Determinants of Severity in Acute Pancreatitis

A Nation-wide Multicenter Prospective Cohort Study

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Objective: The aim of this study was to compare and validate the different classifications of severity in acute pancreatitis (AP) and to investigate which characteristics of the disease are associated with worse outcomes.

Summary of Background Data: AP is a heterogeneous disease, ranging from uneventful cases to patients with considerable morbidity and high mortality rates. Severity classifications based on legitimate determinants of severity are important to correctly describe the course of disease.

Methods: A prospective multicenter cohort study involving patients with AP from 23 hospitals in Spain. The Atlanta Classification (AC), Revised Atlanta Classification (RAC), and Determinant-based Classification (DBC) were compared. Binary logistic multivariate analysis was performed to investigate independent determinants of severity.

Results: A total of 1655 patients were included; 70 patients (4.2%) died. RAC and DBC were equally superior to AC for describing the clinical course of AP. Although any kind of organ failure was associated with increased morbidity and mortality, persistent organ failure (POF) was the most significant determinant of severity. All local complications were associated with worse outcomes. Infected pancreatic necrosis correlated with high morbidity, but in the presence of POF, it was not associated to higher mortality when compared with sterile necrotizing pancreatitis. Exacerbation of previous comorbidity was associated with increased morbidity and mortality.

Conclusion: The RAC and DBC both signify an advance in the description and differentiation of AP patients. Herein, we describe the complications of the disease independently associated to morbidity and mortality. Our findings are valuable not only when designing future studies on AP but also for the improvement of current classifications.

Keywords: acute pancreatitis, Atlanta classification, determinant-based classification, follow-up study, infection, local complications, morbidity, mortality, necrosis, organ failure, revised Atlanta classification, revision of the Atlanta classification, severity

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The incidence of acute pancreatitis (AP) is rising globally, implying a significant burden on health care systems.[1,2] Although approximately two-thirds of the AP patients have an uneventful course of disease, the remainder third suffer considerable morbidity and an increased risk of death.[3] Given this heterogeneity, a solid severity classification is needed to identify different subsets of patients. An appropriate stratification method demands unified definitions and terminologies to obtain good internal and external validity. Several attempts have emerged[4–7], but it was not until the International Symposium in Atlanta 1992 that a system was widely adopted.[8] The Atlanta classification (AC) provided descriptive terms for local and systemic complications as well as a dichotomous stratification into mild and severe disease. However, after 20 years, substantial progress has been made in the understanding of pathophysiological pathways, disease-related complications, imaging, and treatment of AP.[9–14] Thus, in 2012, 2 new classifications were introduced: The Revision of the Atlanta Classification (RAC) and the Determinant-Based Classification (DBC).[15,16] The RAC provides definitions for diagnostic criteria for AP, local complications (including detailed radiological definitions), systemic complications, the description of an early and late phase, and a 3-category severity classification.[15]

The DBC was based on factors that are causally associated with severity of AP, that is, local and systemic ''determinants.''[16] The DBC provides a 4-category severity classification.

The severity categories of the AC, the RAC, and the DBC are outlined in Table 1. Since their publication, the latter 2 classifications have been studied in various settings. Most studies were purely retrospective or retrospective analysis of prospective databases as well as a majority of these works analyzed results from just 1 or 2 centers.[3,17–30] The only purely prospective multicenter study was focused solely on patients admitted to the intensive care unit (ICU), thus involving only severe cases.[31] Furthermore, most of the above-mentioned studies came from referral centers. These properties compromise the external validity of available data regarding the assessment of the severity classifications on AP. Some assumptions or discrepancies of the new classifications needed external validation, for example, the role of acute peripancreatic fluid collections (APFCs), which are not mentioned in any category of the DBC; the role of infected pancreatic necrosis (IPN), which is not part of any category in the RAC, early versus late OF (which are not particularly addressed in any of them), single versus multiple OF, etc.

We aimed to perform a nation-wide prospective study specifically designed to validate the different classifications of severity and to investigate which independent characteristics of the disease are associated with worst outcomes.

