

# Elevated Serum Creatinine as a Marker of Pancreatic Necrosis in Acute Pancreatitis

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- OBJECTIVES:** Pancreatic necrosis is a serious complication of acute pancreatitis. The identification of simple laboratory tests to detect subjects at risk of pancreatic necrosis may direct management and improve outcome. This study focuses on the association between routine laboratory tests and the development of pancreatic necrosis in patients with acute pancreatitis.
- METHODS:** In a cohort of 185 patients with acute pancreatitis prospectively enrolled in the Severity of Acute Pancreatitis Study, patients with contrast-enhanced computerized tomography performed were selected ( $n=129$ ). Serum hematocrit, creatinine, and urea nitrogen on admission and peak values within 48 h of admission were analyzed. The volume of intravenous fluid resuscitation was calculated for each patient.
- RESULTS:** Of 129 patients, 35 (27%) had evidence of pancreatic necrosis. Receiver operating characteristic curves for pancreatic necrosis revealed an area under the curve of 0.79 for admission hematocrit, 0.77 for peak creatinine, and 0.72 for peak urea nitrogen. Binary logistic regression yielded that all three tests were significantly associated with pancreatic necrosis ( $P<0.0001$ ), with the highest odds ratio, 34.5, for peak creatinine. The volume of intravenous fluid resuscitation was similar in patients with and without necrosis. Low admission hematocrit ( $\leq 44.8\%$ ) yielded a negative predictive value of 89%; elevated peak creatinine ( $>1.8$  mg/dl) within 48 h yielded a positive predictive value of 93%.
- CONCLUSIONS:** We confirm that a low admission hematocrit indicates a low risk of pancreatic necrosis (PNec) in patients with acute pancreatitis. In contrast, an increase in creatinine within the first 48 h is strongly associated with the development of PNec. This finding may have important clinical implications and warrants further investigation.

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## INTRODUCTION

Acute pancreatitis (AP) is a complex process in which pancreatic enzyme activation causes local pancreatic damage, resulting in an acute inflammatory response. AP is a common disorder that leads to 210,000 hospital admissions per annum in the United States (1–4). The clinical course of AP is usually mild and often resolves without sequelae. Nonetheless, about 20% of patients experience a severe AP attack, resulting in an intense inflammatory response, a variety of local and systemic complications, a prolonged hospital course, and significant

morbidity and mortality (5,6). In these patients, the inflammatory response may progress to the systemic inflammatory response syndrome, multiorgan failure, and/or pancreatic necrosis (PNec). However, the individual patient response to pancreatic injury is highly variable and often unpredictable. Clinical clues to the development of these feared complications may guide patient management and are therefore desirable.

Pancreatic necrosis is a condition associated with severely diminished blood flow to the pancreas, resulting in segmental pancreatic parenchymal ischemia and infarction. PNec occurs

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in approximately 15% of AP patients and is detected by the loss of vascular enhancement on computerized tomography (CT) or magnetic resonance imaging (5,7). Early recognition of patients at increased risk of PNec is of critical importance; PNec confers a high risk of late morbidity and mortality, especially if the necrotic segment becomes infected. Some studies have observed the development of PNec to occur within the first 2–4 days after an acute attack (7). Other studies based on serial CT scans, however, have described the late development of PNec (8,9). Of all patients with eventual PNec assessed in one study, 28% developed late PNec after a normal admission contrast-enhanced computed tomography (CECT) (9).

Hemoconcentration reflects a decrease in plasma volume and is demonstrated by elevated hematocrit (Hct) levels. Clinical studies have demonstrated that a Hct  $\geq 44\%$  is associated with the development of PNec (10). However, many AP subjects with an elevated Hct do not develop PNec (positive predictive value (PPV) ranging from 21% to 68%) (11).

Urea nitrogen (BUN), one of the components of Ranson's criteria for AP severity (12), is combined with creatinine (Cr) level measurements to clinically estimate patient fluid status. However, BUN levels are sensitive to mild intravascular volume changes. We hypothesize that severe intravascular volume depletion and the associated stress response that diminishes visceral blood flow and leads to PNec will also affect the kidneys, resulting in an increase in serum Cr levels. We tested this hypothesis in a cohort of prospectively ascertained patients admitted to two teaching hospitals.

