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Validation of Modified Determinant-Based Classification of severity for acute pancreatitis in a tertiary teaching hospital

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ABSTRACT

Background: The relative merits of two recent classifications of acute pancreatitis severity, the Determinant-Based Classification (DBC) and the Revised Atlanta Classification (RAC), have been debated. A Modified DBC (MDBC) was recently proposed in intensive care unit (ICU) patients. By dividing the DBC 'severe' category into two groups, the MDBC classified non-mild acute pancreatitis into 4 groups rather than 2 in RAC and 3 in DBC. In this study we aim to validate MDBC in both ICU and non-ICU patients and evaluate infected necrosis as a determinant of severity.
Methods: Prospective data collected on consecutive patients admitted to a tertiary teaching hospital were retrospectively analyzed. Patients were assigned to the categories of severity defined by the DBC, RAC and MDBC. Clinical interventions and outcomes were compared between categories.
Results: A total of 1102 patients were enrolled and the overall mortality was 5.7%. When MDBC was applied, the four Groups were significantly different in regard to ICU admission rates (30%, 40%, 69% and 87%) and mortality (2%, 15%, 40% and 57%). Groups 2 and 3 were different in intervention rates and morbidity, providing evidence that IN is an important determinant of severity.
Conclusions: This study validates the MDBC proposal to subdivide the DBC 'severe' category into two groups for ICU and non-ICU patients in a tertiary hospital.

Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases that requires hospitalization and takes a significant physical, emotional and financial toll [1,2]. Clinicians have long recognized that the severe category of the original Atlanta classification was heterogeneous comprising patients with different clinical courses and outcomes. The recent development of two different systems for classifying the severity of AP, the Determinant-Based Classification (DBC) and the Revised Atlanta Classification (RAC), has aroused considerable interest and debate [3,4]. The RAC has defined a new subgroup within the 'severe' category of the original Atlanta system, the 'moderately severe' grade [5,6], giving the RAC three grades of severity. Based on the two key determinants of severity (i.e. organ failure and infected necrosis) the DBC went further by defining three subgroups within the severe category, namely 'moderate', 'severe' and 'critical', giving 4 categories of severity [7]. The major difference between the RAC and DBC relates to the handling of infected necrosis (IN). The RAC does not consider IN a criterion for severe disease while the DBC does [7]. Exploring differences between the two classifications provide opportunities for further refinement [8]. It is recognized that the purpose of severity classification is different from severity prediction and that the requirements for severity classification of AP depends on the clinical setting [8].

Several studies have compared the performance of RAC and DBC in a range of clinical settings [9–18] (Table 1). These were single-center retrospective studies using prospectively collected data,

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Table 1
Studies Comparing the Revised Atlanta Classification, Determinant-Based Classification, and Modified Determinant-Based Classification. (SC: single center, DBC: Determinant-Based Classification, RAC: Revised Atlanta Classification, MC: multicenter).

First Author (Year)	Ref	Setting	Study design	Key findings
Nawaz (2013)	[9]	Tertiary (SC) Pittsburgh, USA	Retrospective based on a prospective database	DBC and RAC were comparable predictors for mortality, ICU admission and ICU length of stay. DBC did better for predicting the need for intervention and RAC was better at predicting hospital stay.
Acevedo-Piedra (2014)	[10]	Tertiary (SC) Alicante, Spain	Retrospective based on a prospective database	Numbers of patients in the severe and critical categories of DBC were very small. DBC and RAC had similar patient distributions and outcomes.
Chen (2015)	[11]	Tertiary (SC) Nanjing, China	Retrospective based on a prospective database	RAC and DBC were comparable to classify severity using long-term clinical outcome, significant complications, and interventions. The critical category had very high risk and was distinct from severe category in DBC.
Mircea (2015)	[12]	Tertiary (SC) Bucharest, Romania	Retrospective	Comparable for major outcomes, but RAC was marginally better for hospital length of stay and DBC for ICU admission and length of stay. DBC easier to implement.
Xu (2015)	[13]	Tertiary (SC) Lanzhou, China	Retrospective	RAC and DBC had similar distribution and outcomes. Combination of RAC and DBC was recommended.
Guo (2015)	[14]	Tertiary (SC) Chengdu, China	Retrospective based on a prospective database	Comparable performance between RAC and DBC. Mortality similar and slightly different distribution of severity.
Kadiyala (2016)	[15]	Tertiary (SC) Boston, USA	Retrospective based on a prospective database	The RAC and DBC had essentially equivalent performance for predicting mortality, ICU admission, ICU length of stay, and hospital length of stay. Low proportion in the critical category limited DBC utility. Neither classification considered multiorgan failure, the strongest risk factor associated with mortality.
Bansal (2016)	[16]	Tertiary (SC) Birmingham, UK	Retrospective based on a prospective database	The RAC and DBC performed comparably well. The critical category of DBC had a doubled mortality risk. ICU length of stay and need for intervention were also greater than RAC. Critical category was definitely associated with poor outcome.
Fernandes (2016)	[17]	Tertiary (SC) Lisbon, Portugal	Retrospective	RAC and DBC were similar for outcomes.
Zubia-Olaskaoaga (2016)	[18]	Tertiary (MC) Spain et al.	Prospective observational	Proposed a modified DBC in ICU patients. The severe category of DBC was separated into two groups: transient organ failure with local complications and persistent organ failure and no local complications. MDBC was better than DBC and RAC for mortality, was similar to DBC for morbidity, and was superior to RAC.

