



## Predicting Factors of Pancreatic Infection in Acute Necrotizing Pancreatitis: A Report of 119 Cases

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### Abstract

**Introduction:** acute Necrotizing pancreatitis (ANP) represents the severe form of human acute pancreatitis (15% of cases). Infection of pancreatic necrosis occurs in 40–70% of patients with ANP and have mortality rate about 80% of cases. Therefore, early prediction and diagnosis of infection in ANP are extremely important. So we aimed to identify the risk factors for predicting pancreatic infection in patients with ANP.

**Methods:** One hundred and nineteen patients with ANP were included and divided into two groups based on the presence or absence of pancreatic infection. Demographic and clinical characteristics, laboratory examination results, complications and treatment modalities of these patients were collected from their medical records. Variables were initially screened by univariate analysis and those with statistical significance were then filtered by multivariate analysis to determine the independent risk factors for pancreatic infection in ANP.

**Results:** Patients having ANP with pancreatic infection were more obese and had dyslipidemia more than patients without pancreatic infection. In addition; they had lower partial pressure of arterial CO<sub>2</sub>, as well as a higher computed tomography severity index (CTSI) and Ranson's score than those without pancreatic infection, while their lactate dehydrogenases and CRP levels, hematocrit and glycaemia were much higher. Pancreatic infection also occurred more commonly in patients receiving delayed enteral nutrition than in those who received early enteral nutrition. Multivariate analyses revealed that only high CTSI was independent risk factor for pancreatic infection in ANP.

**Conclusion:** many variables were initially identify by univariate analysis as predicting factors of necrosis infection but only high CTSI was independent risk factor.

**Keywords:** Acute pancreatitis- infection – predictive factor- prognostic

### Introduction

Acute pancreatitis (AP) is defined, according to the consensus of Atlanta in 1992 <sup>[1]</sup>, as an acute inflammatory process affecting the pancreas with participation of peri-pancreatic tissues or remote organs.

In practice, there are two distinct varieties: edematous pancreatitis and necrotizing pancreatitis. The edematous form usually results in spontaneous recovery; however necrotizing form is the severe form of acute pancreatitis (15% to 20% of cases) whose natural evolution can be

divided into two phases. <sup>[2]</sup>. The first 14 days characterized by the presence of systemic inflammatory response syndrome (SIRS) secondary to the release of inflammatory mediators that are responsible for the failure of multiple organs (lung, kidneys, and heart, etc....). The second phase occurs after two weeks of evolution and is dominated by septic complications associated with infection of the pancreatic necrosis, which is seen in 40% to 70% of patients <sup>[2]</sup>. Identifying predictive factors of this complication would be essential to identify a group of patients at risk. In these patients adequate supervision is required at the end to reach an early diagnosis for an adequate care to reduce morbidity and mortality of this disease.

Through this work, we propose to identify predictors of occurrence of this complication.

#### **Patients and Methods:**

This is a case-control, single center study conducted on 126 months from January 2004 to June 2014 in the service of Anesthesiology and General Surgery of the Hospital Sahloul Sousse.

#### **Patients:**

We included in the study all patients hospitalized in the services of Anesthesiology and general surgery for necrotizing pancreatitis acute (Steps D and E of the classification of Balthazar).

We have also included all patients transferred from another hospital for acute necrotizing pancreatitis.

Were excluded from the study:

- Outbreaks of calcifying chronic pancreatitis
- The patients who died during the first week of evolution, a cause other than necrosis infection.
- The unusable files for lack of clinical and laboratory information.

Thus, two groups of cases and controls were established. The endpoint was the occurrence of pancreatic necrosis infection during the course of the disease. The first group consists of patients who had necrosis infection; the second group is that of patients who did not have necrosis infection.