## METHODS

The Severity of Acute Pancreatitis Study protocol was approved by the Institutional Review Board of the University of Pittsburgh. Informed consent was obtained from all patients or appropriate surrogates prior to study enrollment. The diagnosis of AP was based on the presence of two of the following three features: (i) abdominal pain characteristic of AP, (ii) serum amylase and/or lipase  $\geq 3$  times the upper limit of normal, and (iii) characteristic findings of AP on abdominal CT scan. Patients were recruited within 24 h of the time of admission (13). PNec was assessed by CECT. Evidence of PNec on CT was defined as lack of enhancement of pancreatic parenchyma with contrast (14). All CT scans were reviewed by radiologists dedicated to abdominal imaging, who were blinded to laboratory data and clinical course.

The first time point chosen for data analysis in this study was at hospital admission and the second was within 48 h of admission. Routine laboratory tests that could reflect severely diminished blood flow to the pancreas were analyzed, including Hct, BUN, and Cr. On rare occasions not all the laboratory values were available in patients included in the study who were transferred to our institution from outside hospitals. Performance of CECT within 24 h of admission and volume of intravenous hydration was compared in patients who developed PNec and those without PNec.

## Statistics

Continuous measures were compared using Mann–Whitney test and categorical variables were compared using Pearson's  $\chi^2$ -test. Receiver operating characteristic (ROC) curves for PNec were calculated using Hct, Cr, and BUN values on admission and within 48 h. The area under the curve (AUC) was calculated and based on the ROC curves, best-performing cutoffs were selected. Odds ratios were calculated by binary logistic regression analysis. Univariate analysis was performed to assess potential association of each of the variables with PNec. Independent significant variables were confirmed by a multivariate logistic regression step-up model. Sensitivity, specificity, PPV, negative predictive value, and accuracy was calculated for PNec and individual blood tests.

## RESULTS

A total of 185 patients with AP were prospectively enrolled between June 2003 and September 2007. Patients who underwent CECT during their admission were included in the final analysis ( $n = 135$  of 185). Thereafter, six patients were excluded due to chronic illnesses that could confound blood test interpretation, including anemia of chronic disease ( $n = 2$ ) and chronic renal insufficiency ( $n = 4$ ). The final analysis cohort ( $n = 129$ ) consisted of 72 men and 57 women (mean age 50 years (range, 15–87)). Thirty-five patients had CECT evidence of PNec (27%). Patient demographics are presented in **Table 1**.

Seventy-six patients underwent CECT within 24 h of admission; sixteen had evidence of PNec (21%). Fifty-three patients underwent CECT at a later point in the course of AP, of which nineteen had evidence of PNec (36%;  $P = 0.07$ ). Patients received an average of 4.31 (range, 1.8–7.5) of intravenous (IV) fluids within the first 24 h of admission and 3.91 (1.8–7.5) of IV fluids between 24 and 48 h from admission. Out of 129 patients, 71 were managed conservatively, 36 were started on enteral feedings, and 21 on total parenteral nutrition. Enteral feedings were initiated on average on day 9 of hospitalization (range, 2–28 days) and total parenteral nutrition on day 5.3 (range, 1–10 days). Out of the 35 patients with PNec, enteral feedings were used in 22 patients (63%) and total parenteral nutrition in 13 patients (26%). Endoscopic retrograde cholangiopancreatography for biliary decompression was performed in 35 patients (27%).

Receiver operating characteristic curves yielded an AUC of 0.79 (95% confidence intervals (CI): 0.69–0.89) for admission Hct and 0.78 (95% CI: 0.68–0.89) for peak Hct. ROC curves generated for admission Cr had an AUC 0.72 (95% CI: 0.62–0.81) and 0.77 (95% CI: 0.68–0.87) for peak Cr within 48 h; AUC of 0.60 (95% CI: 0.48–0.71) for admission BUN and 0.72 (95% CI: 0.61–0.83) for peak BUN within 48 h. On the basis of above AUC results, admission Hct, peak Cr, and peak BUN within 48 h were selected for further analysis (**Figure 1**).