METHODS

Design

The Atlantis project, a nation-wide prospective cohort study, was created under the auspices of the Spanish Association of Pancreatology (AESPANC) and the Spanish Association of Gastroenterology (AEG) to validate and compare the determinants of severity and the severity classifications as well as to ascertain the role of comorbidity in the course of AP. The latter aim is not addressed in this article. The study followed the ethical standards of the Helsinki Declaration of 2013 and was approved by the local ethical committee at each center. To enter the study, a signed informed consent was required from the patient or a relative.

Patients

Adult (≥18 years of age) patients with AP were prospectively and consecutively enrolled at 23 Spanish centers from June 2013 to February 2015. Among the centers, 20 (87%) were third-level hospitals and 3 (13%) were second-level hospitals. For the diagnosis of AP, presence of at least 2 of the following criteria were required: (1) typical upper abdominal pain, (2) increase in serum amylase and/or lipase above 3 times the upper limit of normal, and (3) imaging compatible with AP.[15] Patients with chronic pancreatitis (calcifications and/or dilated main pancreatic duct) were excluded. Each center had 1 to 2 gastroenterologists or surgeons responsible for patient recruitment and the acquirement of data. The morphological characteristics of the disease, as seen on computed tomography (CT) scan, were described by a local radiologist at each center.[15] All radiologists were blinded for clinical outcomes. CT scan was not performed on all patients with a mild course of disease (short-lasting pain, absence of clinical and biochemical markers of systemic inflammatory response, and quick recovery including rapid oral refeeding). In data analysis, we assumed that these patients did not have local complications.

Outcome Variables

Outcome variables were the following: days from admission to successful oral refeeding, need for invasive treatment, ICU admission, length of hospital stay, and in-hospital mortality. Need for invasive treatment included invasive procedures aimed to treat direct consequences of pancreatic inflammation or infection of pancreatic collections, such as thoracentesis, endoscopic stenting of disrupted Wirsung duct, endoscopic drainage/necrosectomy, percutaneous drainage, and/or surgery. The invasive treatment of collateral problems, such as choledocholitiasis, cholangitis due to biliary stones, acute cholecystitis, etc, was not included in this

TABLE 1. Definitions of Severity: Atlanta Classification, Revised Atlanta Classification, and Determinant-Based Classification

Classification	Mild	Moderate/ Moderately Severe	Severe	Critical
Atlanta Classification	No OF and no local complications	N/A	OF and/or local complications (necrosis, abscess, and/or pseudocyst)	N/A
Revised Atlanta Classification	No OF, no local nor systemic complications	OF that resolves within 48 h (transient OF) and/or local or systemic complications without persistent OF	Persistent OF (>48 h)	N/A
Determinant-Based Classification	No (peri)pancreatic necrosis and no OF	Sterile (peri)pancreatic necrosis and/or transient (<48 h) OF	IPN or persistent (≥48 h) OF	IPN and persistent (≥48 h) OF

IPN indicates infected (peri)pancreatic necrosis; N/A, not applicable; OF, organ failure; (Peri)pancreatic necrosis, necrosis of the pancreas and/or peripancreatic tissue.

outcome variable. Time to oral refeeding and length of hospital stay were dichotomized using a cut-off of >3.5 and >11.5 days, both which equals to the third quartile (Q3) of the variables in our cohort. We followed the STROBE statement for the reporting of data.[32]

Statistical Analysis

Continuous data were evaluated for normality by the Shapiro-Wilk test and were summarized using mean and standard deviation (SD) or median and interquartile range (IQR) depending on the variable distribution. Qualitative variables were expressed as n (%). The trend for worse outcomes in increasingly severe categories was assessed by means of the Linear-by-Linear Association test when dichotomous, and with the Jonckheere-Terpstra test in case of quantitative variables. The different classifications were compared by means of the area under the receiver operator characteristics curve (AUC). Statistical significance between the different AUCs were determined with the Hanley and McNeil method.[33] Alpha level was 0.05, and the Bonferroni correction was used for multiple comparisons (ie, when comparing AUCs between the 3 classifications, according to the Bonferroni correction, the *P* level of significance decreases to 0.017).

