	0.25
Etiology					
Biliary, %	42.7	38.8	32.2	57.0	<0.001
Alcohol, %	18.4	13.5	21.5	18.3	0.011
Post-ERCP, %	15.9	13.8	13.4	20.2	0.001
Hospital transfer, %	23.6	54.5	14.4	12.3	<0.001
Persistent organ failure, %	18.2	23.8	8.6	20.9	<0.001
Pancreatic necrosis, %	25.4	35.7	14.8	30.6	<0.001
Hospital LOS, median (IQR)	7 (4, 14)	8 (5, 17)	4 (3, 8)	10 (6, 22)	<0.001
Mortality, %	4.9	5.3	3.3	6.4	0.04

BWH, Brigham and Women's Hospital; DPSG, Dutch Pancreatitis Study Group; ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range; LOS, length of stay; UPMC, University of Pittsburgh Medical Center.
P-values represent comparison between the three study cohorts (UPMC, BWH, and DSPG).

Table 2a. Performance of admission BUN ≥20 mg/dl, hematocrit ≥44%, creatinine ≥1.8 mg/dl, and APACHE-II ≥8, as well as rise in BUN, hematocrit, and creatinine at 24 h in predicting persistent organ failure

	Sensitivity	Specificity	PPV	NPV	AUC	Complete data[a]
Admission BUN ≥20 mg/dl	54.55 (47.53–61.43)	75.44 (72.41–78.29)	35.19 (29.99–40.66)	87.16 (84.54–89.49)	0.65 (0.61–0.69)	77%
Admission hematocrit ≥44%	59.16 (51.83–66.20)	74.24 (70.98–77.32)	36.57 (31.19–42.21)	87.87 (85.09–90.29)	0.67 (0.63–0.71)	69%
Admission creatinine ≥1.8 mg/dl	24.88 (19.23–31.25)	93.37 (91.51–94.93)	47.75 (38.18–57.44)	83.62 (81.15–85.89)	0.59 (0.56–0.62)	79%
Admission APACHE-II ≥8	68.42 (61.96–74.40)	64.50 (61.57–67.36)	28.94 (25.15–32.97)	90.63 (88.34–92.59)	0.66 (0.63–0.70)	95%
Rise in BUN at 24 h	62.68 (55.74–69.25)	78.71 (75.81–81.41)	41.85 (36.33–47.53)	89.61 (87.21–91.70)	0.71 (0.67–0.74)	77%
Rise in hematocrit at 24 h	29.84 (23.45–36.87)	84.49 (81.72–86.99)	32.57 (25.69–40.05)	82.75 (79.91–85.35)	0.57 (0.54–0.61)	69%
Rise in creatinine at 24 h	50.23 (43.32–57.14)	81.14 (78.39–83.68)	39.34 (33.49–45.42)	87.01 (84.51–89.24)	0.66 (0.62–0.69)	79%

Table 2b. Performance of admission BUN ≥20 mg/dl, hematocrit ≥44%, creatinine ≥1.8 mg/dl, and APACHE-II ≥8, as well as rise in BUN, hematocrit, and creatinine at 24 h in predicting pancreatic necrosis

	Sensitivity	Specificity	PPV	NPV	AUC	Complete data[a]
Admission BUN ≥20 mg/dl	34.45 (28.03–41.32)	69.84 (66.06–73.43)	27.80 (22.43–33.68)	75.96 (72.24–79.42)	0.52 (0.48–0.56)	78%
Admission hematocrit ≥44%	54.41 (47.31–61.38)	77.00 (73.46–80.27)	44.05 (37.82–50.41)	83.54 (80.22–86.50)	0.66 (0.62–0.70)	77%
Admission creatinine ≥1.8 mg/dl	10.75 (6.94–15.69)	90.22 (87.64–92.42)	27.06 (17.99–37.79)	74.97 (71.73–78.01)	0.50 (0.48–0.53)	80%
Admission APACHE-II ≥8	55.83 (49.30–62.22)	56.95 (53.33–60.52)	29.19 (25.07–33.59)	80.22 (76.60–83.51)	0.56 (0.53–0.60)	94%
Rise in BUN at 24 h	57.42 (50.41–64.21)	77.42 (73.92–80.65)	46.15 (39.98–52.42)	84.36 (81.11–87.25)	0.67 (0.64–0.71)	78%
Rise in hematocrit at 24 h	34.31 (27.83–41.27)	78.47 (75.00–81.66)	34.65 (28.11–41.65)	78.21 (74.74–81.41)	0.56 (0.53–0.60)	77%
Rise in creatinine at 24 h	41.59 (34.91–48.50)	78.71 (75.31–81.83)	39.73 (33.28–46.46)	79.97 (76.61–83.04)	0.60 (0.56–0.64)	80%