except for one prospective multicenter study [18]. This was conducted in 46 ICUs with mild AP excluded. The authors proposed a modification of the DBC (MDBC) and found that the MDBC had better discrimination than RAC and DBC [18]. The modification was based on the finding that the DBC 'severe' category comprised two distinct subgroups with significantly different rates of intervention, morbidity and mortality. On this basis, they proposed four 'groups' of severity in addition to mild acute pancreatitis, instead of three categories of DBC (Table 2). The primary aim of the present study was to validate the MDBC using a different clinical dataset, and one that included all AP patients admitted to a tertiary teaching hospital and not just those admitted to ICU. The second aim was to evaluate the importance of infected necrosis as a determinant of severity. And lastly to propose a nomenclature for MDBC groups for both ICU and non-ICU patients.

Methods

This was a retrospective analysis of a prospective database of consecutive patients admitted with acute pancreatitis to Peking Union Medical College Hospital. This is a tertiary teaching hospital with 1800 beds and provides support to secondary and primary health facilities in Beijing and other areas of Northern China, covering a catchment population of about 100 million. A prospectively maintained database from 2002 to 2017 was used to extract data for this study. Any missing data was obtained by reviewing clinical notes, electronic records and communication with the referring hospitals. Patients who were transferred from other hospitals were excluded [5]. We conducted this study and prepared the manuscript in line with the STROBE statement [19]. The Ethics Committee of the hospital approved the database. Consensus was obtained from all patients for clinical research and publication on the condition that their personal information keeps confidential.

The data collected for all cases included age, gender, referral, etiology, organ failures (shock, acute respiratory failure, acute renal failure), local complications (sterile and infected pancreatic necrosis), treatments such as percutaneous or endoscopic drainage, surgical operations, use of inotropes, mechanical ventilation and continuous renal replacement therapy, ICU admission and length of stay (LOS), overall hospital LOS, and hospital mortality. Organ failure scores were calculated in the first 24 h after admission including Acute Physiology and Chronic Health Evaluation (APACHE) II [20], Modified Marshall [21], and Sequential Organ Failure Assessment (SOFA) scores [22].

Table 2
The grades, categories and groups of acute pancreatitis severity using the Revised Atlanta Classification, Determinant-Based Classification, and Modified Determinant-Based Classification methods, respectively. (OF: organ failure, LC: local complication, TOF: transient organ failure, POF: persistent organ failure, SN: sterile necrosis, IN: infected necrosis.).

RAC	**Mild** *(No OF, No LC)*	**Moderately severe** *(TOF and/or LC)*		**Severe** *(POF)*	
DBC	**Mild** *(No OF, No LC)*	**Moderate** *(TOF and/or SN)*	**Severe** *(POF or IN)*		**Critical** *(POF and IN)*
MDBC	Excluded	**Group 1** *(TOF and/or SN)*	**Group 2** *(IN without POF)*	**Group 3** *(POF without IN)*	**Group 4** *(POF and IN)*

Note: DBC has a narrower definition for local complications than RAC, leading to a slightly broader range of mild acute pancreatitis in this table.

Definitions

Acute pancreatitis

The diagnosis of acute pancreatitis was made on the basis of at least two of three criteria: abdominal pain consistent with acute pancreatitis, an initial amylase and/or lipase level greater than three times the upper limit of normal, and/or radiological findings (ultrasound, CT or MRI) consistent with acute pancreatitis [23].

Local complications

In this study, local complications referred to the presence of sterile or infected pancreatic necrosis. A radiologist (XHD) specialized in pancreatology who was blinded to the clinical status of patients reviewed the image findings of all cases and made diagnoses of local complications according to the updated definition [6,7].

Sterile necrosis was defined by the presence of nonviable tissue in pancreas and/or peripancreatic tissues revealed on contrast-enhanced radiological images (hypoperfusion) or intraoperative observation (ischemia/necrosis), in the absence of evidence for infection [7].

Infected necrosis was defined by at least one of the following findings: the presence of gas bubbles in the pancreas and/or peripancreatic tissue on CT, a positive result in Gram staining or culture of samples obtained by image-guided fine needle aspiration, or during the first intervention (either drainage or surgery). Infected necrosis included both infected acute necrotic collections (ANC) and infected walled-off necrosis (WON) [6].

In the reference study [18] intestinal perforation and abdominal hemorrhage were also defined as local complications, but they are not included in the present study for both have not been validated as independent factors for severity in acute pancreatitis.

Organ failure

The definition was based on three organ systems (cardiovascular, respiratory and renal) and the worst measurement during the entire hospitalization was used. Organ failure was defined as either a score of 2 or more for that organ using the SOFA (Sepsis-related Organ Failure Assessment) score [22] or when the following threshold was breached, based on the reference study [18].

- Cardiovascular failure/shock: Systolic arterial pressure less than 90 mmHg or a reduction of 40 mmHg in basal systolic arterial pressure, with signs of tissue hypoperfusion (lactate > 3 mmol/L); saturation of central venous oxygen ($SvcO_2$) less than 70%.
- Respiratory failure: Basal PaO_2 less than 60 mm Hg or PaO_2/FiO_2 less than 300 mm Hg (with supplementary oxygen).
- Acute renal failure: An increase of baseline creatinine by two times (Acute Kidney Injury-2 or Risk, Injury, Failure, Loss, End Stage-I) and/or reduction in urinary flow (oliguria) less than 0.5 mL/kg/hr for at least 12 h.