#### **Data collection**

Demographic and clinical characteristics of the patients, their laboratory results, complications and treatment modalities were collected by reviewing the medical records of the patients. Clinical data consisted of etiology of ANP, length of hospital stay, mortality, Ranson's score and CT severity index (CTSI). The Ranson's score was determined within the first 48 h after admission. Contrast-enhanced CT was performed in all the patients and CTSI was determined within 48 h after their admission to assess the extent of pancreatic inflammation and necrosis. Laboratory data were obtained within the initial 24 h from the onset of disease, including pH value, partial pressure of arterial oxygen (PaO<sub>2</sub>), arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>), bicarbonate, glycaemia, peripheral white blood cell (WBC) count, hemoglobin, hematocrit, lactate dehydrogenase (LDH), C-reactive protein (CRP), serum creatinine, blood urea nitrogen (BUN), and total and direct bilirubin.

#### **Entry and Data Analysis**

They were carried out by means of the SPSS 19.0 software. Continuous variables are shown as mean  $\pm$  standard deviation(SD).

We used absolute and relative frequencies for qualitative variables express.

To ensure the univariate predictors pancreatic necrosis infection, we used the chi<sup>2</sup> test for comparing two proportions and the Student's t test for comparing two means. We have included in the multivariate analysis, all variables with a significance level <5% in the univariate analysis. This was done in a multivariate and step-by-step down logistic regression to identify independent risk factors. The significance level was set at 5%.

#### **Results:**

#### **Demographic and clinical characteristics of the patients**

A total of 119 patients with SAP were enrolled; with a mean age of 54 (18-90) years, including 47 men and 72 women, among them, 50 (42%) were found to have pancreatic infection. The

demographic and clinical characteristics of the patients with or without pancreatic infection are summarized in Table 1. There were no significant differences in age, gender, etiology of SAP between the two groups (all  $P > 0.05$ ). However, obesity and dyslipidemia were more observed in patients with pancreatic infection compared with those without pancreatic infection (64% vs 36%,  $P = 0,012$  and 69,2% vs 30,8%,  $P = 0,035$  respectively). Patients with pancreatic infection had higher Ranson's score ( $3,4 \pm 1,47$  vs  $2,29 \pm 1,28$ ,  $P < 0.001$ ), higher CTSI ( $6,26 \pm 1,92$  vs  $4,34 \pm 1,40$ ,  $P < 0.001$ ), a longer diet length ( $72,53 \pm 42,03$  hours vs  $55,36 \pm 45,1$  hours,  $P = 0,044$ ) a longer length of hospital stay ( $39 \pm 28$  days vs  $15 \pm 7$  days,  $P < 0.001$ ) and higher mortality rate (42% vs 4.34%,  $P < 0.001$ ), respectively, compared with those without pancreatic infection.

#### Laboratory tests findings

Based on their laboratory tests findings, patients with pancreatic infection had lower PaCO<sub>2</sub> ( $30,27$

$\pm 6,64$  mmHg vs  $34,54 \pm 6,55$  mmHg,  $P = 0.006$ ) than patients without pancreatic infection, while their LDH ( $1095,14 \pm 726,29$ U/L vs  $797,61 \pm 447,89$ U/L), CRP level ( $125,08 \pm 126,95$  vs  $79,61 \pm 96,99$ ,  $P = 0,046$ ) glycaemia ( $11,72 \pm 5,11$  vs  $9,06 \pm 5,47$ ,  $P = 0,019$ ), hematocrit ( $44,08 \pm 7,25\%$  vs  $40,37 \pm 6,01\%$ ;  $P = 0,006$ ) and peripheral WBC count ( $16.863 \pm 4,246 \times 10^9/L$  vs  $14.104 \pm 5,141 \times 10^9/L$ ,  $P = 0.005$ ) were much higher (Table 2).

#### Independent risk factors

Among the predictors of pancreatic necrosis infection found in the univariate study, only the CTSI was validated as an independent predictor in the multivariate analysis with  $p = 0.029$ . With a cut-off value of 4.5, the sensitivity, specificity, PPV and NPV in predicting pancreatic infection in patients with necrotizing pancreatitis were 73.5%, 75.4%, 67.9%, and 80%, respectively, with the AUROC of 0.797 (95% CI 0.717–0.876).