APACHE-II, Acute Physiology and Chronic Health Evaluation-II; AUC, area under the receiver-operating characteristic curve; BUN, blood urea nitrogen; NPV, negative predictive value; PPV, positive predictive value.
[a]Percentage of patients for whom complete clinical data were available.

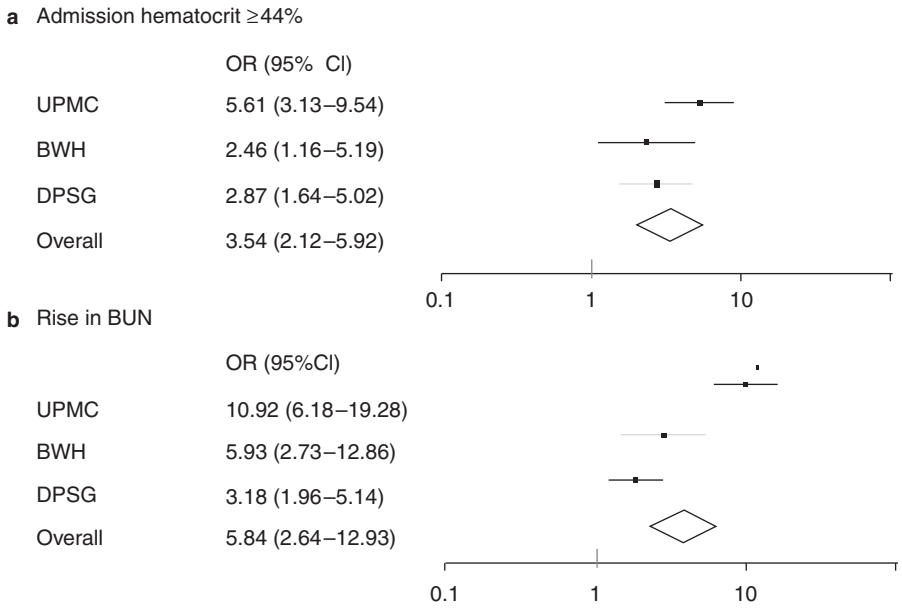

Figure 1. Persistent organ failure forest plots. (**a**) Risk associated with admission hematocrit ≥44%. Random-effects model was used for pooled analysis. (**b**) Risk associated with a rise in blood urea nitrogen at 24 h. Random-effects model was used for pooled analysis. BUN, blood urea nitrogen; BWH, Brigham and Women's Hospital; DPSG, Dutch Pancreatitis Study Group; UPMC, University of Pittsburgh Medical Center.

a three- to sixfold increase in risk of developing persistent organ failure and pancreatic necrosis. In addition, a classification tree was designed that illustrated that the risk for persistent organ failure and pancreatic necrosis exceeded 50% when both the admission hematocrit ≥44% and rise in BUN at 24 h were combined.

Clinical scoring systems have been the center of research interest for the prediction of severe AP for approximately four decades, with a plethora of scores reported in the literature (7). However, in a recent large, prospective head-to-head comparison, all existing scoring systems performed similarly, but with only moderate accuracy in predicting persistent organ failure (7). This study raised the question whether the cumbersome to calculate clinical scores are really needed, or simple laboratory values can perform with similar predictive accuracies. Simple laboratory tests such as