Admission Hct was significantly higher in patients with PNec when compared to subjects without necrosis (46.3% vs. 39.9%,

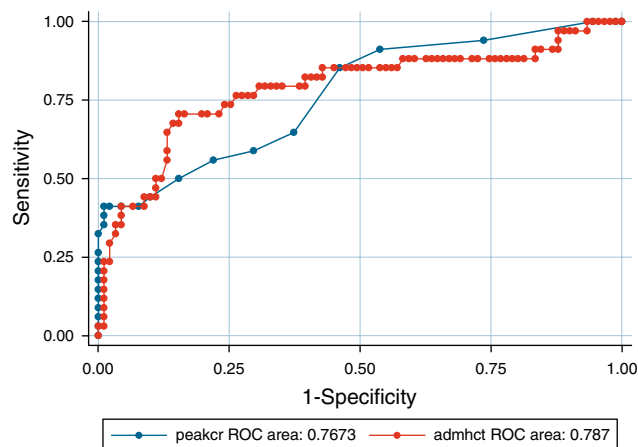
**Table 1.** Demographic results of all patients, patients with PNec and those without PNec

	Total (n=129)	PNec (n=35)	No PNec (n=94)	P value
Age (mean)	49.7	49.3	49.9	0.92 <sup>a</sup>
Gender (man/woman)	72/57	23/12	49/45	0.17 $\pm$
Race (white/other)	110/18	33/2	78/16	N/A
Mean BMI	28.7	31.8	27.6	<b>0.0007<sup>a</sup></b>
<i>Etiology (biliary/all other)</i>				0.96 $\pm$
Biliary	41	11	30	
Idiopathic	40	11	29	
Alcohol	23	8	15	
Post-ERCP	12	2	10	
Hypertriglyceridemia	7	3	4	
Others	6	0	6	
Ranson score (mean)	2	4.2	1.3	<b>&lt;0.00001<sup>a</sup></b>
APACHE II score (mean)	8.3	13	6.7	<b>&lt;0.00001<sup>a</sup></b>
CTSI (mean)	3.1	6.8	1.8	<b>&lt;0.00001<sup>a</sup></b>
Length of stay (days)	15.2	29	10.2	<b>&lt;0.00001<sup>a</sup></b>
OF	34	25	9	<b>&lt;0.00001<math>\pm</math></b>
Multiple OF	14	10	4	<b>&lt;0.00001<math>\pm</math></b>
Single OF	20	15	5	<b>&lt;0.00001<math>\pm</math></b>
Death	5 <sup>b</sup>	3	2	<b>0.09<math>\pm</math></b>

APACHE, Acute Physiology And Chronic Health Evaluation; ERCP, endoscopic retrograde cholangiopancreatography; BMI, body/mass index; CTSI, computerized tomography severity index; OF, organ failure; PNec, pancreatic necrosis.

In bold *P* values  $\leq 0.05$ .

<sup>a</sup>Mann-Whitney test;  $\pm$ Pearson's  $\chi^2$ -test. <sup>b</sup>Two patients died from SIRS and multiple OF within the first 2 weeks of AP onset (days 3 and 14). One patient developed SIRS and multiple OF, had prolonged ICU stay complicated by pseudomonas pneumonia, and eventually expired on day 39. Two patients died from infected PNec and sepsis later in the course of the disease (days 19 and 59).



**Figure 1.** Receiver operating characteristic (ROC) curves for admission Hct and peak Cr within 48h. peakcr, peak Cr within 48h; admhct, admission Hct.

$P < 0.00001$ ); as was peak Cr within 48h (2.2 vs. 1.0 mg/dl,  $P < 0.00001$ ) and peak BUN (28.2 vs. 15.6 mg/dl,  $P = 0.0002$ ).

On the basis of highest sensitivity and specificity scores for admission Hct, peak Cr, and peak BUN generated from ROC curves, binary logistic regression analysis was performed. Patients with admission Hct  $>44.8\%$  were eleven times more likely to develop PNec (odds ratio, 11.3; 95% CI: 4.6–27.9; **Tables 2a** and **2b**). Patients with peak Cr  $>1.8$  mg/dl within 48h had 35-fold higher likelihood of developing PNec (odds ratio, 34.5; 95% CI: 7.3–163) and subjects with peak BUN  $>27$  mg/dl had sevenfold higher likelihood (odds ratio, 7.1; 95% CI: 2.7–18).

A multivariate logistic regression step-up model utilizing admission Hct, peak Cr, and peak BUN as continuous measures, confirmed statistical significance for admission Hct and peak Cr ( $P < 0.0001$  and 0.03, respectively), but not for peak BUN ( $P = 0.52$ ). In univariate analysis, admission Hct  $>44.8\%$  showed high negative predictive value of 88.5%, whereas peak Cr  $>1.8$  mg/dl within 48h revealed high specificity of 98.9%

and PPV of 93.3% as predictive tests for the development of PNec (Table 3). The combination of admission Hct and peak Cr did not provide any additional value.