If the duration of each organ failure was shorter than 48 h then it was defined as *transient*, and *persistent* if the duration was longer than 48 h [24].

Classification of severity of acute pancreatitis

The severity of acute pancreatitis was classified by the Revision of Atlanta Classification (RAC) (4), Determinant-Based Classification (DBC) [7], and modified Determinant-Based Classification (MDBC) [18] (Table 2). Clinical notes were reviewed to determine the exacerbation of pre-existing comorbidity defined by RAC(4). It is of note that the DBC only considered pancreatic necrosis (sterile or infected) as important local complications, resulting in a narrower definition of 'moderate' acute pancreatitis than the RAC 'moderately severe' grade. The MDBC excluded patients with mild acute pancreatitis as they were not admitted to ICU [18]. In contrast, the present study included all hospitalized patients with acute pancreatitis, and not just those admitted to ICU. The MDBC defined four grades of patients with non-mild acute pancreatitis in the present study as follows (Table 2):

- Group 1: patients with transient organ failure (TOF) and/or sterile necrosis (SN) (same as moderate acute pancreatitis of DBC).
- Group 2: patients with infected necrosis (IN) and without persistent organ failure (POF).
- Group 3: patients with POF and without IN.
- Group 4: patients with POF and IN (same as critical acute pancreatitis of DBC).

Statistical analysis

Categorical variables were described by using the absolute and relative frequencies, and continuous variables by mean and SD, or median and range if needed. Chi-square test or Fisher exact test was used to compare the distribution of categorical variables, and Student *t*-test or Mann-Whitney *U* test for continuous variables. A Bonferroni correction factor was used when comparing two groups. To validate the concept of Modified Determinant-Based Classification, we compared clinical characteristics and patient outcomes among the four groups, as well as paralleling the distribution of cases and mortality in the present study against those in the reference study [18]. All tests were two-tailed and $P < 0.05$ was considered statistically significant. A medical statistician offered advice on the study design and analyzed all the data using the program STATA SE 13 (StataCorp, College Station, TX).

Results

Of the 1518 patients admitted, 416 (27.4%) were excluded because they were transferred from other hospitals. Of the included 1102 patients, the mean APACHE II, Modified Marshall and SOFA scores were 5.9, 1.1 and 1.8, respectively. Overall mortality was 5.7%. Median hospital stay was 27 days (range 1–158) and median ICU stay 19 days (range 1–106). Baseline characteristics and patient outcomes were summarized in Table 3.

Distribution of patients based on the different classification systems

When RAC was applied to the present study, 704 (63.9%) patients were mild, 277 (25.1%) were moderately severe and 121 (11.0%) were severe. Application of DBC lead to 742 (67.3%) patients with mild acute pancreatitis, 199 (18.1%) with moderate, 131 (11.9%) severe, and 30 (2.7%) critical. When MDBC was applied, 199 patients were in Group 1, 40 in Group 2, 91 in Group 3, and 30 in Group 4. The proportional distribution of patients with non-mild acute pancreatitis into categories defined by RAC, DBC and MDBC was shown in Fig. 1.

Baseline characteristics of patients classified by the Modified Determinant-Based Classification

There was no significant difference between the groups for age or gender (Table 4). In comparing the groups, particular emphasis was placed on comparing Groups 2 and 3, which is the modification of DBC and on comparing Groups 3 and 4, which are distinguished by the presence or absence of infected necrosis.

Table 3
General characteristics of patients with acute pancreatitis.

Variables	Values
Number of patients	1120
Referred patients, n (%)	204 (18.2)
Age, year, median (range)	55 (14–101)
Gender, n (%)	659 males (58.8)
Etiology, n (%)	
Biliary	605 (54.0)
Idiopathic	165 (14.7)
Alcoholic	129 (11.5)
Hyperlipidemia	95 (8.5)
Other causes	126 (11.3)
Organ failure scores	
APACHE-II	5.9 ± 5.0
Modified Marshall Score	1.2 ± 2.0
SOFA	1.8 ± 2.9
Organ failures	
Respiratory failure, n (%)	239 (21.3)
Renal failure, n (%)	110 (9.8)
Shock, n (%)	99 (8.8)
More than one organ failure, n (%)	74 (6.6)
Local complications	
Sterile necrosis	140 (12.5)
Infected necrosis	74 (6.6)
Treatment and outcomes	
Percutaneous or endoscopic drainage, n (%)	81 (7.2)
Surgical operations n (%)	80 (7.1)
ICU admission, n (%)	175 (15.6)
ICU LOS, median (range)	12 (1–106)
Hospital LOS, median (range)	20 (1–171)
Mortality, n (%)	63 (5.6)

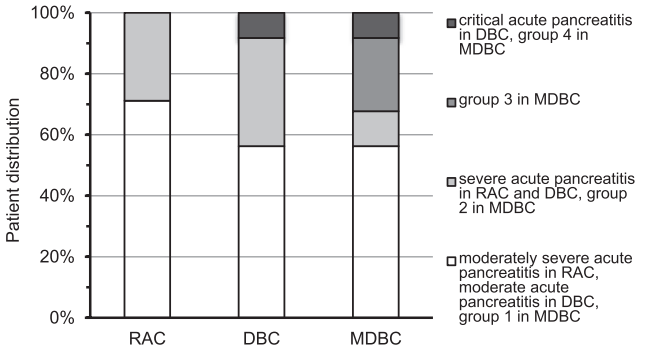

Fig. 1. The proportional distribution of patients (excluding mild) based on Revised Atlanta Classification (RAC), Determinant-Based Classification (DBC) and modified Determinant-Based Classification (MDBC).