The association of several possible determinants of severity was investigated by means of binary logistic regression analysis, both univariate (odds ratio, OR) and multivariate analysis (adjusted OR, aOR). The model used for multivariate analysis included age and comorbidity by means of the Charlson Comorbidity Index (cutoff ≥3), sex, alcoholic etiology, and recurrent AP (≥1 previous episode).[34]

All statistical calculations were performed with SPSS 20.0 (SPSS Inc., Armonk, NY).

RESULTS

Basal Characteristics and Outcomes

In total, 1655 patients were included. The median (IQR) number of patients per center was 73 (IQR: 52 to 87). Baseline patient characteristics and outcomes are presented in Table 2. Median age was 66 years; sex distribution was almost equal between males and females and comorbidity was frequent. The patients tended to be overweight and gallstones was the most frequent etiology. Hypertriglyceridemic AP was infrequent (26 cases, 1.6%) and was not associated with worse course of disease (data not showed). Among the 234 (14.1%) patients who developed OF, 113 cases (48.3% among the patients with OF) lasted for more than 48 hours (persistent OF; POF). Detailed frequency of the subtypes of POF is summarized in Table 2 as well as data regarding the other investigated outcomes. Local complications were described in 444 cases (26.8%) (Table 2). Seventy patients (4.2%) died; for 21 patients (30%), death was caused by sterile OF and 17 (24.3%) patients died from septic OF due to IPN, whereas sepsis not related to IPN was the cause of death in 10 (14.3%) cases. The remaining patients died due to exacerbation of previous comorbidity (6 cases; 8.6%) and other causes (16 patients; 22.9%).

TABLE 2. Basal Characteristics and Outcomes

Characteristics and Outcomes	Overall
N	1655
Age, median (IQR), y	66 (51–79)
Male sex, n (%)	891 (53.8%)
BMI, median (IQR), kg/m^2	26.8 (24.3–29.7)
CCI, median (IQR) points	3 (1–5)
AP episode, n (%)	
First	1233 (74.5%)
Second	273 (16.5%)
Third or more	149 (9%)
Transferred from another center, n (%)	105 (6.3%)
Etiology, n (%)	
Gallstones	984 (59.5%)
Alcohol	251 (15.2%)
Idiopathic	235 (14.2%)
Other	185 (11.2%)
Organ failure, n (%)	
Transient OF (≤48 h)	121 (7.3%)
Overall POF (>48 h)	113 (6.8%)
Early (first week) POF	89 (5.4%)
Late (>7th day) POF	24 (1.5%)
Single organ failure	141 (8.5%)
Multiple organ failure	93 (5.6%)
Sterile POF	76 (4.6%)
Septic POF (infected necrosis)	37 (2.2%)
Local complications *, n (%)	
No local complications	1211 (73.2%)
APFC	163 (9.8%)
Peri(pancreatic) necrosis	281 (17%)
Isolated pancreatic necrosis	73 (4.4%)
Isolated peripancreatic necrosis	75 (4.5%)
Pancreatic and peripancreatic necrosis	133 (8%)
Infected peri(pancreatic) necrosis	59 (3.6%)
Need for invasive treatment, n (%)	87 (5.3%)
Time to oral refeeding, median (IQR), d	2 (1.1–3.5)
ICU admission, n (%)	126 (7.6%)
Hospital stay, median (IQR)	7 (4.6–11.5)
Mortality, n (%)	70 (4.2%)

AP indicates acute pancreatitis; APFC, acute peripancreatic fluid collections; BMI, body mass index; CCI, Charlson comorbidity index; ICU, intensive care unit; IQR, interquartile range (Q1-Q3); OF, organ failure; Peri (pancreatic) necrosis, pancreatic and/or peripancreatic necrosis; POF, persistent organ failure.