As seen in Table 2b, 14 of 15 patients with a Cr >1.8 mg/dl within 48 h, progressed to PNec. All of these 14 patients presented to the emergency room and started on IV fluid resuscitation the same day with the onset of abdominal pain. IV fluids were administered on average of 4.11 (1.8–7.0) within 24 h of admission and 4.21 (1.8–7.0) between 24 and 48 h. Patients who developed PNec without elevated Cr received a similar volume of IV fluids; 5.41 (2.0–7.5) within 24 h and 3.61 (3.0–7.5) between 24 and 48 h ( $P=0.33$  and  $0.73$ , respectively); as did patients without PNec (3.91 within 24 h of admission and 3.71 between 24 and 48 h;  $P=0.78$  and  $0.56$ , respectively).

In the group of 14 patients with PNec and Cr >1.8 mg/dl, 2 had an elevated Cr on admission; in 9 patients Cr exceeded 1.8 mg/dl at 24 h and in 3 of those at 48 h, suggesting that the elevation in Cr is a dynamic process that seems to progress in spite of fluid resuscitation. In this group, 11 patients had an admission Hct of >44.8%. Three patients underwent a CECT within 24 h, whereas the remaining underwent CECT later during their hospitalization. Three of them developed focal PNec (involving <30% of the total pancreatic parenchyma) and had an average peak Cr of 3.0 mg/dl (range, 2.4–3.1), whereas eleven patients developed extensive PNec (involving >30% of the total pancreatic parenchyma) and had a similar average Cr of 4.1 mg/dl (range, 1.9–7.8;  $P=0.7$ ). In addition, similar per-

centage of the patients who developed PNec without elevated Cr had focal ( $n=8$ ) vs. extensive necrosis ( $n=13$ ) on CECT ( $P=0.3$ ).

Most of the patients requiring intensive care management developed PNec (19 out of 26). Of the 103 patients managed on the regular ward, 16 had CECT evidence of PNec. Of these 16 patients, 6 had a peak Cr >1.8 mg/dl within 48 h. These six patients remained hospitalized for a mean of 28 days (range, 12–50). Two patients were followed as outpatients and did not develop any complications; two were readmitted with abdominal pain and inability to tolerate oral nutrition; and the remaining two patients developed infected PNec requiring prolonged hospitalization. One required open surgical debridement.

## DISCUSSION

The development of PNec is a major contributing factor to morbidity and mortality of AP, especially, when the PNec becomes infected (3,6,15). Early identification of patients at risk for PNec should lead to preventative measures, such as vigorous fluid resuscitation, whereas early recognition of developing PNec will alter management to address this complication, such as increased vigilance for the development of infection in necrotic pancreatic tissue and consideration of the use of antibiotic and/or enteral nutrition therapy (16–18). Here we confirmed the utility of admission Hct for categorizing subjects into high- and low-risk groups, and identified rising Cr levels as a factor that is closely associated with the development of PNec.

The pathogenesis of PNec is complex. Animal studies support the role of a compromised blood supply early in the course of AP (19). Active pancreatic inflammation with increased vascular permeability, vascular spasm, systemic hypovolemia with shunting of blood from visceral organs, and increased viscosity of hemoconcentrated blood, may all contribute to regional pancreatic infarctions (20). We recently demonstrated that obesity (13) and chronic alcohol consumption (14) are significant risk factors for the development of PNec. The findings of the present study confirm a strong association with obesity (Table 1), and the importance of vascular dynamics in the process leading to PNec as indicated by elevations of Hct, BUN, and Cr levels in affected subjects. Previous studies have investigated C-reactive protein,  $\alpha$ -2-macroglobulin, polymorphonuclear elastase, human pancreas-specific protein/procarboxypeptidase B and

**Table 2a. Admission Hct as a marker of PNec**

	PNec ( $n=34$ )	No PNec ( $n=92$ )
Adm Hct >44.8%	24	15
Adm Hct $\leq$ 44.8%	10	77

Hct, hematocrit; PNec, pancreatic necrosis.

