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Risk Factors for Acute Fulminant Pancreatitis in Patients Admitted to the Intensive Care Unit: A Retrospective Study

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ABSTRACT

Background/Objectives The term acute fulminant pancreatitis (AFP) has been proposed to define the most severely ill patients and those who are likely to die before they develop persistent organ failure. The objective of our study was to determine the risk factors for developing AFP in patients admitted to the intensive care unit (ICU). **Methods** This was a retrospective study conducted between January 2007 and May 2019 in a ICU. Patients ≥18 years old admitted to the ICU within 3 days of the onset of abdominal pain related to acute pancreatitis were included. We defined AFP according to the modified Marshall scoring system for organ dysfunction based on a score ≥ 2 involving at least 2 organ systems for at least 48 hours or ≤ 48 hours if the patient died during the first 7 days of hospitalization. **Results** Sixty-three patients were analyzed (AFP group, n=27 - non-AFP group, n=36). In multivariate analysis, AFP was associated with a lower level of fluid loading before ICU admission (OR [95%CI] = 0.89 [0.82; 0.97], p<0.001) and a higher modified Marshall score (OR [95%CI] = 2.31 [1.53; 3.49], p<0.001). On day 7, mortality was higher in the AFP group (48% *vs*. 3%, p<0.001), and 29% of patients with AFP died within 48 hours of admission to the ICU before developing persistent organ failure. **Conclusions** A lower level of fluid resuscitation prior to admission to the ICU and a higher modified Marshall score on ICU admission were independently associated with higher risks of developing AFP.

INTRODUCTION

Despite improvements in treatments, the mortality rate due to severe acute pancreatitis (AP) remains high, ranging from 15 to 20% [1]. In the early phase of the disease, mortality is generally due to a cytokine storm and a systemic inflammatory reaction, while later mortality is caused by sepsis related to infected pancreatic necrosis, although both causes lead to various degrees of organ failure [1].

In 2012, the Atlanta classification was revised, and the severity of AP was classified as mild, moderate or severe according to the presence or absence of local and/or systemic complications [2]. Since the revision of the Atlanta Classification in 2012, two other classification systems have been proposed as better means of characterizing the severity of acute pancreatitis: the determinant-based classification [3] and its subsequent modification [4]. Nevertheless, these classification systems do not identify a critical form of AP that leads to multiple organ failure during the early phase of the disease, which is referred to as "acute fulminant pancreatitis" (AFP) [5-7]. The concept of AFP is controversial with regard to the most recent classification of AP, particularly with respect to the definition of organ failure and the recommended management strategy [3,8]. Nevertheless, it is indisputable that patients die before meeting the criteria for severe AP, as defined in the latest recommendations [2]. AFP thus appears to be a unique entity characterized by a high mortality rate of 42 to 90% [5-7] that has been inadequately investigated [11,12]. Nevertheless, the identification of patients at risk for AFP may lead to their earlier admission to the intensive care unit (ICU) and/or a more accurate assessment of disease severity on admission to the ICU.

The objective of this study was to determine the factors predictive of AFP in patients admitted to ICU based on the recent definitions of organ failure.

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Methods

This was a retrospective monocentric study conducted in a surgical ICU of a university hospital. We included all adult patients admitted with a diagnosis of AP between January 2007 and May 2019. The study was approved by the Rennes Academic Hospital ethics committee (N°35RC18_30011_PAF) and "Commission Nationale de l'Informatique et des Libertés" (CNIL, N°2205295). All living patients received written information, and consent to participate was obtained.

A request was made to the medical informatics department to identify all the patients with a diagnosis of pancreatitis who had been admitted to the ICU. We reviewed all medical records, and adult patients ≥18 years old who were admitted to the ICU within 3 days of the onset of abdominal pain related to AP were eligible. Pregnant women, patients under legal protection and those who refused to participate were excluded from the analysis. The diagnosis of AP was established according to the international recommendations based on the presence of at least two of the following: abdominal pain, serum lipase level at least 3 times the upper limit of normal and/or characteristic findings on imaging studies (contrast-enhanced computed tomography of the abdomen or abdominal ultrasonography) [2].

