

## ORIGINAL ARTICLE

# Does the Duration of Abdominal Pain Prior to Admission Influence the Severity of Acute Pancreatitis?

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### ABSTRACT

**Context** In a prior report involving patients with hemoconcentration at admission, those with necrotizing pancreatitis presented significantly earlier than those with interstitial disease suggesting that duration of abdominal pain prior to presentation may have prognostic significance in acute pancreatitis. **Objectives** The aim of the present study was to determine whether the duration of abdominal pain prior to admission influences the severity of acute pancreatitis. **Methods** During a five-year period, all patients presenting directly to our hospital with their first episode of acute pancreatitis were enrolled in a cohort study. We analyzed data obtained from records of all such patients and performed a separate analysis on those with hemoconcentration (hematocrit equal to, or greater than, 44%) at presentation to determine whether duration of abdominal pain prior to presentation was associated with severity of acute pancreatitis. Duration of abdominal pain was categorized as persisting for either less than 12 h or 12 h or more prior to arrival. Prognostic markers of severity included admission hematocrit and blood urea nitrogen (BUN), as well as the development of systemic inflammatory response syndrome (SIRS) during the initial 24 h of hospitalization. Outcome measures included pancreatic necrosis based on contrast-enhanced CT scanning, need for intensive care, length of hospitalization, and death. Radiologic severity of peripancreatic inflammatory changes was assessed within 48 h of admission in accordance with the Balthazar-Ranson scoring system (A-E). **Results** Among a total of 318 patients, there were 62 (19.5%) with hemoconcentration at admission. Among the 318 patients, there was no significant difference in the prevalence of pancreatic necrosis when comparing the less than 12 h group to the 12 h or more group. Among the 62 patients with hemoconcentration, those admitted within 12 h compared to those admitted 12 h or more following the onset of abdominal pain had an increased radiologic severity of acute pancreatitis (Balthazar-Ranson grade D or E: 83.3% vs. 40.0%; P=0.006) and an increased prevalence of pancreatic necrosis (21.1% vs. 2.3%; P=0.028). **Conclusion** Duration of abdominal pain prior to admission impacts the severity of acute pancreatitis only among patients with hemoconcentration at presentation.

### INTRODUCTION

In a prior report from our institution involving patients with hemoconcentration at admission, those with necrotizing pancreatitis presented significantly earlier than those with interstitial disease [1]. This result suggests that duration of abdominal pain prior to presentation may have prognostic significance in acute pancreatitis. However, the majority of patients in this

study were transferred from other hospitals. Therefore, it remains unclear whether this result is applicable to patients presenting directly to our institution. Our hypothesis was that patients who seek medical attention more promptly for their abdominal pain have more severe pancreatic injury as evidenced by an increased prevalence of local complications on radiographic imaging, and that hemoconcentration in the setting of an earlier presentation would be a more reliable risk factor for pancreatic necrosis.

The aim of the present study was to determine whether the duration of abdominal pain impacts the severity of acute pancreatitis among patients who were admitted directly to our institution. Our secondary aim was to make this determination in the subset of patients with hemoconcentration at admission.

### METHODS

A cohort study was performed using data collected on all patients admitted directly to Brigham and Women's Hospital with their first episode of acute pancreatitis

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**Key words** Acute Disease; Early Diagnosis; Pancreatitis /radiography; Severity of Illness Index; Tomography, X-Ray Computed

**Abbreviations** BUN: blood urea nitrogen; SIRS: systemic inflammatory response syndrome

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between June 2005 and June 2010. Patients with acute pancreatitis who were transferred from other hospitals, those whose hospitalization occurred directly after undergoing an ERCP, and those whose acute pancreatitis developed during the hospitalization were excluded. Acute pancreatitis was defined by at least two of the following criteria: characteristic abdominal pain, serum amylase and/or lipase values exceeding three times the upper limit of normal, and a computed tomography (CT) scan or magnetic resonance imaging (MRI) demonstrating characteristic changes of acute pancreatitis [2].

Data collected included: age; prognostic markers of severity including admission hematocrit, blood urea nitrogen (BUN), and systemic inflammatory response syndrome (SIRS) in the first 24 hours; and outcome measures including pancreatic necrosis, need for admission to the intensive care unit, length of hospitalization, and death. SIRS scores were calculated for all patients based on the most extreme laboratory value or clinical measurement obtained during the initial 24 hours of hospitalization. Mortality was defined as death occurring during hospitalization. Pancreatic necrosis was defined by findings of parenchymal nonenhancement on at least one contrast-enhanced CT scan according to the criteria set forth by the Atlanta symposium [2]. Patients who did not have a contrast-enhanced CT or MRI scan performed during hospitalization were considered to have interstitial pancreatitis.