**Table 2b. Peak Cr (48 h) as a marker of PNec**

	PNec ( $n=34$ )	No PNec ( $n=93$ )
Peak Cr >1.8 mg/dl	14	1
Peak Cr $\leq$ 1.8 mg/dl	20	92

Cr, creatinine; PNec, pancreatic necrosis.

**Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of admission Hct and peak Cr within 48 h as predictive tests for the development of PNec**

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Admission Hct	70.6% (53.8–83.2)	83.7 (74.8–89.9)	61.5 (45.9–75.1)	<b>88.5</b> (80.1–93.6)
48-h peak Cr	41.2 (26.4–57.8)	98.9 (94.2–99.8)	<b>93.3</b> (70.2–98.8)	82.1 (74.0–88.1)

CI, confidence interval; Cr, creatinine; Hct, hematocrit; NPV, negative predictive value; PPV, positive predictive value.

Bold values are most clinically important values.

serum macrophage migration inhibitory factor, as potential markers of PNec (21–24). With the exception of C-reactive protein, these serum markers are solely used for research purposes and are not widely available to the majority of clinicians. Additionally, C-reactive protein performs best as a predictor of PNec at 72 h following admission (23).

Hemoconcentration on admission and failure of Hct to decrease within 24 h are the only routinely performed laboratory tests that have been extensively studied (10,25,26) in relation to the development of PNec. The present study confirms that a lack of hemoconcentration at the time of admission indicates a low risk of PNec. Although an elevated Hct is a risk factor for PNec, an elevated Hct alone has a poor PPV, previously reported between 21% and 62% (11) and in our study 61.5%, indicating that there are other etiologic factors that are not captured by this test. Admission Hct has the advantage of classifying patients into low- and high-risk categories; elevated values serve as an indicator for the need for more aggressive fluid resuscitation.

A critical finding of our study is that an elevated serum Cr of  $>1.8$  mg/dl within 48 h of admission is strongly associated with the development of PNec. As noted above, 14 out of 15 patients with elevated serum Cr within 48 h progressed to PNec (PPV 93%). Both BUN and Cr are markers of renal function; acute changes from baseline suggest intravascular hypovolemia. Why Cr appeared to be more accurate marker of PNec than BUN is unclear. We hypothesize that Cr levels may be less sensitive to small changes in intravascular volume and better reflect visceral organ injury. Thus, hemoconcentration on admission represents a risk factor for the development of PNec, whereas elevated Cr during early hospitalization reflects visceral organ injury and is strongly associated with the presence of PNec. However, it is also important to recognize that serum Cr has significant limitations. Although very specific, only 14 out of 34 patients who developed PNec yielded an elevated Cr resulting in a low sensitivity of 41%.

For clinical studies, the Ranson's and Acute Physiology And Chronic Health Evaluation-II score systems are considered among the best predictors of severity, but they are seldom used in clinical practice. We found that ROC curves yielded an AUC of 0.85 for Ranson's and 0.81 for Acute Physiology And Chronic Health Evaluation-II score (data not shown). Although the performance characteristics of these methods are better than Cr, many of the measurements and variables required to calculate these scores are not routinely ordered (e.g. LDH, fluid sequestration, base deficit, etc.). The high specificity and PPV of serum Cr levels for the development of PNec may serve as a simpler and readily available surrogate than the more cumbersome scoring systems (e.g. Ranson's and Acute Physiology And Chronic Health Evaluation-II) in routine clinical practice.

The above findings are especially important for the 6% of the AP patients on the regular ward who developed PNec, but were otherwise medically stable and were managed outside

of the intensive care unit. The clinician should be aware that an elevated serum Cr of  $>1.8$  mg/dl within 48 h of admission, despite adequate hydration, appears to be strongly associated with evolving PNec. Special attention should be directed to this subgroup of patients with consideration of performing a CECT or magnetic resonance imaging, when they are not clinically improving. Such patients should also be followed closely post hospital discharge.

The timing of CECT evaluation is of great significance. Experts in the field suggest that PNec may not be fully apparent on a CECT for up to 3 days after disease onset, and an early CECT may underestimate the severity of AP (3). Early CT imaging may, however, be needed in some patients to confirm the diagnosis of AP, exclude other diagnosis, and to identify severity and complications. In this study, the timing of the CECT was determined by the emergency room physicians who initially evaluated the patients and the primary team managing them during hospitalization, with more than 50% of the patients undergoing CECT within the first 24 h.