The primary objective was the identification of the risk factors for AFP. The secondary objectives were to evaluate the impact of AFP on the duration of mechanical ventilation, ICU length of stay, hospital length of stay and mortality, and the prognosis value of the modified Marshall score for organ dysfunction for AP and the SOFA score at admission in ICU. AFP was defined by a score ≥ 2 involving at least 2 of the 3 organ systems (respiratory, cardiovascular and/or renal) according to the modified Marshall scoring system for organ dysfunction during the first 7 days of hospitalization [2]. Organ failure had to be present for > 48 hours or ≤ 48 h if the patient died. Patients who had AFP were compared to other patients admitted to the ICU for AP who did not meet the criteria for AFP.

We recorded age, sex, body mass index (BMI) and medical history. Cardiovascular risk factors included arterial hypertension, diabetes, dyslipidemia and/or tobacco addiction. Chronic cardiac disease was a composite criterion including congestive heart failure, chronic ischemic heart disease, and/or atrial fibrillation. Chronic respiratory disease included chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease (GOLD) of at least stage 2 and sleep apnea. Chronic renal failure was defined as an estimated glomerular filtration rate less than 60 ml/min.1.73 m^{-1}.

We recorded the delay between the onset of symptoms and hospitalization, the delay between symptom onset and ICU admission and the delay between admission to the hospital and ICU admission. The cause of AP was reported (gallstones, alcohol, postoperative, hypertriglyceridemia, drugs, post-endoscopic retrograde cholangiopancreatography or unknown).

On admission to the hospital, we notified the presence of systemic inflammatory response syndrome (SIRS). The presence of at least two of the following criteria defined SIRS: fever >38.0°C or hypothermia <36.0°C, tachycardia >90 beats/minute, tachypnea >20 breaths/minute, leukocytosis >12.10^9/l or leukopenia <4.10^9/l. We recorded the serum lipase, blood urea, serum creatinine, and hematocrit values. The Bedside Index for Severity in Acute Pancreatitis (BISAP) score was calculated.

Between admission to the hospital and admission to the ICU, the variations in blood urea and hematocrit levels were recorded as increased (difference > 0) or equal or decreased (difference ≤ 0), and we reported the fluid loading (ml/kg.h-^{1} crystalloids) received by the patients before ICU admission.

On admission to the ICU, severity was assessed by the BISAP score, the sequential organ failure assessment (SOFA) score [13], the modified Marshall scoring system for organ dysfunction for AP and the related number of organ failures (defined as a score ≥ 2 in the respiratory, cardiovascular and renal systems) [2]. We reported the presence of acute renal failure defined as stage ≥ 1 according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [14]. We calculated the APACHE II score with the worst physiological variables recorded during the first 24 h of hospitalization in the ICU [15].

Over the first 7 days of ICU hospitalization or until discharge or death, we recorded the need for and duration of mechanical ventilation, the occurrence of acute respiratory distress according to the Berlin definition, and the worst PaO_2/FiO_2 value [16]. We reported vasopressor use and dose, the need for renal replacement therapy, the occurrence of abdominal compartmental syndrome, and need for laparostomy or more radical surgery. We reported the fluid loading (ml/kg.h-^{1}) the patient received in the ICU over the first 3 days of ICU hospitalization or until discharge or death. ICU length of stay, hospital length of stay and mortality at seven days, 28 days and one year were reported.

Statistical analysis

Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). The continuous and categorical variables are expressed as the means ± SDs or medians (interquartile ranges [IQRs]) and numbers (percentages). For group comparisons, Student's tests and the Mann-Whitney test, if necessary, were used to compare quantitative variables. Chi^2 tests and Fisher's exact tests, if necessary, were used to compare qualitative variables. The risk factors for developing AFP were determined using a logistic regression model. Clinically relevant variables and those identified by univariate analysis with p ≤ 0.20 were

included in a multivariate model, and backward selection was applied. A Hosmer-Lemeshow test was used to test the calibration of the model. The results of the final model are reported as the crude odds ratio (OR) and 95% confidence interval (95% CI). A value of p <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were used to determine the likelihood ratios for the abilities of the modified Marshall score for organ dysfunction and SOFA score to predict mortality at admission. Sensitivity, specificity and positive- and negative predictive values were calculated for the different cut-off points. The Youden's J statistic was calculated to assess the optimal cut-off point for the two scores. Survival was compared using the log-rank test, and Kaplan-Meier survival curves were constructed according to the optimal cut-off.