**Table 1:** Demographic and clinical characteristics of patients with and without pancreatic infection

	Non-pancreatic infection (n = 69)	Pancreatic infection (n = 50)	P value
Gender, n (%)			0.924
Male	27 (39.1)	20 (40)	
Female	42 (60.9)	30 (60)	
Age, years (mean $\pm$ SD)	53.5 $\pm$ 18.5	55 $\pm$ 16	0.651
Etiology of pancreatitis n (%)			
Biliary disease	32(46.3)	28(56)	0.163
Dyslipidemia	4 (5.9)	9 (18)	<b>0.035</b>
Unknown	33(47.8)	13(26)	
Diet length, hours (mean $\pm$ SD)	55,36 $\pm$ 45,1	72,53 $\pm$ 42,03	<b>0,044</b>
Severity (mean $\pm$ SD)			
Ranson's score	2,29 $\pm$ 1,28	3,4 $\pm$ 1,47	<b>&lt;0.001</b>
CTSI	4,34 $\pm$ 1,40	6,26 $\pm$ 1,92	<b>&lt;0.001</b>
Hospital stay, days (mean $\pm$ SD)	15 $\pm$ 7	39 $\pm$ 28	<b>&lt; 0.001</b>
Mortality, n (%)	3(4.34)	21(42)	<b>&lt; 0.001</b>

**Table 2:** Comparison of biochemical parameters between patients with and without pancreatic infection

	Pancreatic (n = 50)	infectionNon-pancreatic infection (n = 69)	P value
Glycaemia(mmol/L)	11,72 ± 5,11	9,06 ± 5,47	<b>0.019</b>
BUN (mmol/L)	7,16±3,15	6,82±8,03	0.801
Serum creatinine (µmol/L)	101,55±52,59	108,75±142,70	0.765
ASAT (U/L)	134,31±131,88	129,82±182,66	0.894
ALAT (U/L)	159,97±202,30	128,50±176,89	0.408
Total bilirubin (µmol/L)	32,76±18,71	29,28±22,54	0.457
Directbilirubin (µmol/L)	11,31±10,04	9,61±11,25	0.476
CRP (mg/L)	125,08±126,95	79,53± 96,99	<b>0.046</b>
LDH (U/L)	1095,14±726,29	797,61±447,89	<b>0.024</b>
Hemoglobin (g/dL)	14,53±2,49	13,33± 2,24	<b>0.013</b>
Hematocrit (%)	44,08±7,25	40,37±6,01	<b>0.006</b>
WBC (× 109/L)	16.89±4.24	14.10±5.14	<b>0.005</b>
Arterial blood pH	7,459± 0,058	7,434± 0,056	0.056
PaO2 (mmHg)	87,46±23,52	98,87±56,97	0.292
PaCO2 (mmHg)	30,27±6,64	34,54±6,55	<b>0.006</b>
HCO3(mmol/L)	22,41±4,73	23,77±4,51	0.2

**Table 3:** CTSI of Mortelet

Pancreatic inflammation		Pancreatic necrosis	
Normal pancreas	<b>0 point</b>	None	<b>0 point</b>
intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat	<b>2 points</b>	Necrosis <30%	<b>2 points</b>
pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis	<b>4 points</b>	Necrosis >30%	<b>4 points</b>
<b>Extrapancreatic complications</b> one or more of pleural effusion, ascites, vascular complications, parenchymal complications and or gastrointestinal involvement			<b>2 points</b>

## Discussion

### Obesity

Two studies with respectively 149 and 27 patients, found an increased incidence of systemic complications without increasing local complications in obese patients [3,4].

Funnell et al. published a study that showed that obese patients are at higher risk of pancreatic necrosis, sepsis, systemic complications and death. The incidence of local complications, especially infection of pancreatic necrosis, was significantly higher in obese patients, with a similar trend for overweight people. This suggests that a greater amount of retroperitoneal fat may be a factor in necrosis and secondary infection with abscess formation [5,6].

Our study confirms that obesity is a risk factor for the extension of necrosis, such as an Odd-Ratio = 1.33 and for the infection of pancreatic necrosis with a Relative Risk = 3.