Animal studies indicate that giving intravenous contrast very early in the course of AP, prior to adequate fluid resuscitation may have detrimental effects on pancreatic perfusion and can predispose to the development of, or increase the extent of PNec (27,28). To date, a limited number of small retrospective human studies have not demonstrated an association of early CECT and PNec (29,30). However, the question of whether early use of contrast worsens the extent of PNec cannot be answered by uncontrolled clinical observations because of the large variability between patients, differences in the amount of prior fluid resuscitation and the inability to study the pancreatic tissue at risk directly. Nevertheless, in the present study, there were no significant differences detected in development of PNec between AP patients who did or did not undergo CECT within 24 h of admission. We also assessed the amount of intravenous hydration within the first critical 48 h. Similar volume of IV fluids was administered in patients with PNec when compared to those without PNec. Therefore, intravenous hydration patterns alone could not account for the development of elevated Cr levels or PNec in these patients.

One of the limitations of the current study is that 50 of the original 185 patients (27%) did not undergo CECT and the exact prevalence of PNec in this cohort remains unknown. Second, the CECT scans performed in subjects managed outside the intensive care unit were likely done because of clinical suspicion that complications existed, delaying expected clinical improvement. Third, the present study did not thoroughly evaluate subjects with prior renal insufficiency or chronic anemia because such patients were excluded from the analysis. Fourth, an increase in serum Cr has been observed to occur in up to 4% of subjects with normal baseline renal function following intravenous contrast administration (31). Contrast-induced nephrotoxicity, however, did not appear to be responsible for the elevated Cr in the 14 patients with PNec, as only 3 of them

received intravenous contrast within the first 24 h of admission. Despite these limitations, our intention is to demonstrate the potential utility of serum Cr levels in detecting conditions leading to PNec. Future studies are needed to confirm and better define the context of these observations.

This study brings attention to a number of questions. Early and aggressive hydration constitutes the current intervention to prevent PNec. However, the effectiveness of such an intervention and the amount of intravascular fluids required has not been studied in a randomized prospective fashion. Despite the use of Hct and Cr levels to predict the development of PNec, a CECT or magnetic resonance imaging is still required to diagnose PNec. Finally, elevated serum Cr levels indicate a high risk of PNec, but appropriate management steps and interventions are yet to be defined. Future studies with emphasis on visceral injury and utilization of interventions aimed at restoring intravascular volume and renal protection are needed.

In conclusion, early recognition of subjects at high risk for PNec and identification of patients with a high likelihood of unidentified PNec are important goals in determining optimal management of patients with AP. The present study assessed routine blood tests as clinical markers of PNec and confirmed that admission Hct has a high negative predictive value for PNec, allowing subjects without hemoconcentration to be categorized as low risk. Additionally, and for the first time, our study demonstrates that a serum Cr >1.8 mg/dl within 48 h of admission is strongly associated with the development of PNec.

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#### CONFLICT OF INTEREST

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

**Specific author contributions:** acquisition of data, analysis and interpretation of data and drafting of the paper: Venkata Muddana; critical revision of the paper for important intellectual content, obtaining funding and supervision: David C. Whitcomb; analysis and interpretation of data and statistical analysis: Asif Khalid; critical revision of the paper for important intellectual content and supervision: Adam Slivka; conception and design, acquisition of data, analysis and interpretation of data, drafting of the paper, statistical analysis and obtaining funding: Georgios I. Papachristou.

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**Potential competing interests:** No potential competing interests exist.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Pancreatic necrosis is a serious complication of acute pancreatitis with high morbidity and mortality.
- ✓ The identification of simple laboratory tests to detect subjects at risk of pancreatic necrosis may direct management and improve outcome.
- ✓ Serum hematocrit has been extensively studied and it has been shown that hemoconcentration alone has a poor positive predictive value for pancreatic necrosis.

### WHAT IS NEW HERE

- ✓ We confirmed that a low admission hematocrit has a high negative predictive value of 88.5%, indicating a low risk of pancreatic necrosis.
- ✓ Our study demonstrates for the first time that an elevated serum Cr >1.8 mg/dl within 48 h of admission is strongly associated with the development of pancreatic necrosis, with a positive predictive value of 93%.
- ✓ The clinician should be aware that in medically stable patients with acute pancreatitis an elevated serum Cr of >1.8 mg/dl, despite adequate hydration, appears to be strongly associated with evolving pancreatic necrosis.

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