Local and systemic complications

By definition all organ failures were transient in Group 2 and were persistent in Group 3, and as expected Group 3 had higher incidence of acute respiratory failure ($p < 0.001$) and renal failure ($p < 0.001$) than Group 2, but not for shock ($p = 0.095$). The organ failure scores (APACHE II score, Modified Marshall Score, and SOFA) were all significantly higher for Group 3 than Group 2 ($p < 0.001$). Group 4 ($n = 31$) had more patients with sterile necrosis (before infection was confirmed) ($p < 0.001$), shock ($p < 0.001$) and a higher rate of multiple organ failure ($p < 0.001$) than Group 3, but not for acute respiratory failure ($p = 0.780$) or renal failure ($p = 0.069$). Group 4 also had significantly higher Modified Marshall Score ($p < 0.001$) and SOFA ($p < 0.001$) than Group 3, but not for APACHE II score ($p = 0.101$).

Treatment and length of hospital stay

Group 2 ($n = 40$) had higher rates of drainage (63% vs 21%) than Group 3 ($n = 91$), but had less use of ventilation (8% vs 29%) and continuous renal replacement therapy (CRRT) (5% vs 20%). Group 4 ($n = 30$) had higher rates of drainage (53% vs 21%) and surgery (37% vs 14%) than Group 3, as well as more use of ventilation (53% vs 29%) and inotropes (83% vs 15%) but not CRRT. Group 3 had more ICU admissions (69% vs 40%), longer ICU LOS (14 vs 8 days) and shorter hospital LOS (28 vs 56 days) than Group 2. There was a trend toward higher rate of ICU admission (87% vs 69%) in Group 4 than Group 3, and Group 4 had a significantly longer ICU LOS (25 vs 14 days) and a longer hospital LOS than Group 3 (39 vs 28 days).

Mortality

A total of 63 (5.7%) patients died in this series. No death occurred in patients with mild acute pancreatitis. When RAC was applied, the mortality rate was 3% in the 'moderately severe' grade and was 45% in the 'severe' grade ($p < 0.001$). When DBC was applied, the mortality rate was 2% in the 'moderate' category, 32% in the 'severe' category, and 57% in the 'critical' category ($p < 0.001$). According to MDBC, the mortality rates were 2%, 15%, 40% and 57% in Group 1, 2, 3 and 4, respectively ($p < 0.001$). In inter-Group analysis, however, Group 3 had significantly higher mortality than Group 2 ($p = 0.008$), but not for Group 4 and Group 3 ($p = 0.138$). Fig. 2 shows the very similar mortality rates (percentage) for the 4 MDBC groups in the present study compared with the reference study [18]. The contribution of each MDBC group to the overall mortality was also compared between the reference study and the present study (Fig. 3). Group 4 was responsible for 27% of deaths in the present study and 48% in the reference study [18].

The median hospital length of stay was 12 (range 6–16), 37 (2–102), 13 (1–89) and 25 (2–112) days in those who died in MDBC Groups 1 ($n = 4$), 2 ($n = 6$), 3 ($n = 36$) and 4 ($n = 17$), respectively. Patients who died in Group 4 had significantly longer hospital length of stay than those in Group 3 ($p = 0.001$), but no statistically significant difference was found between Group 1 and Group 2 ($p = 0.163$) or between Group 2 and Group 3 ($p = 0.215$). 31 (49%) patients died within the first two weeks of admission. In Group 3, 21 (58%) patients died within the first two weeks, displaying a predominant early mortality in those with POF but no IN. In contrast, only 6 (35%) patients of Group 4 died in the first two weeks and there is a bimodal distribution of mortality in this group of patients with POF and IN.

Discussion

This study provides strong validation for the Modified Determinant-Based Classification (MDBC) [18] in a series of hospitalized patients, rather than just ICU patients. It supports the MDBC proposal that the DBC 'severe' category comprises two distinct groups of patients (Groups 2 and 3). Patients who have infected pancreatic necrosis (IN) without persistent organ failure (POF) (Group 2) have a very different clinical course and outcome from those with POF and no IN (Group 3) [18]. In addition, this study confirms that the DBC 'critical' category (MDBC Group 4) is valid, with a significantly worse outcome than Group 3. This study also underscores the importance of IN as an independent determinant of severity [25] and should be included in the classification of non-mild acute pancreatitis.

The recent introduction of the two different severity classifications for acute pancreatitis, namely the Determinant-Based Classification (DBC) and the Revised Atlanta Classification (RAC), inevitably raises issues about which one is more valid, which

Table 4
Characteristics of patients in the four groups according to modified determinant-based classification.