Among patients with admission hematocrit equal to, or greater than, 44% who underwent a contrast-enhanced CT scan within 48 h of admission, an evaluation of the radiologic extent of the pancreatic and peripancreatic inflammatory changes was made in accordance with the Balthazar-Ranson scoring system: grade A: normal pancreas; grade B: pancreatic enlargement; grade C: pancreatic inflammation and/or peripancreatic fat inflammation; grade D: single peripancreatic fluid collection; grade E: 2 or more fluid collections and/or retroperitoneal air [3]. For purpose of this evaluation,

we did not include additional points based on the presence or extent of pancreatic necrosis because of the difficulty in grading the extent of pancreatic necrosis during the early stages of acute pancreatitis [4]. In addition, our major interest was in the extent of the peripancreatic inflammatory response that might correlate with intravascular volume depletion resulting in hemoconcentration. All radiographic images were independently reviewed by study radiologists who were blinded to the aims of the study.

Patients with an admission hematocrit of 44% or more were dichotomized into a less than 12 h group or a 12 h or more group in accordance with the time lapse between the onset of their abdominal pain and presentation to our hospital. Information regarding the time lapse was gathered either on the basis of an interview on the day of admission or by a careful review of the medical records.

### ETHICS

This study was approved by the Partners Institutional Review Board. The study protocol conforms to the ethical guidelines of the “World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects” adopted by the 18<sup>th</sup> WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59<sup>th</sup> WMA General Assembly, Seoul, South Korea, October 2008. Written informed consent was obtained from each patient.

### STATISTICS

Data are reported as frequencies, mean±SD, or median and interquartile range (IQR). The Fisher’s exact test was used for all categorical variables and the Mann-Whitney/Wilcoxon rank sum test was used for all continuous variables. All statistical analysis was performed using SAS® v.9.1 (SAS Institute, Cary, North Carolina, USA). Two-tailed P values less than 0.05 were considered significant.

### RESULTS

A total of 847 patients with acute pancreatitis were evaluated, of whom 529 patients (62.5%) were excluded according to aforementioned criteria (Figure 1). In particular, 303 patients (35.8%) were excluded because they had experienced one or more prior episodes of acute pancreatitis, 140 (16.5%) because they had been transferred from other hospitals and 86 (10.2%) for other reasons. Only the 318 patients (37.5%) who presented directly to our hospital were enrolled into this study. Of these 318 patients, 62 (19.5%) patients had an admission hematocrit equal to, or greater than, 44%.

Table 1 presents a comparison of parameters of disease severity among the 318 patients who presented directly to our hospital: 111 patients (34.9%) were admitted within 12 h and 207 (65.1%) 12 h or more from the onset of pain. There were no statistically significant differences observed between the two groups in any

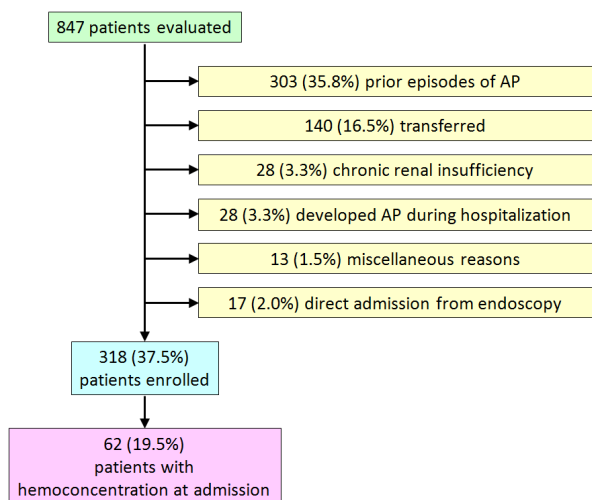


Figure 1. Selection of eligible patients with acute pancreatitis (AP).

**Table 1.** Analysis of the 318 patients comparing those admitted within 12 h (n=111) vs. those admitted 12 h or more (n=207) from the time of onset of abdominal pain. Values are expressed as frequencies, mean±SD, or median and interquartile range (IQR).

