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Pain intensity and prognosis of acute pancreatitis in an international, prospective study

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Introduction

Acute pancreatitis (AP) is a common inflammatory disease, with increasing incidence in many countries across the world[1–3]. The disease is characterized by abdominal pain, which is often described as severe and intense[4]. The clinical course may vary significantly, ranging from a mild disease that resolves spontaneously to more severe cases. Severe disease can include organ failure and pancreatic necrosis, resulting in significant morbidity and mortality[5]. As such, early identification of patients at risk of severe pancreatitis is crucial for optimizing management and improving outcomes.

Several systems have been used for the early prediction of AP severity, including the Glasgow-Imrie Criteria[6], Ranson's Criteria[7], the Bedside Index of Severity in Acute Pancreatitis score[8], and the Acute Physiology and Chronic Health Evaluation II score[9]. However, none of these includes pain assessment, despite pain being the presenting symptom. Higher pain intensity may reflect more widespread tissue damage, including pancreatic necrosis and local oedema. As such, specific features of pain, for example abdominal tenderness[10], shorter duration of pain[11,12], pain relapse during oral feeding[13], and increased pain severity[14], have been associated with severe AP. Given the variability in outcomes of AP, it remains uncertain whether pain intensity alone is sufficient for evaluating pain in AP and whether the assessment of pain intensity would increase the predictive accuracy for the clinical outcomes of AP.

The overall objective of this study was to investigate the relationship between pain intensity and outcomes of AP using prospectively collected data from the PAINAP database[14–16]. The hypothesis was that increased pain intensity on admission would be associated with increased AP severity and risk of complications. The primary aim was to evaluate the association between pain intensity on admission and clinical outcomes of AP. The secondary aim was to determine the predictive accuracy of pain intensity for AP severity and AP-related complications.

Methods

Study design

The database used for this post-hoc analysis was from the international, prospective PAINAP study, which has been described in detail in previous publications[14–16]. The study was observational, with the treatment of patients decided solely by the treatment-responsible physicians at each inclusion site. Patients were recruited upon admission within a 3-month interval in 2022, with a 1-month follow-up for each patient. All centres obtained local approval before commencing data collection and the study followed the principles of the Helsinki Declaration. In total, 118 centres across 27 countries participated in the study. All adult patients (≥18 years) admitted directly to inclusion sites with first-time AP were eligible for inclusion. Patients referred from other hospitals were excluded. Other exclusion criteria included chronic pancreatitis, recurrent AP, and pregnancy. For this post-hoc analysis, patients with missing data for key variables (age, sex, pain intensity on admission, or outcomes of AP) were excluded.

Outcome variables

The PAINAP database included patient demographic details (age, sex, continent of inclusion site, aetiology, and co-morbidity quantified by the Charlson Co-morbidity Index[17]), pain characteristics (duration before admission and intensity on admission), and AP outcomes (severity and local complications according to the revised Atlanta classification[18], organ failure (including type of organ failure), length of admission reported in days, and mortality). Patients were categorized as having pancreatic necrosis (yes/no) if they developed acute necrotic collections and/or walled-off necrosis. Likewise, patients were categorized as having fluid collections (yes/no) if they developed acute fluid collections and/or pseudocysts. Pain duration before admission was categorized as <12, 12–24, or >24 h. Pain intensity and duration on admission were measured using a

numeric rating scale (NRS) of zero to ten, based on interview of the patients or documentation in medical records. Patients were stratified based on pain intensity on admission; they were divided into three categories (no/mild pain (NRS 0–3), moderate pain (NRS 4–6), and severe pain (NRS 7–10)) based on previous reporting and validation of NRS categorization in other conditions[19–22]. Furthermore, patients were categorized based on the use of analgesia before admission (yes/no). This information was registered based on interview and medical files. A representative sample from the PAINAP database was previously re-collected and validated against the original data, demonstrating a moderate to strong correlation, as previously described[14].