RESULTS

During the study period, 296 patients were admitted with a diagnosis of AP. Sixty-three patients were analyzed (AFP group, n=27 and non-AFP group, n=36) **(Figure 1).** The median time between the onset of abdominal pain and admission to the ICU did not differ between the two groups (AFP group = 62 hours [IQR: 52-70] and non-AFP group = 59 hours [IQR: [49-67], p=0.170). The median time between admission to the hospital and admission to the ICU did not differ between the two groups (AFP group = 48 hours [IQR: 48-64] and non-AFP group = 48 hours [IQR: [24-51], p=0.129). The median time between the onset of abdominal pain and admission to the hospital did not differ between the two groups (AFP group = 6 hours [IQR: 4-12] and non-AFP group = 6 hours [IQR: 2-18], p=0.961).

The results of the univariate analysis are provided in **Table 1.** We selected the following covariates in the logistic regression model: age, sex, BMI, chronic respiratory insufficiency, alcohol use as the etiology of AP, SIRS at admission to the hospital, an increase in the blood urea nitrogen level after admission to the hospital and fluid loading. Moreover, on admission to the ICU, the presence of acute renal failure, the BISAP score, the modified Marshall scoring system and the number of organ failures were also included. In multivariate analysis, the risk of developing AFP in the ICU was associated with fluid loading before ICU admission (OR [95% CI] = 0.89 [0.82; 0.97], p<0.001) and the modified Marshall score (OR [95% CI] = 2.31 [1.53; 3.49], p<0.001).

During the first 7 days of hospitalization in the ICU, AFP patients received significantly more mechanical ventilation, norepinephrine and renal replacement therapy and were significantly more likely to experience ARDS **(Table 2).** The ROC curves for the modified Marshall score and SOFA score predicting mortality on ICU admission are displayed in **Figure 2** and the area under the curve did not significantly differ between the 2 scores (0.819 *vs.* 0.802, p=0.321). The best cut-off for the modified Marshall score and SOFA score to predict survival were ≤ 5 and ≤ 7, respectively and the sensitivity, specificity, positive and negative predictive values are reported in **Table 2.**

During hospitalization in the ICU, the duration of mechanical ventilation was significantly longer in the AFP group **(Table 3).** ICU length of stay and hospital length of stay did not differ between the two groups (6 [2-38] *vs.* 6 days [4-15], p=0.770 and 21 [4-52] *vs.* 20 days [14-42], p=0.266, respectively). The mortality at day 7 was significantly higher in the AFP group (48% *vs.* 3%, p<0.001), and was the same at day 28. At one year, mortality was significantly higher in the AFP group (63% *vs.* 8%, p<0.001, respectively). Only one patient died in the first week in the non-AFP group due to extensive digestive tract ischemia. **Figure 3** shows the survival probability according to AFP status.