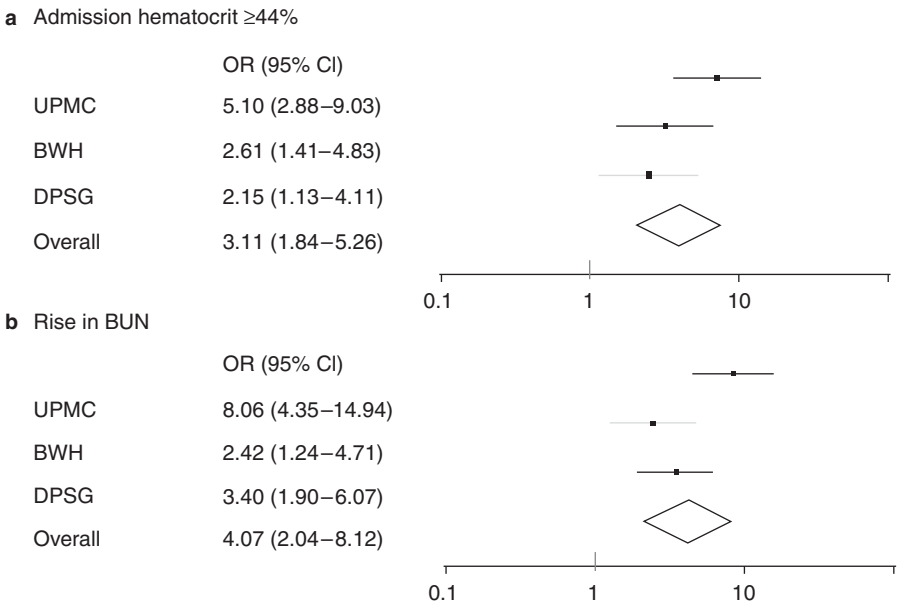

Figure 2. Pancreatic necrosis forest plots. (**a**) Risk associated with admission hematocrit ≥44%. Random-effects model was used for pooled analysis. (**b**) Risk associated with a rise in blood urea nitrogen at 24 h. Random-effects model was used for pooled analysis. BUN, blood urea nitrogen; BWH, Brigham and Women's Hospital; DPSG, Dutch Pancreatitis Study Group; UPMC, University of Pittsburgh Medical Center.

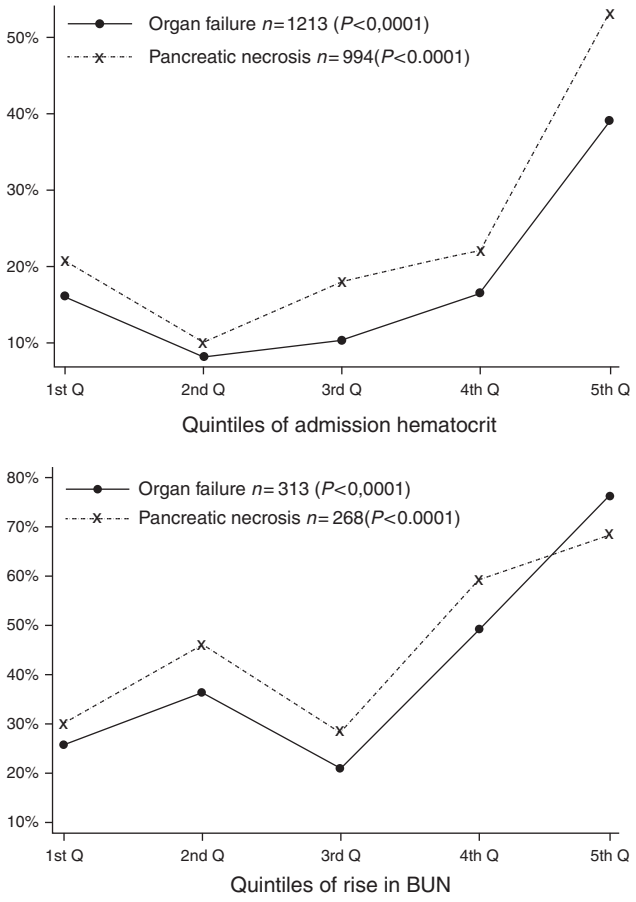

Figure 3. Persistent organ failure and pancreatic necrosis by hematocrit on admission (left) and by extent of rise in blood urea nitrogen (BUN) levels at 24 h.

for BUN, hematocrit, and creatinine are widely available and inexpensive. They reflect intravascular volume status, which is closely related to organ failure development, as well as pancreatic tissue perfusion and pancreatic necrosis. Changes in their value at 24 h from admission may reflect response to the initial treatment and tailor further management decisions.