*Patients with a mild course of disease did not undergo a CT scan for ethic reasons (futile exposure to radiation) and were assumed as not having local complications.

Validation and Comparison of the Severity Classifications

Increasing severity categories were associated to increasingly worse outcomes in all 3 classifications (Table 3). The AUCs of the individual classifications for the different outcome variables are shown in supplementary Table 1, http://links.lww.com/SLA/B407. The AC had a trend toward a lower AUC for ICU admission than the RAC and a statistically significant lower AUC for the need for ICU admission and invasive treatment than the DBC. Finally, the AC had a statistically significant lower AUC than the RAC and DBC regarding mortality. There were no significant differences between the RAC and DBC.

Determinants of Morbidity and Mortality

Effect of the Duration of OF on Outcomes

Compared with patients without organ failure, transient OF and POF were both associated with increased morbidity and mortality (Table 4), where POF had greater morbidity than transient OF. When excluding patients without OF, POF had an aOR of 16 (7.2 to 35.5) for mortality compared with transient OF.

Local Complications and Outcomes

Compared with not having local complications, APFC as well as the various groups with necrosis were independently associated with increased morbidity and mortality (Table 5).

Local complications were not associated with mortality if POF was added to the model (data not shown). Hence, the relationship between POF and local complications was additionally studied (Supplementary Table 2, http://links.lww.com/SLA/B407).

TABLE 3. Outcomes According to the Different Severity Classifications

Classification	Severity Category	Time to Oral Refeeding Median (IQR), d	Need for Invasive Treatment n (%)	Intensive Care Unit Admission n (%)	Hospital Stay Median (IQR), d	Mortality n (%)
Atlanta	Mild n = 1175	1.6 (1–2.8)	3 (0.3%)	2 (0.2%)	6.2 (4.1–8.7)	1 (0.1%)
	Severe n = 480	3.4 (1.6–9.7)	84 (17.5%)	124 (25.8%)	13.8 (7.9–25.5)	69 (14.4%)
	P	<0.001	<0.001	<0.001	<0.001	<0.001
Revision of Atlanta	Mild n = 1076	1.6 (0.9–2.6)	2 (0.2%)	1 (0.1%)	5.9 (4–8.2)	1 (0.1%)
	Moderately severe n = 466	2.9 (1.5–6.1)	31 (6.7%)	43 (9.2%)	11.4 (7.4–18.3)	10 (2.1%)
	Severe n = 113	10.6 (3.3–27.5)	54 (47.8%)	82 (72.6%)	39.1 (16.4–69.9)	59 (52.2%)
	P	<0.001	<0.001	<0.001	<0.001	<0.001
Determinant-based	Mild n = 1247	1.6 (1–2.8)	4 (0.3%)	3 (0.2%)	6.3 (4.2–9.1)	1 (0.1%)
	Moderate n = 274	3.1 (1.6–7.1)	8 (2.9%)	35 (12.8%)	12.9 (7.6–19.2)	11 (4%)
	Severe n = 97	9.4 (3.4–26.2)	38 (39.2%)	52 (53.6%)	34.3 (16.5–66)	38 (39.2%)
	Critical n = 37	24.2 (10.1–67.2)	37 (100%)	36 (97.3%)	88 (54.4–119.7)	20 (54.1%)
	P	<0.001	<0.001	<0.001	<0.001	<0.001

P: statistical significance according to the Linear-by-Linear Association test (dichotomous outcome variables) or Jonckheere-Terpstra test (quantitative outcome variables). IQR indicates interquartile range.

Compared with not having local complications, APFC, isolated peripancreatic or pancreatic necrosis as well as combined peri(-pancreatic) necrosis were all independently associated with increased risk of POF. Combined pancreatic and peripancreatic necrosis had a stronger association to POF than the other local complications (aOR 35.7).