	Admission <12 h (n=111)	Admission ≥12 h (n=207)	P value
Age (years; mean±SD)	54±19	54±17	0.883 <sup>a</sup>
Admission hematocrit (%; median (IQR))	39.5 (36.7-43.0)	39.5 (35.8-43.6)	0.841 <sup>a</sup>
Admission BUN (mg/dL; median (IQR))	13 (10-19)	13 (10-19)	0.922 <sup>a</sup>
SIRS (first 24 h)	36 (32.4%)	60 (29.0%)	0.525 <sup>b</sup>
Pancreatic necrosis	4 (3.6%)	5 (2.4%)	0.724 <sup>b</sup>
Need for intensive care unit	13 (11.7%)	15 (7.2%)	0.214 <sup>b</sup>
Length of hospitalization (days; median (IQR))	4 (2-6)	4 (2-7)	0.224 <sup>a</sup>
Death	4 (3.6%)	3 (1.5%)	0.246 <sup>b</sup>

<sup>a</sup> Mann-Whitney/Wilcoxon rank sum test

<sup>b</sup> Fisher's exact test

parameter of disease severity. In addition, severity of acute pancreatitis was evaluated among the 82 patients whose time of pain onset was confirmed prospectively on the day of admission (36 patients (43.9%) within 12 h vs. 46 patients (56.1%) 12 h or more). There were no statistically significant differences between the two groups in any of the parameters of disease severity (data not shown).

Table 2 presents a comparison of parameters of disease severity among the 62 patients with hemoconcentration: 19 (30.6%) were admitted within 12 h and 43 (69.4%) were admitted 12 h or more from the onset of pain. Patients admitted within 12 h had a significant increase in the prevalence of pancreatic necrosis compared to those admitted 12 h or more (4/19, 21.1% vs. 1/43, 2.3%; P=0.028). In addition, among the 48 patients (77.4%) who received a CT scan within 48 h of admission based on the discretion of the treating physician, those who presented within 12 h had a significant increase in radiologic severity within 48 h of admission compared to those admitted 12 h or more (Balthazar-Ranson grades D or E: 15/18, 83.3% vs. 12/30, 40.0%; P=0.006).

## DISCUSSION

In the present study, patients with hemoconcentration at admission had more radiologically severe acute pancreatitis within 48 h of admission and a significant

increase in the prevalence of pancreatic necrosis if they presented within 12 h from onset of abdominal pain when compared to patients presenting 12 h or more from the start of their pain.

The accuracy of hemoconcentration as a prognostic marker of severity has undergone considerable study in the past 15 years [5, 6, 7, 8, 9]. Whereas initial studies concluded that hemoconcentration was an early prognostic marker for necrotizing pancreatitis [5, 6] and organ failure [6], more recent studies have concluded that early hemoconcentration is associated with pancreatic necrosis [7] and increased mortality [8] only among transferred patients as opposed to direct admissions to a hospital [7, 8, 9].

There are important differences between these earlier studies and our present study. First, none of the previous studies evaluated the impact of duration of abdominal pain prior to admission on the development of pancreatic necrosis. Secondly, several of these earlier studies included patients with previous episodes of acute pancreatitis [7, 8]. Since the initial episode of acute pancreatitis is generally the most severe [2, 10], studies of possible prognostic markers of severity should be restricted to the initial episode.

The present study establishes the importance of hemoconcentration and duration of pain as prognostic markers of severity among directly admitted patients experiencing their initial episode of acute pancreatitis.

**Table 2.** Analysis of the 62 patients with admission hematocrit equal to, or greater than, 44% comparing those admitted within 12 h (n=19) vs. those admitted 12 h or more (n=43) from the time of onset of abdominal pain. Values are expressed as frequencies, mean±SD, or median and interquartile range (IQR).

	Admission <12 h (n=19)	Admission ≥12 h (n=43)	P value
Age (years; mean±SD)	53±16	52±15	0.789 <sup>a</sup>
Admission BUN (mg/dL; median (IQR))	13 (11-19)	15 (12-21)	0.878 <sup>a</sup>
SIRS (first 24 h)	12 (63.2%)	19 (44.2%)	0.270 <sup>b</sup>
Balthazar-Ranson (grades D or E) <sup>c</sup>	15/18 (83.3%)	12/30 (40.0%)	0.006 <sup>b</sup>
Pancreatic necrosis	4 (21.1%)	1 (2.3%)	0.028 <sup>b</sup>
Need for intensive care unit	6 (31.6%)	4 (9.3%)	0.055 <sup>b</sup>
Length of hospitalization (days; median (IQR))	5 (3-10)	5 (3-10)	0.993 <sup>a</sup>
Death	2 (10.5%)	0 (0%)	0.090 <sup>b</sup>

<sup>a</sup> Mann-Whitney/Wilcoxon rank sum test

<sup>b</sup> Fisher's exact test

<sup>c</sup> A total of 48 patients received a CT scan within 48 h of admission

In a prior study utilizing artificial neural networks [11], hemoconcentration and duration of abdominal pain prior to admission have also been shown to correlate with the severity of acute pancreatitis. Among 6 risk variables that correlated most strongly with severity of acute pancreatitis, the most significant one was a shorter duration of pain prior to admission and the third most significant was hemoconcentration at admission [11]. Accordingly, there is increasing evidence linking hemoconcentration with duration of pain as prognostic markers of severity.