	Group 1 (n = 211)	Group 2 (n = 43)	Group 3 (n = 90)	Group 4 (n = 31)	p value (2 vs 3)	p value (3 vs 4)
	TOF ± SN	*IN (- POF)*	*POF (- IN)*	*POF + IN*		
Age, year, median (range)	55 (17–91)	55 (16–78)	50 (20–90)	45 (23–79)	0.905	0.127
Gender of male, n (%)	126 (60)	27 (63)	61 (68)	16 (52)	0.570	0.107
Etiology, n (%)						
Biliary	112 (53)	18 (42)	39 (43)	9 (29)	0.995	0.228
Alcoholic	35 (17)	6 (14)	12 (13)	3 (10)		
Hyperlipidemia	27 (13)	7 (16)	14 (16)	9 (29)		
Idiopathic	25 (12)	9 (21)	18 (20)	9 (29)		
Organ failure scores (first 24 h)						
APACHE-II	8.1 ± 4.0	6.5 ± 4.4	14.7 ± 6.7	16.3 ± 5.0	<0.001	0.101
Modified Marshall Score	2.3 ± 1.0	2.1 ± 1.6	4.5 ± 2.7	6.6 ± 2.6	<0.001	<0.001
SOFA	3.3 ± 1.7	3.3 ± 2.3	7.0 ± 3.4	10.0 ± 3.7	<0.001	<0.001
Organ failures						
Shock, n (%)	37 (18)	15 (35)	19 (21)	28 (90)	0.095	<0.001
Respiratory failure, n (%)	120 (57)	16 (37)	76 (84)	27 (87)	<0.001	0.780
Renal failure, n (%)	44 (21)	5 (12)	41 (46)	20 (65)	<0.001	0.069
≥2 organs failure, n (%)	13 (6)	3 (7)	32 (36)	26 (84)	<0.001	<0.001
Local complications						
Sterile necrosis	58 (28)	30 (70)	30 (33)	22 (71)	<0.001	<0.001
Infected necrosis	0	43 (100)	0	31 (100)	<0.001	<0.001
Treatment and outcomes						
Use of inotropes, n (%)	10 (5)	9 (21)	13 (14)	25 (81)	0.346	<0.001
Use of mechanical ventilation, n (%)	5 (2)	3 (7)	26 (29)	16 (52)	0.004	0.022
Use of continuous renal replacement therapy, n (%)	1 (1)	2 (5)	18 (20)	10 (32)	0.020	0.216
Percutaneous or endoscopic drainage, n (%)	23 (11)	26 (61)	17 (19)	15 (46)	<0.001	0.002
Surgical operations, n (%)	35 (17)	16 (37)	15 (17)	14 (45)	0.005	0.001
ICU admission, n (%)	68 (32)	16 (37)	62 (69)	26 (84)	<0.001	0.160
ICU LOS, median (range)	8 (2–50)	9 (2–44)	15 (1–53)	27 (2–106)	<0.001	0.001
Hospital LOS, median (range)	29 (5–142)	70 (2–171)	28 (1–96)	44 (2–171)	<0.001	0.054
Mortality, n (%)	4 (2)	5 (12)	35 (39)	19 (61)	0.006	0.003

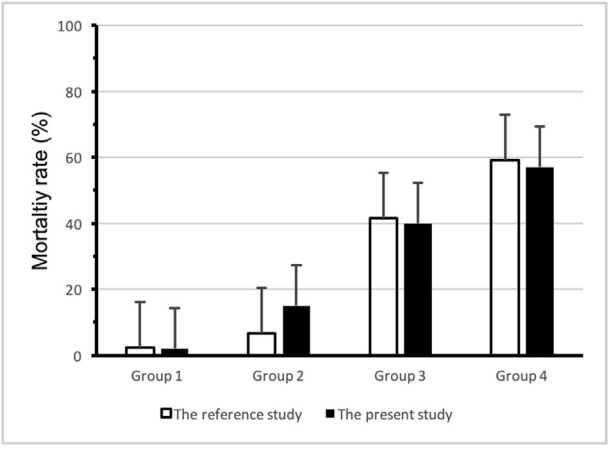

Fig. 2. The mortality with standard error of mean for the four groups according to Modified Determinant-Based Classification from a multicenter prospective ICU study [18] compared with the present study of ICU and non-ICU patients.

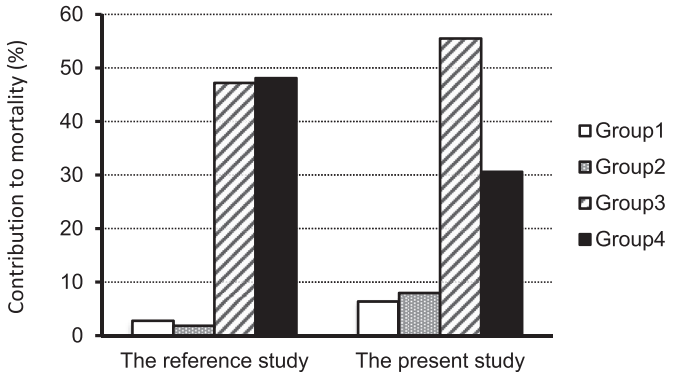

Fig. 3. The proportional contribution to mortality by Groups 1, 2, 3 and 4 according to Modified Determinant-Based Classification in the reference study [18] compared with the present study for patients with non-mild acute pancreatitis.

should be used and in what setting [8]. Although a large body of evidence suggests that the performance of the DBC and RAC are reasonably comparable, both classifications have limitations (Table 1). The DBC has been criticized because it is sometimes difficult to diagnose infected necrosis [4] and because patients with 'critical' severity are uncommon in certain settings [15], while RAC has been criticized for overlooking infected necrosis as an independent determinant of severity [26].