### LDH

The serum level of LDH was significantly higher in cases of severe acute pancreatitis. It is considered a good marker for pancreatic necrosis [7]. In addition, it is often associated with a variety of secondary complications of severe acute pancreatitis and is considered to be a prognostic factor [8]. Therefore, serum LDH was included as component of several severity scores including the score of Ranson [9]. Ogawa et al. found that 38% of patients with severe acute pancreatitis have LDH levels  $\geq 700$  U / L. The mortality of these patients was 30% at 24-48 hours after start of pancreatitis [10]. Rau et al. compared the serum levels of LDH, human pancreatic specific protein (HPSP) and procarboxypeptidase B (PCPB) in 70 patients with acute pancreatitis; they concluded that the day 5 LDH assay thrust provides the best discrimination between edematous pancreatitis and necrotizing acute pancreatitis [11]. ZENG and ZHAN et al. found that the serum levels of LDH was significantly higher in the group of patients infected than in the group of non-infected patients. They showed that the LDH was an independent risk factor for pancreatic necrosis infection.

Therefore, monitoring of LDH levels in the patients with acute necrotizing pancreatitis can reliably predict pancreatic necrosis infection [12]. In our study, univariate analysis found a significant difference between the 2 groups but not multivariate analysis shows that the serum levels of LDH is an independent predictor.

### CRP

CRP is considered a good predictor for the presence of necrosis in the acute pancreatitis [13,14]. The literature is conflicting evidence regarding its predictive value of pancreatic necrosis infection. In fact, two studies have shown that the levels of CRP are associated with the development of secondary necrosis infection in ANP, this has been demonstrated by univariate and multivariate regression analysis. They concluded that CRP can be used as a marker of differentiation between sterile necrosis and infected necrosis in ANP [15,16]. Dambrauskas et al. and Iler et al. found no significant difference between the patients infected and uninfected, by measuring CRP during the early phase of the disease [13,17]. In our study, the difference was significant between the two groups in the univariate regression analysis. While, the multivariate analysis did not show that CRP was an independent predictor of pancreatic necrosis infection.

### WBC

The rate of white blood cells is one of the parameters component score of Ranson. In our study, infected patients had a significantly greater leukocytosis than non-infected during the first 48 hours of the thrust. However, ZHAN and ZENG et al. found in their study that the rate of white blood cells was significantly lower in the group of infected patients than in the group of non-infected patients [12].

### HEMATOCRIT

The systemic inflammatory response syndrome during acute pancreatitis is accompanied by an increase in the permeability of the vascular wall and liquid passage from plasma sector into the interstitial sector. This is the cause of impaired pancreatic microcirculation induced by the

hemoconcentration. This hemoconcentration has been the subject of numerous clinical studies to assess the severity of acute pancreatitis from 1960<sup>[18]</sup>. The results are contradictory. Some authors found that increased hematocrit at admission is a predictor of severe pancreatitis<sup>[19,20]</sup>. However, others have found no significant differences in hematocrit at admission between patients with severe acute pancreatitis and those with moderate acute pancreatitis<sup>[21]</sup>. It was also studied whether undiminished hematocrit during the first 24 hours of hospitalization could be used as a prognostic marker for the development of severe acute pancreatitis, but again this has not been confirmed<sup>[19,22]</sup>. In our study, hematocrit was significantly higher in infected patients.

### GLYCEAMIA

In general, patients with type 2 diabetes have a higher risk to develop acute pancreatitis. This risk is estimated at 2.83<sup>[23-25]</sup>. Hyperglycemia is common in early acute pancreatitis, it is used in prognostic models<sup>[26,27]</sup>. Hyperglycemia in the early phase of acute pancreatitis appears to be complex; it may be due to different mechanisms such as uncontrolled diabetes or pre-existing lesions of endocrine pancreas during the severe acute pancreatitis<sup>[28]</sup>. In our study, hyperglycemia at admission was significantly correlated to the development of infection of pancreatic necrosis. It is important in the management of acute pancreatitis, to ensure an optimal balance of blood sugar levels.