Two large studies have reported that early BUN levels represent an independent predictor of mortality. The initial study utilized large hospital databases and suggested that with each 5 mg/dl increase in BUN the odds ratio for mortality in AP increases by 2.2. It also showed that BUN is the most accurate predictor of in-hospital mortality when compared with other routine laboratory parameters such as calcium, hemoglobin, creatinine, white blood cell count, and glucose levels (16). The follow-up report, conducted by the same collaborative centers as the present study, suggested that BUN ≥20 mg/dl was associated with a 4.6 odds ratio for mortality (14).

With regard to hematocrit, elevated levels on admission have been associated with development of pancreatic necrosis, organ failure, as well as prolonged hospitalization and need for intensive care unit (17–19). The cutoff values of hematocrit proposed in these studies ranged from 39% to 47%, with 44% being the most commonly reported. One study even reported different cutoff levels for men (hematocrit >43%) and women (>39.6%) associated with an odds ratio of 2.2 for pancreatic necrosis development (19).

The role of creatinine as a predictive marker was examined by a relatively small prospective study, which showed that peak creatinine >1.8 mg/dl within the first two days from hospital admission had the highest odds ratio for development of pancreatic necrosis (OR=35) when compared with admission hematocrit and BUN

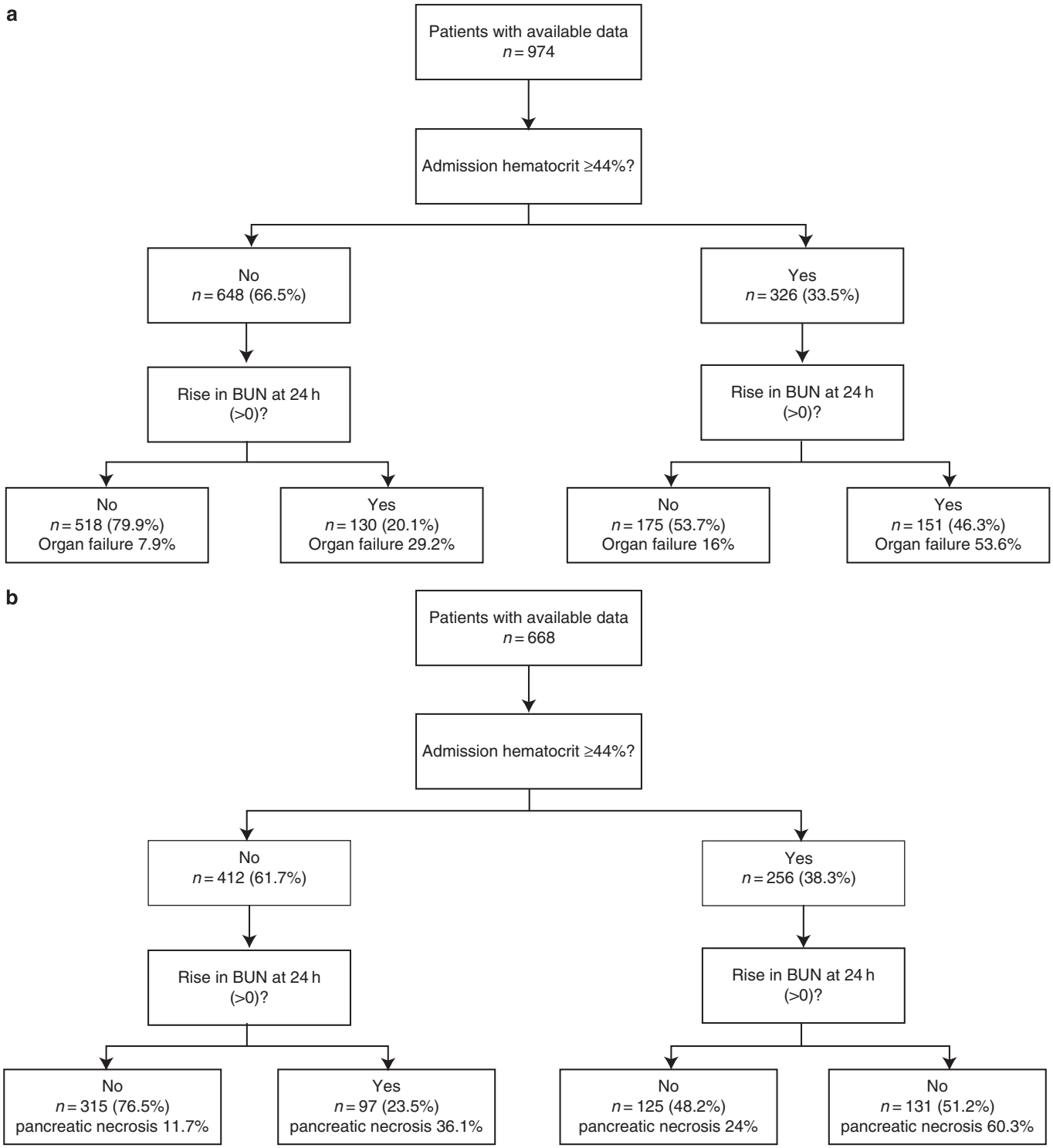

Figure 4. (**a**) Classification tree predicting persistent organ failure based on admission hematocrit ≥44% and rise in blood urea nitrogen (BUN) at 24 h. (**b**) Classification tree predicting pancreatic necrosis based on admission hematocrit ≥44% and rise in BUN at 24 h.

levels (21). However, a follow-up study did not confirm these impressive results (20,22).

Changes in laboratory values over time have also been studied. Rise in BUN levels within the first two days has been correlated with increased mortality (14). A rise in hematocrit within the first 24 h has been associated with development of pancreatic necrosis and organ failure (17,18).

The above studies have shown promising results. However, cutoff levels and definition of AP severity varied significantly between reports. In addition to mortality, which is an important

but rare clinical outcome in AP, recent revised classifications of disease severity have focused on persistent organ failure and pancreatic necrosis as the most clinical relevant outcomes. This notion is further supported by expert opinions, stating that accurate prediction of severity requires the end point for the prediction to be causally associated with severity (30). Furthermore, persistent organ failure develops within the first few days in the majority of patients, and is considered to be the main determinant of