There is also evidence that the absence of hemoconcentration at admission correlates strongly with the development of mild acute pancreatitis [12] including a recent scoring algorithm entitled the Harmless Acute Pancreatitis Score (HAPS) [13]. In that report, the absence of hemoconcentration was associated with severity of acute pancreatitis in only 2% [13]. In the present study, only 1.6% (4/256) of patients without hemoconcentration developed necrotizing pancreatitis.

Prognostic markers of pancreatic necrosis are extremely important in the care of patients with acute pancreatitis due to the high mortality associated with necrotizing pancreatitis (approximately 15%) [14] compared to interstitial pancreatitis (approximately 3%) [15]. In previous reports, an increased BUN at admission was a prognostic marker of mortality in acute pancreatitis [16, 17]. However, there have been no prior studies that have evaluated admission BUN as a prognostic marker of pancreatic necrosis. Also, in a previous report, the development of SIRS in the initial 24 h of hospitalization was a prognostic marker of pancreatic necrosis [18]. In the present study, however, there was no significant difference in admission BUN and prevalence of SIRS when comparing patients admitted within 12 h *versus* those admitted 12 h or more from pain onset, either in the entire cohort of patients (Table 1) or among those with hemoconcentration (Table 2).

Patients in our study who sought medical attention within 12 h from the start of their pain had more widespread peripancreatic inflammatory response visualized on their CT scans compared to those presenting 12 h or more. More widespread peripancreatic inflammation may have caused an increase in the intensity of abdominal pain, thereby necessitating an earlier presentation to the hospital. A more robust peripancreatic inflammatory response may also have resulted in an accelerated intravascular volume depletion, resulting in more severe impairment of the pancreatic microcirculation.

For the purpose of our study, we graded the radiologic severity on contrast-enhanced CT scans obtained during the first 48 h based only on the extent of the peripancreatic inflammatory response, without adding additional score for the presence or extent of pancreatic necrosis. Our primary interest was in the correlation of severity of the peripancreatic inflammatory response to the development of hemoconcentration and necrotizing

pancreatitis. Furthermore, the accuracy of the Balthazar-Ranson scoring system has been found to be similar to the accuracy of other CT scoring systems for assessing the radiographic severity of acute pancreatitis [19].

There are several strengths to our study. First, we included only patients experiencing their first episode of acute pancreatitis. In general, the first episode of acute pancreatitis is more severe when compared to subsequent episodes [2, 10]. Also, patients with prior episodes of acute pancreatitis might present earlier to obtain more timely relief of abdominal pain. Second, we excluded patients whose characteristics would confound the relationship between duration of abdominal pain and severity of acute pancreatitis. In particular, we excluded patients who had been transferred from other hospitals because as a group they generally have more severe disease than those who are direct admissions [2, 8].

There are several limitations to our study. First, the sample size is small. Observed trends are more robustly demonstrated with a large patient population. Second, information regarding duration of abdominal pain prior to arrival to our hospital was obtained retrospectively in many patients. Data obtained retrospectively may not be as accurate as data obtained prospectively. Because of this concern, we conducted a subset analysis of Table 1 restricted only to those patients whose time to arrival was obtained prospectively on the day of admission. In this subset analysis, there was also no statistical difference in any variable when comparing the less than 12 h group with the 12 h or more group. Third, we were not able to evaluate the impact of differences in intravenous fluid resuscitation in our results. At present, there is no consensus regarding the optimal rate of fluid resuscitation to prevent local complications (such as pancreatic necrosis) but not increase the risk of systemic complications (such as pulmonary edema) [20, 21, 22]. In conclusion, among patients with hemoconcentration who were experiencing their first episode of acute pancreatitis, those admitted within 12 h after the onset of abdominal pain compared to those admitted 12 h or later had more severe pancreatic injury as evidenced by an increased prevalence of pancreatic necrosis. Duration of abdominal pain prior to admission impacts the severity of acute pancreatitis among patients with hemoconcentration at presentation.

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#### Conflicts of interest None

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