Statistical analyses

The STATA software packages (StataCorp LP, College Station, Texas, USA; version 17.0) and R (version 4.3) were used for statistical analyses. For patient characteristics, categorical data are presented as n (%), whereas continuous data are presented as mean(s.d.) or median (interquartile range (i.q.r.)), depending on the data distribution. Missing data are presented as n (%) for each data variable. Before any statistical analyses, patients were categorized into three groups based on pain intensity on admission according to the definitions given above (no/mild pain, moderate pain, or severe pain). To identify outcome variables associated with pain intensity, univariable analyses across these three groups were performed using one-way ANOVA, the Kruskal–Wallis test, Fisher's exact test, or the chi-squared test, as appropriate according to data type (categorical/continuous) and data distributions. Outcomes associated with pain intensity on univariable analysis were selected for multivariable analysis using binary logistic regression. These multivariable models were adjusted for baseline characteristics that were unevenly distributed between groups ($P < 0.050$), including age, continent, biliary and alcoholic aetiology, and Charlson Co-morbidity Index. Furthermore, the models were adjusted for pre-admission pain duration and the use of analgesia pre-admission based on clinical rationale in accordance with the TRIPOD guidelines[23]. Results are presented as OR (95% c.i.). To assess how pain intensity influenced the probability of clinical outcomes of AP, the area under the curve of the receiver operating characteristics (AUC-ROC), sensitivity, specificity, positive and negative predictive values, prevalence, and likelihood ratios were calculated using a diagnostic accuracy test with outcomes developed during admission (for example disease severity and organ failure) as the reference standard and NRS as the test variable (NRS ≥7 defined as abnormal). The prevalence (~ pre-test probability) and likelihood ratios were subsequently used to construct nomograms for estimating the post-test probabilities of each outcome assessed. Finally, the multivariable models and probability tests described above were repeated in two subgroup analyses (one analysis excluded patients with pain duration ≤24 before admission and one analysis excluded patients with pain duration >24 h before admission) to assess the robustness of associations across different timings of presentation. $P < 0.050$ was considered statistically significant.

Results

In total, 1727 patients were included, of whom 183 (11%) reported no/mild pain on admission, 503 (29%) reported moderate pain on admission, and 1041 (60%) reported severe pain on admission

(Fig. 1). Baseline characteristics stratified according to admission pain intensity are reported in Table 1. Of the total population, 810 patients (47%) were female and the median age was 55 (i.q.r. 40–71) years. Biliary aetiology was the most common aetiology (998 patients (58%)). The proportion of patients with alcoholic aetiology was higher for patients with severe pain (253 patients (24%)) and patients with moderate pain (95 patients (19%)) compared with patients with no/mild pain (28 patients (10%)). A Charlson Co-morbidity Index >2 was more frequent for patients with no/mild pain (77 patients (43%)) compared with patients with moderate pain (179 patients (36%)) and patients with severe pain (338 patients (34%)). Finally, most patients had pain for >24 h before admission (799 patients (47%)).

Outcomes associated with pain intensity

On univariable analysis, AP severity according to the revised Atlanta classification[18] ($P = 0.002$), respiratory organ failure ($P = 0.028$), renal organ failure ($P < 0.001$), pancreatic necrosis ($P = 0.019$), fluid collections ($P = 0.028$), and length of admission ($P = 0.003$) were associated with pain intensity (Table S1). The results of the multivariable models are reported in Table 2. Severe pain on admission was associated with increased odds of moderately severe/severe AP (OR 1.66 (95% c.i. 1.09 to 2.53); $P = 0.017$), renal organ failure (OR 3.04 (95% c.i. 1.34 to 6.87); $P = 0.008$), and pancreatic necrosis (OR 2.37 (95% c.i. 1.22 to 4.61); $P = 0.011$) compared with no/mild pain. Moderate pain on admission was also associated with increased odds of pancreatic necrosis (OR 2.02 (95% c.i. 1.01 to 4.03); $P = 0.046$) compared with no/mild pain, whereas it was associated with decreased odds of fluid collections (OR 0.56 (95% c.i. 0.33 to 0.96); $P = 0.035$) compared with no/mild pain.