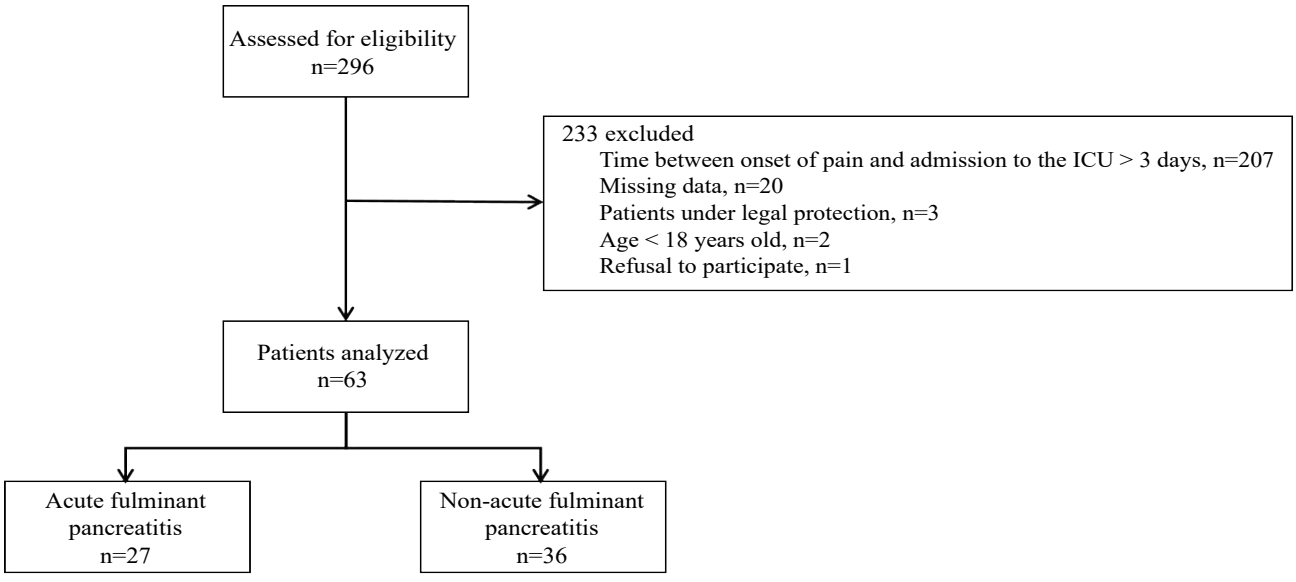

Figure 1. Flow chart.

Table 1. Characteristics at baseline, hospital admission and intensive care unit admission.

	Total n=63	Acute fulminant pancreatitis n=27	Nonacute fulminant acute pancreatitis n=36	p
Age, y	59 [44-70]	62 [53-70]	57 [43-71]	0.158
Male sex	52 (83%)	20 (74%)	32 (89%)	0.182
BMI, kg.m^{-2}	28.08 ± 4.34	29.24 ± 4.92	27.18 ± 3.65	0.064
Cardiovascular risk factors[a]	27 (43%)	13 (48%)	14 (39%)	0.462
Cardiovascular disease[b]	8 (13%)	5 (19%)	3 (8%)	0.272
Cancer	5 (8%)	3 (11%)	2 (6%)	0.643
Chronic respiratory insufficiency	4 (6%)	4 (15%)	0 (-)	0.030
Chronic renal insufficiency	2 (3%)	1 (4%)	1 (3%)	1.000
Cause of acute pancreatitis				
Alcohol	24 (38%)	7 (26%)	17 (47%)	0.085
Gallstone	18 (28%)	9 (34%)	9 (25%)	0.469
ERCP[c]	5 (8%)	2 (7%)	3 (8%)	1.000
Drugs	3 (5%)	2 (7%)	1 (3%)	0.572
Postoperative	2 (3%)	2 (7%)	0 (-)	0.180
Hypertriglyceridemia	1 (2%)	0 (-)	1 (3%)	1.000
Unknown	10 (16%)	5 (19%)	5 (14%)	0.733
At hospital admission				
SIRS[d]	25 (40%)	7 (26%)	18 (50%)	0.053
Lipasemia,	2028 [1116-7656]	2235 [1369-8736]	1857 [992-5314]	0.402
Blood urea nitrogen, mmol.l^{-1}	6.5 [5.2-8.5]	7.0 [5.5-9.2]	5.9 [4.7-8.2]	0.344
Creatinine, µmol.l^{-1}	81 [69-110]	81 [70-104]	82 [67-115]	0.866
Hematocrit, %	47 [44-51]	48 [44-51]	47 [44-51]	0.705
BISAP[e] score	1 [0-2]	1 |1-2]	1 [0-2]	0.535
Between hospital and ICU[f] admission				
Blood urea nitrogen increase, yes	38 (60%)	22 (82%)	16 (44%)	0.003
Hematocrit increase, yes	26 (41%)	12 (44%)	14 (39%)	0.658
Fluid loading, ml/kg.h^{-1}	0.8 [0.4-1.2]	0.7 [0.3-1.0]	0.9 [0.6-1.4]	0.028
At ICU admission				
At ICU[f] admission				
BISAP score[e]	3.0 [2.0-4.0]	4.0 [2.5-4.0]	2.0 [1.0-3.0]	0.001
SOFA score[g]	4 [2-8]	8 [7-12]	2 [1-3]	<0.001
Modified Marshall score	3 [2-7]	7 [5-10]	2 [1-3]	<0.001
Organ failure[h], n				
0	7 (11%)	0 (-)	7 (19%)	
1	22 (35%)	3 (11%)	19 (53%)	<0.001
2	14 (22%)	6 (22%)	8 (22%)	
3	20 (32%)	18 (67%)	2 (6%)	
Acute renal failure[i]	41 (65%)	23 (85%)	18 (50%)	0.004