severity in the early phase of AP. Pancreatic necrosis is usually diagnosed later in the disease course and may lead to infected necrosis and sepsis; therefore, it reflects severe disease in the late phase of AP. On the basis of the above, the present study utilized persistent organ failure and pancreatic necrosis as determinants of severity and performed head-to-head comparisons all three simple laboratory tests (BUN, hematocrit, and creatinine) aiming to determine the ultimate early predictive tool. Our findings complement existing literature by showing that (1) not only rise in BUN but also hematocrit ≥44% on admission is an accurate marker of severe disease, and (2) the risk of severe disease exceeds 50% when both hemoconcentration on admission and rise in BUN at 24 h are present. Furthermore, when compared with the prior report from the same collaborative centers in 2011, the present study utilizes updated and larger cohorts of patients and focuses on comparing all three simple laboratory tests in predicting the two most relevant clinical outcomes, persistent organ failure and pancreatic necrosis.

Current society guidelines (International Association of Pancreatology (IAP)/American Pancreatic Association (APA)) suggested systemic inflammatory response syndrome as a preferred predictive tool for AP severity, based on its simplicity (31). It was recognized that other scoring systems such as APACHE-II and single serum markers such as BUN are neither clearly inferior nor superior to systemic inflammatory response syndrome (7). In the present study, APACHE-II was included in the analysis. First, it is, along with Ranson, the most studied score (8). APACHE-II has the advantage of utilizing several grades for each physiologic variable rather than cutoff values. Finally, in a large prospective report, APACHE-II on admission revealed significantly higher accuracy in predicting organ failure compared with Ranson (0.71±0.05 vs. 0.64±0.01) (7).

In the present study, admission hematocrit ≥44% and rise in BUN at 24 h performed similarly to APACHE-II in predicting persistent organ failure, and was better for pancreatic necrosis. On the basis of our findings, we propose that admission hematocrit ≥44% and rise in BUN at 24 h are the predictive markers that a busy clinician needs to memorize and utilize in daily practice for triaging and early management decisions rather than calculating clinical scores.

A classification tree was designed with the first splitter being admission hematocrit ≥44% and the second decision point being a rise in BUN at 24 h. More than half of the patients with both admission hematocrit ≥44% and a rise in BUN at 24 h developed persistent organ failure and pancreatic necrosis. On the other end, approximately a tenth of patients with admission hematocrit <44% and no rise in BUN developed persistent organ failure and pancreatic necrosis.