Influence of pain intensity on outcomes

Overall, the discriminatory ability of severe pain (NRS ≥7) for predicting outcomes of AP was poor, with low to fair AUC-ROCs for AP severity (0.54 (95% c.i. 0.52 to 0.57)), organ failure (0.57 (95% c.i. 0.54 to 0.60)), respiratory organ failure (0.55 (95% c.i. 0.51 to 0.59)), renal organ failure (0.61 (95% c.i. 0.57 to 0.65)), pancreatic necrosis (0.54 (95% c.i. 0.50 to 0.57)), and fluid collections (0.53 (95% c.i. 0.50 to 0.57)) (Table 3). The sensitivity was moderate for all outcomes, with the highest value (81% (95% c.i. 72% to 88%)) for renal organ failure. The specificity was lower across all outcomes, ranging from 41% to 42%. Similarly, the positive predictive values were consistently low (9–30%), whereas the negative predictive values were generally higher (77–97%). The highest negative predictive value was observed for renal organ failure. The positive and negative likelihood ratios were poor, indicating that the utilization of pain intensity (cut-off NRS ≥7) did not significantly alter the post-test probability of any outcome compared with the pre-test probability (Fig. 2).

Subgroup analyses

The results of the subgroup analyses were consistent with the primary results, except that only renal organ failure and pancreatic necrosis remained significantly associated with severe pain (Tables S2–S5).

Discussion

In this study of patients admitted with first-time AP across a large geographical area, severe pain intensity on admission was associated with more severe AP, renal organ failure, and
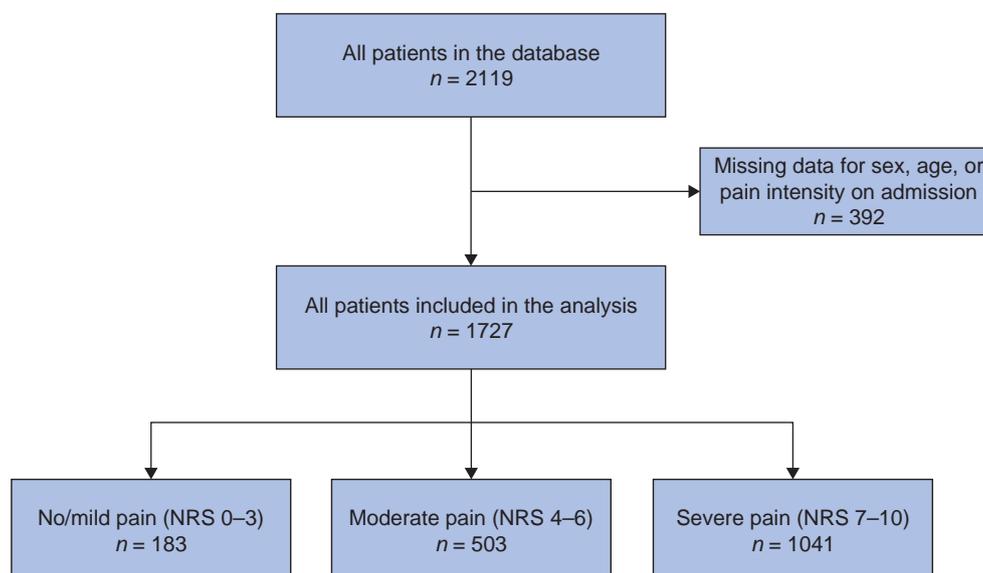
Fig. 1 Flow chart for patient inclusion in the study

NRS, numeric rating scale.