Data are expressed as the means (SD) or medians [IQR 25-75] and numbers (percentages). [a]Cardiovascular risk factors included arterial hypertension, diabetes, dyslipidemia and tobacco addiction. [b]Chronic cardiac disease included congestive heart failure, chronic ischemic heart disease, and atrial fibrillation. [c]ERCP: endoscopic retrograde cholangiopancreatography. [d]SIRS: systemic inflammatory response syndrome. [e]BISAP: Bedside Index for Severity in Acute Pancreatitis. [f]ICU: intensive care unit. [g]SOFA: Sequential Organ Failure Assessment. [h]Organ failure was defined as a score ≥ 2 involving at least one of the 3 organ systems (respiratory, cardiovascular and renal) according to the modified Marshall scoring system for organ dysfunction. [i]Acute renal failure defined as stage ≥ 1 according to the Kidney Disease Improving Global Outcomes guidelines.

Table 2. Severity and treatment in the ICU.

	Total n=63	Acute fulminant pancreatitis n=27	Nonacute fulminant acute pancreatitis n=36	p
APACHE II[a]	16 ± 8	22 ± 7	12 ± 6	<0.001
Mechanical ventilation	39 (62%)	27 (100%)	12 (33%)	<0.001
Duration of mechanical ventilation, days	11 [2-28]	6 [2-28]	14 [7-30]	0.265
ARDS[b]	39 (62%)	24 (89%)	15 (42%)	<0.001
ARDS severity	39 (0)	24 (0)	15 (0)	
Mild	4 (10%)	3 (13%)	1 (7%)	0.025
Moderate	18 (46%)	7 (29%)	11 (73%)	
Severe	17 (44%)	14 (58%)	3 (20%)	
Worst PaO2/FiO2	115 [84-184]	99 [75-149]	141 [111-193]	0.056
Vasopressor use	29 (46%)	25 (93%)	4 (11%)	<0.001
Dose of vasopressors, µg/kg.min^{-1}	0.32 [0.29-0.90]	0.40 [0.30-1.01]	0.28 [0.21-0.35]	0.106
RRT[c]	12 (19%)	11 (41%)	1 (3%)	<0.001
Abdominal compartmental syndrome	17 (27%)	11 (41%)	6 (17%)	0.033
Laparostomy/necrosectomy	5 (8%)	5 (19%)	0 (-)	0.011
Surgical treatment	12 (19%)	12 (44%)	0 (-)	<0.001
Fluid loading[d]**, ml/kg.h^{-1}**	1.1 [0.7-1.9]	1.6 [1.0-2.4]	0.8 [0.5-1.6]	<0.001

Data are expressed as the means (SDs) or medians [IQR 25-75] and numbers (percentages). [a]APACHE II: Acute Physiology And Chronic Health Evaluation II. [b]ARDS: acute respiratory distress syndrome, [c]renal replacement therapy. [d]The first 3 days of ICU hospitalization