The present study confirms that the four groups defined by the MDBC are clinically distinct. The reference study demonstrated, in ICU patients, that the DBC 'severe' category comprises two subgroups of patients: those with infected necrosis but no persistent organ failure (Group 2) and those with persistent organ failure but no infected necrosis (Group 3) [18]. In our study, Group 1 has a low mortality, short ICU LOS, minimal demand for life supporting measures and limited use of drainage and surgery. While being more severe than the DBC 'moderate' category (Group 1) and less severe than the DBC 'critical' category (Group 4), Group 2 has a relatively low mortality, but infected necrosis requires drainage and surgery, which results in a longer hospital LOS. In contrast, Group 3 tends to have a more fulminant course, leading to a high rate of early death and ICU admission [27]. But this group has less need for drainage or surgery and, as a result, has a shorter hospital LOS than Group 2 [5,18]. Finally, patients in Group 4 have a prohibitive mortality, long ICU LOS, strong demand for intensive care support, drainage and surgery. Other investigators have reported similar findings with this most challenging group [16,26,28]. The MDBC highlights the importance of infected necrosis (IN) in determining severity. The present study confirms that IN does occur without

persistent organ failure (POF) (Group 2) and that IN is associated with an extremely high mortality when both IN and POF (Group 4) are present together. This mortality has a trend toward being significantly higher than for POF alone (57% vs 40%, $p = 0.138$) (Table 4 and Fig. 2) [25]. The lack of statistical significance in mortality between Group 3 and Group 4 could be explained by limited sample size (type II error), but more effective treatment strategies might also be responsible. The step-up approach with drainage and minimally invasive debridement results in fewer adverse events and less organ failure compared with open necrosectomy. This may reduce the impact of IN on mortality, although these patients still require more interventions and a longer hospital stay (Table 4).

It has been suggested that the DBC 'critical' category (with both POF and IN) is not practical because it is infrequent [15], but this depends on the context of the study. In a community-based study only 5% of patients were classified in the severe/critical category of DBC [10]. In a hospital-based study no difference in mortality was found between the severe and the critical categories of DBC [14]. However, patients in this study had an overall mortality of 3% and infected necrosis rate of 4%, both considerably lower than the present study. The present study was conducted in a tertiary teaching hospital in which about 27% of patients were transferred from other institutes. It is not surprising that there are proportionally more patients with 'critical' severity. The 'critical' category (Group 4, $n = 30$) in the present study consisted of less than 3% of entire cohort but contributed nearly one-third of the mortality (Figs. 1 and 3). Furthermore, there is a consistent step-wise increase in mortality through the four groups, exactly similar to that of the reference study (Fig. 2) [18]. These results argue for the inclusion of the DBC and MDBC 'critical' category. Given the above findings, it appears that it makes sense to classify the severity of acute pancreatitis according to clinical setting. A non-specialist in a smaller center, for instance, needs to decide whether patients have mild diseases that can be treated locally or whether they warrant transfer to a dedicated unit because of more severe conditions. In this setting two categories of severity suffice. But to a specialist taking care of transferred patients with more severe disease, a more sophisticated classification is appropriate. Future trials investigating predictors of severity and novel interventions will be assisted by more categories that are better defined. An example would be trials examining minimally invasive interventions for infected necrosis. It would be helpful to distinguish Group 2 (with IN but no POF) and Group 4 (with both IN and POF), since their clinical courses and outcomes are widely divergent.

The question of nomenclature of MDBC was also considered. The Spanish ICU study used the non-descriptive term 'group' for the 4 categories of severity, and they also excluded the mild category [18]. It is proposed that the MDBC be adopted using the descriptors and definitions for the categories of severity (mild, moderate, moderately severe, severe, critical) in acute pancreatitis detailed in Table 5. We believe this represents an important area for further debate.

A question that arises from this study is whether the timing of organ failure and mortality differs between the MDBC categories. Neither DBC nor RAC considers the timing of organ failure or whether early organ failure is associated with a high mortality [27,29,30]. The reference study [18] has emphasized the differences in mortality between the four groups but did not show the distribution of mortality against time. It is recognized that early multiorgan failure claims about half of deaths in acute pancreatitis [27]. Of the 63 deaths in the present study, 31 (49%) occurred in the first two weeks, and is consistent with other reports [27,29,31]. The MDBC 'severe' category (Group 3) also had a strong tendency to early mortality (58%), while the 'critical' category (Group 4) presents a bimodal distribution of mortality with much lower proportion (35%) of early death. This suggests that early and late mortality are due to different mechanisms, with a inflammatory cytokine basis for early and infected necrosis for late systemic inflammation, organ dysfunction and death [31,32]. Despite remarkable improvements in intensive care, early mortality remains the most pressing challenge in the management of acute pancreatitis [30]. To make further progress, there needs to be a better understanding of the key mechanisms driving early multiple organ dysfunction [31,33,34], without which management will be generic and supportive rather than specific treatments targeting key mechanisms.