Table 1 Baseline characteristics stratified according to pain intensity

	Total population (n = 1727)	No/mild pain, NRS 0–3 (n = 183)	Moderate pain, NRS 4–6 (n = 503)	Severe pain, NRS 7–10 (n = 1041)	P	Missing data
Sex					0.192	0 (0)
Male	917 (53)	99 (54)	250 (50)	568 (55)		
Female	810 (47)	84 (46)	253 (50)	473 (45)		
Age (years), median (i.q.r.)	55 (40–71)	61 (44–76)	56 (41–71)	54 (40–69)	0.003	0 (0)
Continent					<0.001	0 (0)
Europe	1177 (68)	101 (55)	356 (71)	720 (69)		
Asia	350 (20)	48 (26)	106 (21)	196 (19)		
Australia	142 (8)	30 (17)	30 (6)	82 (8)		
Other continents*	58 (4)	4 (2)	11 (2)	43 (4)		
Aetiology**						0 (0)
Biliary	998 (58)	109 (60)	312 (62)	577 (55)	0.042	
Alcoholic	366 (21)	28 (10)	95 (19)	253 (24)	<0.001	
Post-ERCP	64 (4)	5 (3)	20 (4)	39 (4)	0.799	
Hypertriglyceridaemia	62 (4)	9 (5)	14 (3)	39 (4)	0.377	
Other	305 (18)	45 (25)	77 (15)	183 (18)	0.019	
CCI category					0.003	52 (3)
0	593 (35)	51 (28)	153 (31)	389 (39)		
1–2	488 (29)	53 (29)	162 (33)	273 (27)		
>2	594 (36)	77 (43)	179 (36)	338 (34)		
Pain duration before admission (h)					0.480	17 (1)
<12	435 (25)	45 (25)	124 (25)	266 (26)		
12–24	476 (28)	43 (24)	151 (30)	282 (27)		
>24	799 (47)	93 (51)	225 (45)	481 (47)		
Analgesia pre-admission					0.141	0 (0)
No	195 (11)	23 (13)	45 (9)	127 (12)		
Yes	1532 (89)	160 (87)	458 (91)	914 (88)		

Values are n (%) unless otherwise indicated. *Other continents were South America (n = 8), North America (n = 24), and Africa (n = 26). **Subset of patients had overlapping aetiologies. NRS, numeric rating scale; i.q.r., interquartile range; ERCP, endoscopic retrograde cholangiopancreatography; CCI, Charlson Co-morbidity Index.

pancreatic necrosis compared with no/mild pain. Moderate pain intensity on admission was only associated with increased odds of pancreatic necrosis (as well as decreased odds of fluid collections) compared with no/mild pain. However, the discriminatory performance of pain intensity was poor, with low AUC-ROCs and no significant effect on post-test probability for all outcomes. Although pain severity may reflect underlying disease burden in AP, it lacks sufficient accuracy for early risk

stratification when used in isolation. However, the high negative predictive values observed in this study suggest that the absence of severe pain on admission may help reassure clinicians and support the decision for outpatient management in low-risk patients.

The pathophysiology of pain in AP is incompletely understood and the majority of the evidence comes from chronic pancreatitis or experimental models of AP. Traditionally, pancreatic pain has

Table 2 Multivariable analyses of pain intensity and the odds of developing moderately severe/severe AP, organ failure (any, respiratory, or renal), pancreatic necrosis, or fluid collections (*n* = 1660)

	Adjusted OR (95% c.i.)*	P
Moderately severe/severe AP		
Moderate pain (*versus* no/mild pain)	1.01 (0.65,1.59)	0.958
Severe pain (*versus* no/mild pain)	1.66 (1.09,2.53)	0.017
Organ failure		
Moderate pain (*versus* no/mild pain)	0.69 (0.37,1.27)	0.233
Severe pain (*versus* no/mild pain)	1.79 (1.05,3.08)	0.034
Respiratory organ failure		
Moderate pain (*versus* no/mild pain)	0.73 (0.37,1.43)	0.362
Severe pain (*versus* no/mild pain)	1.45 (0.80,2.66)	0.223
Renal organ failure		
Moderate pain (*versus* no/mild pain)	0.81 (0.32,2.08)	0.661
Severe pain (*versus* no/mild pain)	3.04 (1.34,6.87)	0.008
Pancreatic necrosis		
Moderate pain (*versus* no/mild pain)	2.02 (1.01,4.03)	0.046
Severe pain (*versus* no/mild pain)	2.37 (1.22,4.61)	0.011
Fluid collections		
Moderate pain (*versus* no/mild pain)	0.56 (0.33–0.96)	0.035
Severe pain (*versus* no/mild pain)	0.92 (0.57–1.49)	0.725

*Adjusted for age, continent, biliary and alcoholic aetiology, Charlson Co-morbidity Index, pre-admission pain duration, and the use of analgesia pre-admission. AP, acute pancreatitis.