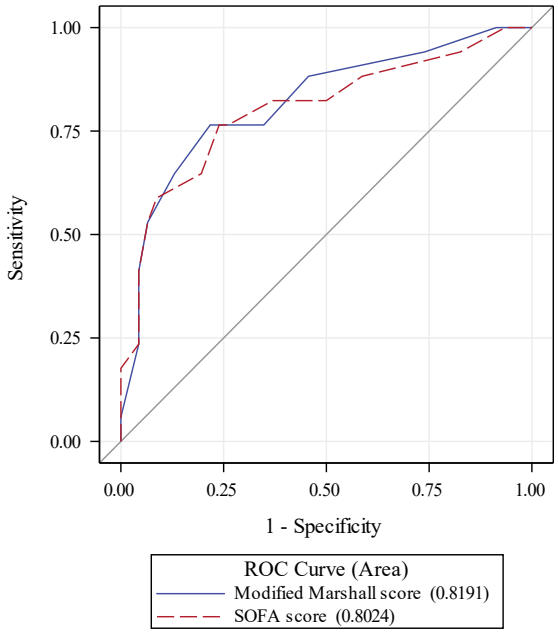

Figure 2. Receiver operating characteristic curves with the modified Marshall score for organ dysfunction and SOFA score predicting hospital mortality.

Table 3. Sensitivity, specificity, positive and negative predictive values for the modified Marshall score for organ dysfunction and SOFA score to predict Mortality. [95% Confidence Interval].

	Sensitivity (%)	Specificity (%)	Positive predictive values (%)	Negative predictive values (%)
Modified Marshall score ≥ 5	76.5 [56.3; 96.6]	78.3 [66.3; 90.2]	56.5 [36.3; 76.8]	90.0 [80.7; 99.3]
SOFA score ≥ 7	76.5 [56.3; 96.6]	76.1 [63.8; 88.4]	54.2 [34.2; 74.1]	89.7 [80.2; 99.3]

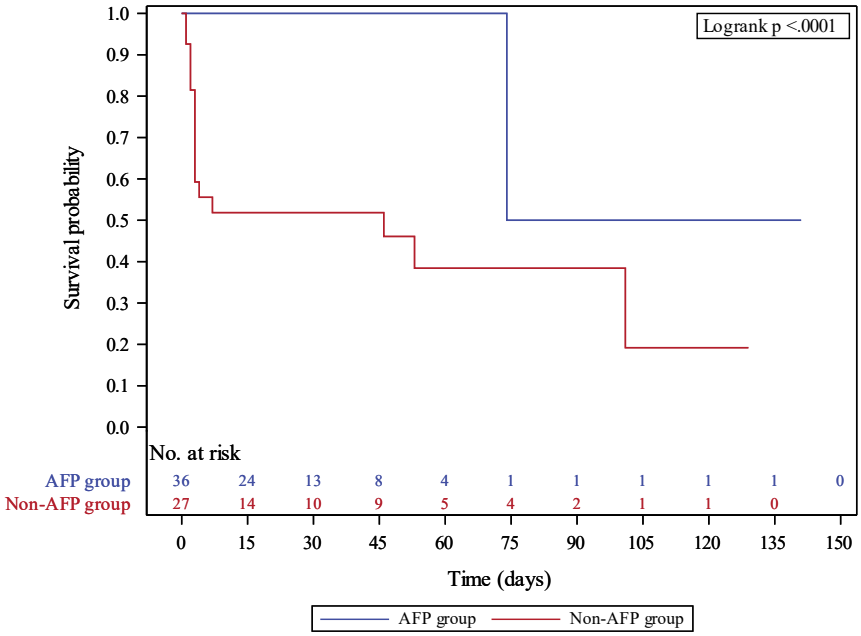

Figure 3. Survival probability according to AFP status.

DISCUSSION

The identification of risk factors for progression to the most severe form of pancreatitis would make it possible to refer patients to the ICU at an early stage and to better assess the severity of the disease at ICU admission, facilitating the rapid implementation of therapies aimed at reducing further organ failure. We found that a lower level of fluid loading prior to admission to the ICU and a higher modified Marshall score on admission to the ICU were independently associated with a higher risk of developing AFP in the ICU.