Effect of IPN

IPN was associated with a higher aOR than sterile peri (pancreatic) necrosis regarding time to oral refeeding > Q3, need for invasive treatment, ICU admission, hospital stay >Q3, and mortality [reference category: patients without peri (pancreatic) necrosis, Table 6]. In addition, POF was more frequent in IPN (62.7%) than in sterile necrosis (16.2%), $P < 0.001$. When POF was added as a covariate in multivariate analysis (Table 6), IPN was anew associated with higher aOR (CI 95%) than sterile peri (pancreatic) necrosis regarding time to oral refeeding >Q3, invasive treatment and hospital stay >Q3. However, in this latter model, mortality was similar between infected and noninfected peri (pancreatic) necrosis. POF with concurrent IPN correlated to a higher aOR for time to oral refeeding >Q3 and need for ICU admission compared with sterile POF (Supplementary Table 3, http://links.lww.com/SLA/B407).

Association Between Early (Within the First Week) versus Late (>First Week) POF and Outcomes

Late POF was associated with a higher need for invasive treatment than early POF (Supplementary Table 4, http://links.lww.com/SLA/B407). If IPN was added to the model, no independent association was found between late OF and need for invasive treatment, [aOR 1 (0.1 to 7)].

Single Organ Failure Versus Multiple Organ Failure: Effect on Outcomes

Multiple organ failure was independently associated with higher morbidity and mortality than single organ failure (Supplementary Table 5, http://links.lww.com/SLA/B407).

TABLE 4. Association Between Duration of Organ Failure and Outcomes

		Time to Oral Refeeding*	Need for Invasive Treatment	Intensive Care Unit Admission	Hospital Stay*	Mortality
No OF (n = 1421)	n (%) or median (IQR)	1.8 (1–3.1)	28 (2%)	14 (1%)	6.6 (4.4–10.2)	2 (0.1%)
	OR	1	1	1	1	1
	aOR	1	1	1	1	1
Transient OF (n = 121)	n (%) or median (IQR)	3.3 (1.6–7.5)	5 (4.1%)	30(24.8%)	13.3 (7.1–23.1)	9 (7.4%)
	OR	3.3 (2.2–4.9)	2.1 (0.8–5.7)	33 (17–64.7)	5.1 (3.4–7.6)	57 (12.2–267)
	aOR	3.3 (2.2–5)	2.7 (1–7.2)	57.1 (26.7–122.2)	4.7 (3.1–7)	47.5 (10.1–224)
POF (n = 113)	n (%) or median (IQR)	10.6 (3–27.5)	54 (47.8%)	82 (72.6%)	39.1 (16.4–70)	59 (52.2%)
	OR	12 (6.8–21.8)	45.5 (27–77)	266 (136–519)	25 (11.2–57)	775 (185–3256)
	aOR	12.6 (7–22.6)	64.9 (35.8–117.8)	623 (269–1444)	25.2 (11.2–56.5)	767 (181–3251)

Multivariate analysis includes sex, comorbidity and age by means of the Charlson Comorbidity Index (cutoff ≥3), recurrent AP (≥1 previous episode), and alcoholic etiology. aOR indicates adjusted odds ratio; IQR, interquartile range (Q1-Q3); OF, organ failure; OR, odds ratio; POF, persistent organ failure.

*OR and aOR of the variables ''time to oral refeeding'' and ''hospital stay'' are given for starting effective oral refeeding >3.5 days (Q3) from presentation and having a hospital stay >11.5 days (Q3).