### ARTERIAL BLOOD GAS (ABG)

Approximately 30-50% of patients with severe acute pancreatitis (SAP) develop hypoxia or acute respiratory distress syndrome (ARDS), which are the main causes of death at the beginning of the SAP<sup>[29,30]</sup>. Autopsy results confirm that pulmonary complications were among the most common causes of death during the first week of disease progression<sup>[31]</sup>. Hypoxia is associated with multiple organ failure and high mortality<sup>[32-34]</sup>. In one study<sup>[35]</sup> Interestingly 166 patients with SAP, the authors concluded that approximately one third of patients had one or more pulmonary

complications such as pleural effusion, atelectasis, hemothorax or ARDS. In this study, hypoxia appears as an independent risk factor for death. The occurrence of secondary complications of SAP does not seem to be directly linked to lung damage but rather to hypoxia and development of ARDS. In the study of ZENG and ZHAN<sup>[12]</sup>, a low PaO<sub>2</sub> was an independent risk factor for pancreatic necrosis infection in patients with SAP. In our study, we did not find a significant difference for the PaO<sub>2</sub> between the 2 groups.

Regarding the value of PaCO<sub>2</sub>, our results are consistent with that of ZENG and ZHAN that show a significantly lower PaCO<sub>2</sub> in infected patients, without being an independent risk factor in the multivariate analysis.<sup>[12]</sup>

### RANSON'S SCORE

Ranson's score is validated in assessing the severity of acute pancreatitis but on the predictive value for the development of infection of pancreatic necrosis, the literature data are contradictory. Rau et al. and Rich et al. published two prospective studies<sup>[14,15]</sup>. They found a significant difference between infected patients and non-infected patients, which is consistent with our results. However, in two other retrospective studies the difference was not significant between the two groups<sup>[12,36]</sup>.

### CTSI

Several studies confirm the results of our study show that the CT severity index (CTSI) is an independent predictor of pancreatic necrosis infection<sup>[12,13]</sup>. There is a good correlation between the CTSI and morbidity and mortality rates in the SAP<sup>[37-40]</sup>.

The classification of Balthazar present drawbacks:

- It does not include the immediate complications of AP.
- A significant inter-observer variance
- A difficulty in evaluating of the number of streams
- A difficulty in evaluation of the percentage of pancreatic necrosis especially between 30 and 50% of the parenchyma.

Mortele<sup>[41]</sup> published a new classification (Table 3) trying to overcome the shortcomings of the classification of Balthazar. This classification:

- take into account the immediate complications of AP.
- A low inter-observer variance
- Assessment of the number of streams is less complex.
- The evaluation of the percentage of necrosis is easier practice not as difference in patients necrosis between 30 and 50% and those with necrosis > or = 50%.

But the correlation between the CTSI of Mortele and morbidity and mortality is not yet established.

Enteral feeding:

The intestine is the immune organ providing a first barrier against foreign antigens and microbes. Previous studies have reported that the immune response of the intestine has been strongly associated with enteral nutrition. The lack of enteral stimulation could induce immune-suppression<sup>[42,43]</sup>. Further, enteral nutrition, especially early, modulates the inflammatory response and maintain the integrity of the gut by the release of the immunomodulatory agents and an increase in antioxidant activity<sup>[44,45]</sup>. Early enteral nutrition reduces the rate of infection of pancreatic necrosis. This was confirmed by the results of several studies including ours.

In a comparative study<sup>[46]</sup> it was found that patients in group "early enteral nutrition" had a significantly lower incidence of multiple organ failure, pancreatic necrosis infection and a shorter stay in intensive care. However, enteral nutrition did not influence the incidence of surgery or mortality.

Another recently published study<sup>[47]</sup> showed that the delayed enteral nutrition is associated with an increase incidence of infection of pancreatic necrosis. From these findings, we can assume that enteral nutrition should be started within the first 48 hours of hospitalization for acute pancreatitis.

## Conclusion

many variables were initially identify by univariate analysis as predicting factors of necrosis infection but only high CTSI was independent risk factor

Among the factors identified, some can direct management:

- Adequate hydration to fight against hemoconcentration.
- A good glycemetic control.
- Fight against hypocapnia.
- An oral feeding as early as possible.

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