The rationale behind vascular filling in patients with AP is to slow the progression to pancreatic necrosis promoted by the intensity of the systemic inflammatory response, leading to an increase in vascular permeability, interstitial fluid extravasation, and impairment of the pancreatic microcirculation [17]. However, the optimal strategy regarding fluid resuscitation (timing, amount, infusion rate, type of fluid) is debated due to the lack of methodologically robust studies [17]. The American College of Gastroenterology recommended the administration of 250 to 500 ml/h over the first 12 to 24 hours of hospitalization [18], but such a strategy may be potentially deleterious for patients with the most severe pancreatitis or futile after 24 hours of hospitalization [17,19]. Instead of an arbitrary fluid-loading strategy, a goal-directed fluid-loading strategy guided by hemodynamic or biological parameters has been proposed. In a retrospective study of 3 prospective cohorts, a hematocrit ≥ 44% at admission and an increase in blood urea nitrogen at 24 hours were significantly associated with an increased risk of organ failure and pancreatic necrosis [20]. A prospective randomized study compared two early vascular filling protocols (20 ml/kg bolus + 3 ml/kg.h^{-1} *vs.* 10 ml/kg bolus + 1.5 ml/kg.h^{-1}) [21]. Aggressive vascular filling supplemented with adjustments at 12 h intervals based on hematocrit and blood urea nitrogen variations improved the clinical situation at 36 hours and was associated with reduced likelihood of developing SIRS [21]. We found that a lower level of fluid resuscitation before ICU admission was associated with an increased risk of developing AFP. At admission to the hospital, the presence of SIRS; the levels of hematocrit, blood urea nitrogen, creatinine; and BISAP scores did not differ between the two groups, but patients who subsequently experienced AFP had a significant increase in blood urea nitrogen before ICU admission. It may be hypothesized that these patients did not receive adequate fluid resuscitation, favoring the development of AFP. Our study does not make it possible to determine whether the administration of fluid resuscitation was performed soon after hospital admission or was distributed more evenly between hospital admission and ICU admission. Nevertheless, the median time from hospital admission to ICU admission was short, promoting early aggressive administration of intravenous fluid, although the level of fluid loading in the non-AFP group was relatively low in comparison with the current recommendations [17].

The modified Marshall scoring system yields an instantaneous score, similar to the SOFA scoring system, but is limited to 3 organ systems (respiratory, cardiovascular and renal) and does not take into account the use of vasopressors and mechanical ventilation, allowing it to be calculated before admission to the ICU [2]. It is a reliable tool for the prediction of mortality in both the early and late phases of disease [22,23]. In our study, the modified Marshall score at admission to the ICU was independently associated with the risk of developing AFP. We chose to enter only this score and not the SOFA score into the logistic regression model because it is easier to use than the SOFA score and better reflects the clinical situation of patients at the time of admission to the ICU before mechanical ventilation has been established and vasopressors have been administered.

Our data show that the majority (13/27) of patients with AFP died within the first week of hospitalization, including 7 (26%) within 48 hours of admission to the ICU, before they had developed persistent organ failure. Only 4 patients died after day 28, with an overall mortality of 63% (17/27). These data are consistent with those in the literature for the most serious form of AP, which has been reported to have a mortality rate between 42 and 90% [5-7]. These data support the concept of AFP as a unique entity, as suggested previously, and suggest the need for a more precise definition to better characterize this population [5-7, 9-12]. We believe that our study makes it possible to more precisely identify these patients based on a validated definition of organ failure but with a greater weight on the initial intensity of disease.

Our study has several limitations that need to be pointed out. It was a retrospective study with recruitment over a long observation period of more than 10 years. During this period, recommendations for the management of AP and organ replacement therapies evolved. Finally, considering the long study period, relatively few patients were analyzed. This is due to the strict criterion for admission to intensive care within 3 days of the onset of pain, but this small number of patients could lead to the lack of statistical power. However, despite these limitations, our results remained robust based on the narrow confidence intervals. We did not have abdominal CT scan data that would allow us to better classify disease severity. However, early initial imaging does not predetermine the subsequent course of AP [2]. As our study was performed to evaluate risk factors for developing AFP before and at admission in the ICU, we did not report these data.

CONCLUSION

We identified that a lower level of fluid loading prior to admission to the ICU and a higher modified Marshall score on admission to the ICU were associated with a higher risk of developing AFP in the ICU. This particular form of AP deserves to be recognized as a unique entity to facilitate the better characterization and management of this population.

Conflict of interest

There is no conflict of interest.

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