The strength of the present study is that it has a relatively large sample size and is based on prospective data from all patients admitted with acute pancreatitis including those with mild severity. It enrolled all hospital admissions rather than just ICU patients. There are a number of limitations though. First, it was conducted in a tertiary hospital with a large proportion of patients with severe and critical acute pancreatitis and the results should only be interpreted in that context. It is accepted that the results are less relevant to secondary hospital settings. Second, the study design is likely to underestimate the rate of sterile and infected necrosis. But the majority of patients with infected necrosis can be diagnosed based clinical signs and images [35]. Usually the clinical deterioration of patients prompts a 'septic screen' to identify the source of infection. Third, the long study period inevitably allowed for variation in clinical decision-making, including the diagnosis of end points such as presence or absence of pancreatic necrosis, ICU admission, and approaches to intervention. But this study did involve the incorporation of the updated definitions of acute pancreatitis, particularly for radiological diagnoses and organ failures [6]. Lastly, abdominal compartment syndrome (ACS) can contribute to early death in patients with SAP [36], but this could

Table 5
The Proposed Nomenclature and Definition of Modified Determinant-Based Classification of Severity in Acute Pancreatitis.

DETERMINANTS	NO LOCAL COMPLICATIONS	STERILE LOCAL COMPLICATIONS	INFECTED LOCAL COMPLICATIONS
NO ORGAN FAILURE	**MILD**	**MODERATE**	**MODERATELY SEVERE**
TRANSIENT ORGAN FAILURE	**MODERATE**	**MODERATE**	**MODERATELY SEVERE**
PERSISTENT ORGAN FAILURE	**SEVERE**	**SEVERE**	**CRITICAL**

not be determined in the present study as intra-abdominal pressure was not routinely measured. Needless to say there is the need for prospective validation studies of MDBC in different cohorts and healthcare systems. Despite these limitations in study design, the data are remarkably similar to the reference study [18], and therefore provides strong validation for the MDBC categories.

In conclusion, this study has validated the Modified Determinant-Based Classification of severity in a tertiary hospital setting and draws on the strengths of both the DBC and RAC [6,7]. As such it represents a step forward [8]. Using the key determinants of severity, persistent organ failure and infected necrosis [25], to construct a severity classification makes sense. It provides meaningful categories designated by tightly defined descriptors instead of numbers. It is acknowledged that having five categories of severity is not necessary in secondary hospital settings where the decision is often about whether to transfer a patient or not, but this granularity is useful in the tertiary hospital and intensive care settings. These refined categories will result in improved reporting of audit outcomes, better comparison of clinical management and outcomes over time and between different centers, and more accurate allocation of patients in clinical trials.

Conflicts of interest

The authors reported no conflict of interest.