This study has potential limitations. First, aspects of demographics and clinical outcomes differed between the three prospective cohorts. To compensate for the cohort heterogeneity, a random-effects model was used in the pooled analysis measuring the odds ratios for the risk for persistent organ failure and pancreatic necrosis. Second, as none of the three cohort studies was designed for this comparative purpose, 5–30% of laboratory measurements were missing in various analyses. This may have introduced a selection bias into our study toward excluding transferred patients or those with mild disease. However, our sample size was very large and this may offset the potential of selection bias. Finally, as contrast-enhanced computerized tomography scans were performed on the basis of the discretion of treating physicians, a small number of pancreatic necrosis cases could have been missed. It is, however, unlikely that clinically significant pancreatic necrosis would not be detected in the course of hospitalization, particularly given the overuse of computed tomography imaging in AP throughout the United States and Western Europe. Nonetheless, because the amount of missing laboratory and imaging data is a potential cause of bias, the results of this study should be interpreted with caution.

In conclusion, this is the largest to-date international multicenter study that settles the debate on severity prediction in AP aiming to provide handy information and guidance to clinicians. We propose hematocrit levels ≥44% on admission and rise in BUN at 24 h as the preferred predictive tools to be utilized in clinical practice on the basis of their accuracy, availability, and low cost compared with other laboratory parameters and scoring systems.

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CONFLICT OF INTEREST

Guarantor of the article: Georgios I. Papachristou, MD.

Specific author contributions: Efstratios Koutroumpakis: Acquisition of data, analysis and interpretation of data, drafting of the manuscript. Koutroumpakis has approved the final draft submitted. Bechien U. Wu: Analysis and interpretation of data, study supervision, critical revision of the manuscript for important intellectual content. Wu has approved the final draft submitted. Olaf J. Bakker: Analysis and interpretation of data, study supervision, critical revision of the manuscript for important intellectual content. Bakker has approved the final draft submitted. Anwar Dudekula: Statistical analysis, and analysis and interpretation of data. Dudekula has approved the final draft submitted. Vikesh K. Singh: Drafting of the manuscript, interpretation of data, and critical revision of the manuscript for important intellectual content. Singh has approved the final draft submitted.

Marc G. Besselink: Interpretation of data and critical revision of the manuscript for important intellectual content. Besselink has approved the final draft submitted. Dhiraj Yadav: Interpretation of data and critical revision of the manuscript for important intellectual content. Yadav has approved the final draft submitted. Hjalmar C. van Santvoort: Interpretation of data and critical revision of the manuscript for important intellectual content. van Santvoort has approved the final draft submitted. David C. Whitcomb: Study supervision, interpretation of data, and critical revision of the manuscript for important intellectual content. Whitcomb has approved the final draft submitted. Hein G. Gooszen: Study supervision, interpretation of data, and critical revision of the manuscript for important intellectual content. Gooszen has approved the final draft submitted. Peter A. Banks: Study supervision, interpretation of data, and critical revision of the manuscript for important intellectual content. Banks has approved the final draft submitted. Georgios I. Papachristou: Study concept and design, study supervision, analysis and interpretation of data, and drafting of the manuscript. Papachristou has approved the final draft submitted.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Predicting severe acute pancreatitis remains challenging.
- ✓ A recent large prospective study that compared existing prognostic clinical scores showed that they performed with moderate accuracy (around 70–80%) and were all comparable in predicting the development of persistent organ failure.
- ✓ Simple, routine, and widely available laboratory tests, including serum blood urea nitrogen (BUN), hematocrit, and creatinine, have also been proposed as markers of disease severity.
- ✓ BUN was shown to be an accurate predictor of mortality in a large prospective study from the United States and The Netherlands.

WHAT IS NEW HERE

- ✓ Admission hematocrit ≥44% and rise in BUN at 24 h revealed the highest accuracy and outperformed simple laboratory tests and the acute physiology and chronic health evaluation-II score in predicting persistent organ failure and pancreatic necrosis.
- ✓ In pooled analysis, admission hematocrit ≥44% and rise in BUN at 24 h both showed a three- to sixfold increase in risk of developing persistent organ failure and pancreatic necrosis.
- ✓ The risk for persistent organ failure and pancreatic necrosis exceeds 50% when both admission hematocrit ≥44% and rise in BUN at 24 h are combined.

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