TABLE 5. Local Complications and Outcomes

		Time to Oral Refeeding*	Need for Invasive Treatment	Intensive Care Unit Admission	Hospital Stay*	Mortality
No local complications (n = 1211)	n (%) or median (IQR)	1.6 (1–2.8)	1 (0.1%)	20 (1.6%)	6.1 (4.1–8.9)	23 (1.9%)
	OR	1	1	1	1	1
	aOR	1	1	1	1	1
APFC (n = 163)	n (%) or median (IQR)	2.5 (1.4–4.4)	6 (3.7%)	13 (8%)	9.5 (6.8–14.7)	7 (4.3%)
	OR	2.6 (1.8–3.8)	46 (6–387)	5.2 (2.5–10.6)	3.3 (2.3–4.8)	2.3 (1–5.5)
	aOR	2.7 (1.8–3.9)	49 (6–411)	5.2 (2.5–10.7)	3.8 (2.6–5.5)	2.9 (1.2–6.9)
Isolated peripancreatic fat necrosis (n = 75)	n (%) or median (IQR)	4.4 (1.9–13.2)	8 (10.7%)	12 (16%)	13.3 (8.7–24)	7 (9.3%)
	OR	7.7 (4.6–12.8)	144 (18–1172)	11.3 (5.3–24.2)	8.5 (5.1–14.2)	5.3 (2.2–12.8)
	aOR	8.1 (4.8–13.6)	147 (18–1199)	11.5 (5.4–24.8)	10.1 (5.9–17.1)	6.9 (2.8–17.2)
Isolated parenchymal necrosis (n = 73)	n (%) or median (IQR)	3.3 (1.7–10.3)	10 (13.7%)	18 (24.7%)	13.6 (8–20.5)	7 (9.6%)
	OR	4 (2.4–6.8)	192 (24–1524)	19.5 (9.8–38.9)	6.9 (4.1–11.5)	5.5 (2.3–13.2)
	aOR	4.2 (2.4–7.1)	212 (26–1692)	20 (9.9–40.7)	7.9 (4.6–13.5)	7.3 (2.9–18.1)
Pancreatic and peripancreatic necrosis (n = 133)	n (%) or median (IQR)	8 (2.5–23.5)	62 (46.6%)	63 (47.4%)	26 (14.2–59.2)	26 (19.5%)
	OR	11.6 (7.4–18)	1057 (144–7731)	53.6 (31–93.6)	24.4 (14.6–40.73)	12.6 (6.9–22.8)
	aOR	12 (7.5–18.7)	1143 (155–8430)	53.2 (30.1–94)	29.7 (17.4–50.6)	16.8 (8.9–31.5)

Multivariate analysis includes sex, comorbidity and age by means of the Charlson Comorbidity Index (cutoff ≥3), recurrent AP (≥1 previous episode), and alcoholic etiology.
aOR indicates adjusted odds ratio; APFC, acute peripancreatic fluid collections; IQR, interquartile range; OF, organ failure; OR, odds ratio; Peri (pancreatic) necrosis, pancreatic and/or peripancreatic necrosis; POF, persistent organ failure.
*OR and aOR of the variables ''time to oral refeeding'' and ''hospital stay'' are given for starting effective oral refeeding >3.5 days (Q3) from presentation and having a hospital stay >11.5 days (Q3).

TABLE 6. Effect of Sterile and Infected Necrosis on Outcomes

		Time to Oral Refeeding*	Need for Invasive Treatment	Intensive Care Unit Admission	Hospital Stay*	Mortality
No peri (pancreatic) necrosis (n = 1374)	n (%) or median (IQR)	1.7 (1–3.1)	7 (0.5%)	33 (2.4%)	6.4 (4.3–9.6)	30 (2.2%)
	OR	1	1	1	1	1
	aOR†	1	1	1	1	1
	aOR‡	1	1	1	1	1
Sterile peri (pancreatic) necrosis (n = 222)	n (%) or median (IQR)	3.7 (1.9–11.5)	22 (9.9%)	51 (23%)	14.7 (8.5–25.5)	20 (9%)
	OR	5.1 (3.7–6.9)	21.5 (9.1–50.9)	12.1 (7.6–19.3)	7.7 (5.6–10.6)	4.4 (2.5–8)
	aOR†	5.1 (3.7–7)	20.9 (8.6–50.7)	11.6 (7.2–18.8)	8.4 (6–11.8)	5.6 (3.1–10.3)
	aOR‡	4.4 (3.2–6.2)	8.9 (3.4–23)	7.5 (4.2–13.5)	7.4 (5.3–10.4)	1.7 (0.7–4)
Infected peri (pancreatic) necrosis (n = 59)	n (%) or median (IQR)	23.9 (9.9–58)	58 (98.3%)	42 (71.2%)	66.3 (43.5–98.4)	20 (33.9%)
	OR	54 (16.6–178)	11327 (1371–93,583)	100 (52–194.4)	180.5 (24.7–1321.6)	23 (12–44)
	aOR†	54.7 (16.6–179.9)	12729 (15,003–107,791)	99.9 (51–195.4)	213 (29–1569)	31.2 (15.4–63.4)
	aOR‡	30 (8.8–102.1)	7217.7 (815–63,851)	28.4 (11.5–70.1)	134.7 (18–1005.3)	1.9 (0.7–4.8)