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References

[1] Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179–87. https://doi.org/10.1053/j.gastro.2012.08.002. e1–3.
[2] Pendharkar SA, Salt K, Plank LD, Windsor JA, Petrov MS. Quality of life after acute pancreatitis: a systematic review and meta-analysis. Pancreas 2014;43:1194–200.
[3] Reply to letter: "Determinant-based classification of severity of acute pancreatitis: have we really reached consensus? Ann Surg 2015;261:e23–4.
[4] Yadav D. Acute pancreatitis: too many classifications-what is a clinician or researcher to do? Clin Gastroenterol Hepatol 2014;12:317–9. https://doi.org/10.1016/j.cgh.2013.09.051.
[5] Talukdar R, Clemens M, Vege SS. Moderately severe acute pancreatitis: prospective validation of this new subgroup of acute pancreatitis. Pancreas 2012;41:306–9. https://doi.org/10.1097/MPA.0b013e318229794e.
[6] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11. https://doi.org/10.1136/gutjnl-2012-302779.
[7] Dellinger EP, Forsmark CE, Layer P, Levy P, Maravi-Poma E, Petrov MS, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg 2012;256:875–80. https://doi.org/10.1097/SLA.0b013e318256f778.
[8] Windsor JA, Johnson CD, Petrov MS, Layer P, Garg PK, Papachristou GI. Classifying the severity of acute pancreatitis: towards a way forward. Pancreatology 2015;15:101–4. https://doi.org/10.1016/j.pan.2015.01.006.
[9] Nawaz H, Mounzer R, Yadav D, Yabes JG, Slivka A, Whitcomb DC, et al. Revised Atlanta and determinant-based classification: application in a prospective cohort of acute pancreatitis patients. Am J Gastroenterol 2013;108:1911–7. https://doi.org/10.1038/ajg.2013.348.
[10] Acevedo-Piedra NG, Moya-Hoyo N, Rey-Riveiro M, Gil S, Sempere L, Martinez J, et al. Validation of the determinant-based classification and revision of the Atlanta classification systems for acute pancreatitis. Clin Gastroenterol Hepatol 2014;12:311–6. https://doi.org/10.1016/j.cgh.2013.07.042.
[11] Chen Y, Ke L, Tong Z, Li W, Li J. Association between severity and the determinant-based classification, Atlanta 2012 and Atlanta 1992, in acute pancreatitis: a clinical retrospective study. Medicine (Baltimore) 2015;94:e638.
[12] Mircea L, Ionut N, Ion L, Sorin P, Gabriel M, Hostiuc S, et al. The Atlanta 2012 versus the determinant-based classifications for acute pancreatitis: which one is better? Pancreat Disord Ther 2015. https://doi.org/10.4172/2165-7092.1000160.
[13] Xu XD, Wang ZY, Zhang LY, Ni R, Wei FX, Han W, et al. Acute pancreatitis classifications: basis and key goals. Medicine (Baltimore) 2015;94, e2182.
[14] Guo Q, Li M, Chen Y, Hu W. Determinant-based classification and revision of the Atlanta classification, which one should we choose to categorize acute pancreatitis? Pancreatology 2015;15:331–6. https://doi.org/10.1016/j.pan.2015.05.467.
[15] Kadiyala V, Suleiman SL, McNabb-Baltar J, Wu BU, Banks PA, Singh VK. The Atlanta classification, revised Atlanta classification, and determinant-based classification of acute pancreatitis: which is best at stratifying outcomes? Pancreas 2016;45:510–5. https://doi.org/10.1097/MPA.0000000000000477.
[16] Bansal SS, Hodson J, Sutcliffe RS, Marudanayagam R, Muiesan P, Mirza DF, et al. Performance of the revised Atlanta and determinant-based classifications for severity in acute pancreatitis. Br J Surg 2016;103:427–33. https://doi.org/10.1002/bjs.10088.
[17] Fernandes SR, Carvalho J, Santos P, Moura CM, Antunes T, Velosa J. Atlanta, revised Atlanta, and Determinant-based classification–application in a cohort of Portuguese patients with acute pancreatitis. Eur J Gastroenterol Hepatol 2016;28:20–4. https://doi.org/10.1097/MEG.0000000000000514.
[18] Zubia-Olaskoaga F, Maravi-Poma E, Urreta-Barallobre I, Ramirez-Puerta M-R, Mourelo-Farina M, Marcos-Neira M-P. Comparison between revised Atlanta classification and determinant-based classification for acute pancreatitis in intensive care medicine. Why do not use a modified determinant-based classification? Crit Care Med 2016;44:910–7. https://doi.org/10.1097/CCM.0000000000001565.
[19] Elm von E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X.
[20] Larvin M, McMahon MJ. Apache-II score for assessment and monitoring of acute pancreatitis. Lancet 1989;2:201–5.
[21] Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638–52.
[22] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the european society of intensive care medicine. Intensive Care Med 1996;22:707–10.
[23] IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1–15. https://doi.org/10.1016/j.pan.2013.07.063.
[24] Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut 2004;53:1340–4.
[25] Petrov MS, Shanbhag S, Chakraborty M, Phillips ARJ, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 2010;139:813–20. https://doi.org/10.1053/j.gastro.2010.06.010.
[26] Choi J-H, Kim M-H, Oh D, Paik WH, Park DH, Lee SS, et al. Clinical relevance of the revised Atlanta classification focusing on severity stratification system. Pancreatology 2014;14:324–9. https://doi.org/10.1016/j.pan.2014.08.001.
[27] Sharma M, Banerjee D, Garg PK. Characterization of newer subgroups of fulminant and subfulminant pancreatitis associated with a high early mortality. Am J Gastroenterol 2007;102:2688–95. https://doi.org/10.1111/j.1572-0241.2007.01446.x.
[28] Thandassery RB, Yadav TD, Dutta U, Appasani S, Singh K, Kochhar R. Prospective validation of 4-category classification of acute pancreatitis severity. Pancreas 2013;42:392–6. https://doi.org/10.1097/MPA.0b013e3182730d19.
[29] Thomson A. Fulminant acute pancreatitis. Ann Surg 2015;261:e23. https://doi.org/10.1097/SLA.0000000000000647.
[30] Frey CF, Zhou H, Harvey DJ, White RH. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. Pancreas 2006;33:336–44.
[31] Frey C, Zhou H, Harvey D, White RH. Co-morbidity is a strong predictor of early death and multi-organ system failure among patients with acute pancreatitis. J Gastrointest Surg 2007;11:733–42. https://doi.org/10.1007/s11605-007-0164-5.
[32] McKay CJ, Evans S, Sinclair M, Carter CR, Imrie CW. High early mortality rate from acute pancreatitis in Scotland, 1984-1995. Br J Surg 1999;86:1302–5. https://doi.org/10.1046/j.1365-2168.1999.01246.x.
[33] Fanous MYZ, Phillips AJ, Windsor JA. Mesenteric lymph: the bridge to future management of critical illness. Jop 2007;8:374–99.
[34] Deitch EA. Gut lymph and lymphatics: a source of factors leading to organ injury and dysfunction. Ann N Y Acad Sci 2010;1207(Suppl 1). https://doi.org/10.1111/j.1749-6632.2010.05713.x. E103–11.
[35] van Baal MC, Bollen TL, Bakker OJ, van Goor H, Boermeester MA, Dejong CH, et al. The role of routine fine-needle aspiration in the diagnosis of infected necrotizing pancreatitis. Surgery 2014;155:442–8. https://doi.org/10.1016/j.surg.2013.10.001.
[36] Radenkovic DV, Johnson CD, Milic N, Gregoric P, Ivancevic N, Bezmarevic M, et al. Interventional treatment of abdominal compartment syndrome during severe acute pancreatitis: current status and historical perspective. Gastroenterol Res Pract 2016;2016:5251806. https://doi.org/10.1155/2016/5251806.