aOR indicates adjusted odds ratio; IQR, interquartile range; OR, odds ratio; Peri (pancreatic) necrosis, pancreatic and/or peripancreatic necrosis.
*OR and aOR of the variables ''time to oral refeeding'' and ''hospital stay'' are given for starting effective oral refeeding >3.5 days (Q3) from presentation and having a hospital stay >11.5 days (Q3).
Multivariate analysis: aOR† includes sex, comorbidity and age by means of the Charlson Comorbidity Index (cutoff ≥3), recurrent AP (≥1 previous episode), and alcoholic etiology. aOR‡ includes the variables listed in aOR† as well as persistent organ failure.

Exacerbation of Previous Comorbidity

In the absence of POF, exacerbation of previous comorbidity correlates to increased morbidity and mortality (Supplementary Table 6, http://links.lww.com/SLA/B407).

DISCUSSION

An applicable classification is based on current knowledge regarding the characteristics associated with the course of disease. Correct stratification of disease severity is required for comparison of inter-institutional data, as well as for the development of management strategies and research. This project aimed to be the first multicenter nation-wide prospective study specifically designed to validate the new classifications of severity in AP and investigate which characteristics of the disease are associated with worse outcomes.

As described in previous validation studies on AP classifications, both the RAC and DBC were superior to the AC in stratifying the patients into homogeneous groups.[3,17–30] There were no significant differences between the RAC and DBC.

Regarding determinants of severity, we show that POF is a significant and decisive marker of both morbidity and mortality and therefore should be part of any classification of AP. Our conclusions are in line with findings from previous studies.[35,36] In addition, we showed that all local complications are associated with worse outcomes, particularly combined parenchymal and peripancreatic necrosis. Cell death by necrosis is associated with a sterile inflammatory reaction through the recognition of damage-associated molecular patterns by Toll-like receptors, nucleotide oligomerization domain-like receptors, and other pattern-recognition receptors present in cells of innate immunity.[37] Any local complication is associated with increased cellular and tissue damage when compared with edematous AP, so a higher inflammatory response and increased risk of sterile POF should be expected. Furthermore, local complications may become infected, increasing the risk for septic POF. Regardless, in some cases, a reverse causation bias may associate POF and local complications, for example, aggressive fluid resuscitation may increase the possibility of fluid collections.[38] These results support the RAC, in which patients with any type of local complication but without POF are classified as moderately severe.[15] The DBC only considers necrotizing pancreatitis to be a determinant of severity; however, according to our data, APFC was also independently associated to worse outcomes.[16]

A major question regarding the determinants of severity in AP is the role of IPN. A meta-analysis from the Auckland group comprising almost 1500 patients showed that co-occurring OF and IPN resulted in higher mortality than sterile OF.[39] On the basis of this study, the DBC differentiates patients suffering from both POF and IPN into the most severe (critical) category of AP, whereas the RAC does not take into account the presence of this combination in severity stratification. Our results initially demonstrated that IPN is associated with increased morbidity and mortality compared with sterile peri(pancreatic) necrosis. However, when POF was added to the multivariate analysis, presence of infection was associated to increased morbidity but not mortality. Also, among patients with POF, the mortality was similar in sterile necrosis and IPN: 51.3% and 54.1%, respectively. As IPN implies invasive treatment and prolonged hospital stay, this situation is important per se regarding morbidity.[40] However, its effect on mortality depends on the development of POF, which is more frequent in infected than in sterile necrosis.[40,41] Coincident POF and IPN was, in our data, associated with increased time to oral refeeding and need for ICU admission compared with sterile POF. IPN frequently correlates with late POF, but with infection added to the model, the distinction between early and late POF dissipates. Multiorgan failure was independently associated with increased morbidity and mortality when compared with single organ failure and should be considered in future classifications. Finally, we addressed exacerbation of previous comorbidity. The concept was introduced by the RAC, although not apparently based on published data. In this work, we demonstrate that exacerbation of comorbidities in the absence of POF is certainly associated with worse outcomes, including mortality. A simplified summary of our findings is summarized in Table 7. In accordance with our findings, we suggest taking into consideration the following proposal in future efforts to improve the current classifications of severity:

(1) A mild category involving AP without complications. These are patients with very little morbidity and no mortality, with an excellent course of disease.
(2) A moderate category (increased morbidity), which can be subdivided into 2 subcategories:
   a) Moderate category with low morbidity: including patients with transient organ failure, exacerbation of previous comorbidity, APFCs, or isolated pancreatic or peripancreatic necrosis. These complications are associated with increased morbidity compared with patients in the mild category.
   b) Moderate category with high morbidity, defined by the presence of combined peripancreatic and parenchymal necrosis and/or IPN. These patients have the highest degree of morbidity, including higher time to oral refeeding, higher need for invasive treatment, and higher hospital stay than patients classified as a). Mortality is low in both moderate subcategories.
(3) A severe category: persistent and/or multiple organ failure. These patients have a high risk of death (50%) and also a very

TABLE 7. Summary

	Increased Morbidity	Maximum Morbidity	Increased Mortality	Maximum Mortality
Organ failure and exacerbation of previous comorbidity	Any organ failure Exacerbation of previous comorbidity	POF Multiple organ failure	Any organ failure Exacerbation of previous comorbidity	POF Multiple organ failure
Local complications	All of them	Combined peripancreatic and parenchymal necrosis	Only if POF present	Only if POF present
		IPN	All of them associated with POF	Combined peripancreatic-parenchymal necrosis and IPN highly associated with POF

IPN indicates infected (peri)pancreatic necrosis; POF, persistent organ failure.

aggressive course of disease in terms of morbidity. Multiple organ failure should be included in this category, as those patients have the same probability of death as those with persistent organ failure.

Strengths of this study is its multicenter setting involving a large number of unselected patients. Previous studies have principally involved cohorts from a few centers highly focused on pancreatology, implicating selected data. In addition, our set-up was prospective and specifically designed to validate and compare the severity classifications as well as to investigate the determinants of severity. All these properties contribute to increased external validity. However, this work also has limitations. As there was no central review of CT scans, imaging assessment relied on local radiologists. Hence, morphological categories such as APFC or peri(pancreatic) fat necrosis may be diversely interpreted depending on the center. It is, however, our opinion that these circumstances reflect the routine clinical situation. In addition, as current guidelines regarding radiation exposure were followed, 802 patients (48.5%) patients with a mild course of disease did not undergo a CT scan. Consequently, there might have been undetected local complications. A majority of the recruiters were gastroenterologists, thus some patients admitted to other departments could have gone unnoticed and therefore be lost for recruitment. However, most patients with AP in Spain are treated by gastroenterologists and the small number of possibly undetected patients in this study could not be considered a selection bias. Finally, no formal sample size calculation was made before the study, but the number of patients recruited was higher than in previous studies addressing similar aims.

In conclusion, our findings confirm the superiority of the RAC and DBC in describing different groups of AP patients compared with the AC. POF and multiple organ failure are major determinant of severity in AP and any kind of local complication corresponds to worse outcomes. Presence of IPN implies more severe disease, although it is not associated with higher mortality than sterile necrotizing pancreatitis if POF is present. Exacerbation of previous comorbidity, in the absence of POF, is associated with a rise in both morbidity and mortality. Our study provides data that could be relevant for the design of future severity classifications.

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