Table 3 Diagnostic performance of severe baseline pain (NRS 7–10) in diagnosing AP outcomes (*n* = 1727)

Outcome	AUC-ROC (95% c.i.)	Sensitivity (95% c.i.)	Specificity (95% c.i.)	PPV (95% c.i.)	NPV (95% c.i.)
AP severity*	0.54 (0.52,0.57)	67 (62,71)	42 (39,45)	30 (28,33)	77 (74,80)
Organ failure	0.57 (0.54,0.60)	73 (66,79)	41 (39,44)	15 (13,17)	92 (89,94)
Respiratory organ failure	0.55 (0.51,0.59)	69 (61,77)	41 (38,43)	10 (8,12)	93 (91,95)
Renal organ failure	0.61 (0.57,0.65)	81 (72,88)	41 (39,44)	9 (7,11)	97 (95,98)
Pancreatic necrosis	0.54 (0.50,0.57)	67 (60,73)	41 (38,43)	14 (12,17)	89 (87,91)
Fluid collections	0.53 (0.50,0.57)	66 (59,72)	41 (38,43)	13 (11,16)	90 (87–92)

*According to the revised Atlanta classification. NRS, numeric rating scale; AP, acute pancreatitis; AUC-ROC, area under the curve of the receiver operating characteristics; PPV, positive predictive value; NPV, negative predictive value.

been attributed to local inflammation, resulting in tissue damage, ischaemia, oedema, necrosis, and increased ductal pressure[24]. Furthermore, the extensive release of inflammatory mediators during an episode of AP may lead to primary hyperalgesia[25]. This is in contrast to the physiology of pain in painful chronic pancreatitis, for which it is well known that neuropathic pain and central sensitization play an important role[26,27]. While neuropathic pain has yet to be confirmed in AP, neurogenic inflammation, in which injured pancreatic tissue interacts with activated neurons, has been suggested to escalate both pain and inflammation, thus linking severe pain to more severe AP[25,28]. Consistently, an increased risk of organ failure with higher pain intensity was observed in patients with AP. In this context, it is, however, interesting that the association between pain intensity and renal organ failure persisted upon multivariable analysis, whereas the association for respiratory organ failure did not. Acute renal injury during AP may result from increased vascular permeability and hypovolaemia due to systemic inflammation and subsequent renal hypoperfusion, which may be further worsened by abdominal hypertension (and pain)[29,30]. Moreover, factors released from the necrotic pancreas, including activated trypsin, may cause direct nephrotoxicity and impaired renal microcirculation[29,30]. As such, pancreatic necrosis (leading to more severe pain) may increase the risk of acute renal failure to a greater extent than that of acute respiratory dysfunction. Finally, medications such as non-steroidal anti-inflammatory drugs and renin-angiotensin-aldosterone-modulating agents may also affect this.

In the present study, the discriminatory ability of pain intensity for predicting outcomes of AP was poor, indicating that reporting pain intensity is insufficient when it comes to prognostication in AP. Pain intensity is typically measured using an NRS (or a visual analogue scale) due to its simplicity[31]. However, a recent Hungarian study suggested that the descriptive qualities of pain in AP may have a higher prognostic value in predicting disease severity and mortality than pain intensity. For instance, the sharpness of pain sensation was associated with increased severity of AP and mortality[4]. These aspects are, however, rarely assessed in clinical practice and pain intensity is generally an insufficient predictor of disease severity in other acute pain conditions[32–34]. Furthermore, it has been recommended that core outcome sets for acute pain should include at least pain intensity, pain interference, physical function, and quality of life[35]. While many aspects of acute pain are consistent across aetiologies, substantial differences can arise due to anatomical variations in pain origin, as well as differences in pain characteristics influenced by inflammation and neural involvement. Therefore, a more disease-specific approach is warranted. Current pain assessment in AP relies mainly on unidimensional scales, specifically focused on pain intensity. For future pain assessment in AP, a more comprehensive multidimensioned tool for pain assessment, as with chronic pancreatitis, may be warranted[36]. The ongoing CAPPOS study undertaken by the authors' group aims to create core outcome sets specifically for pain in AP, including all relevant disease-related aspects of pain, and develop assessment tools for each outcome[37]. This approach may enable
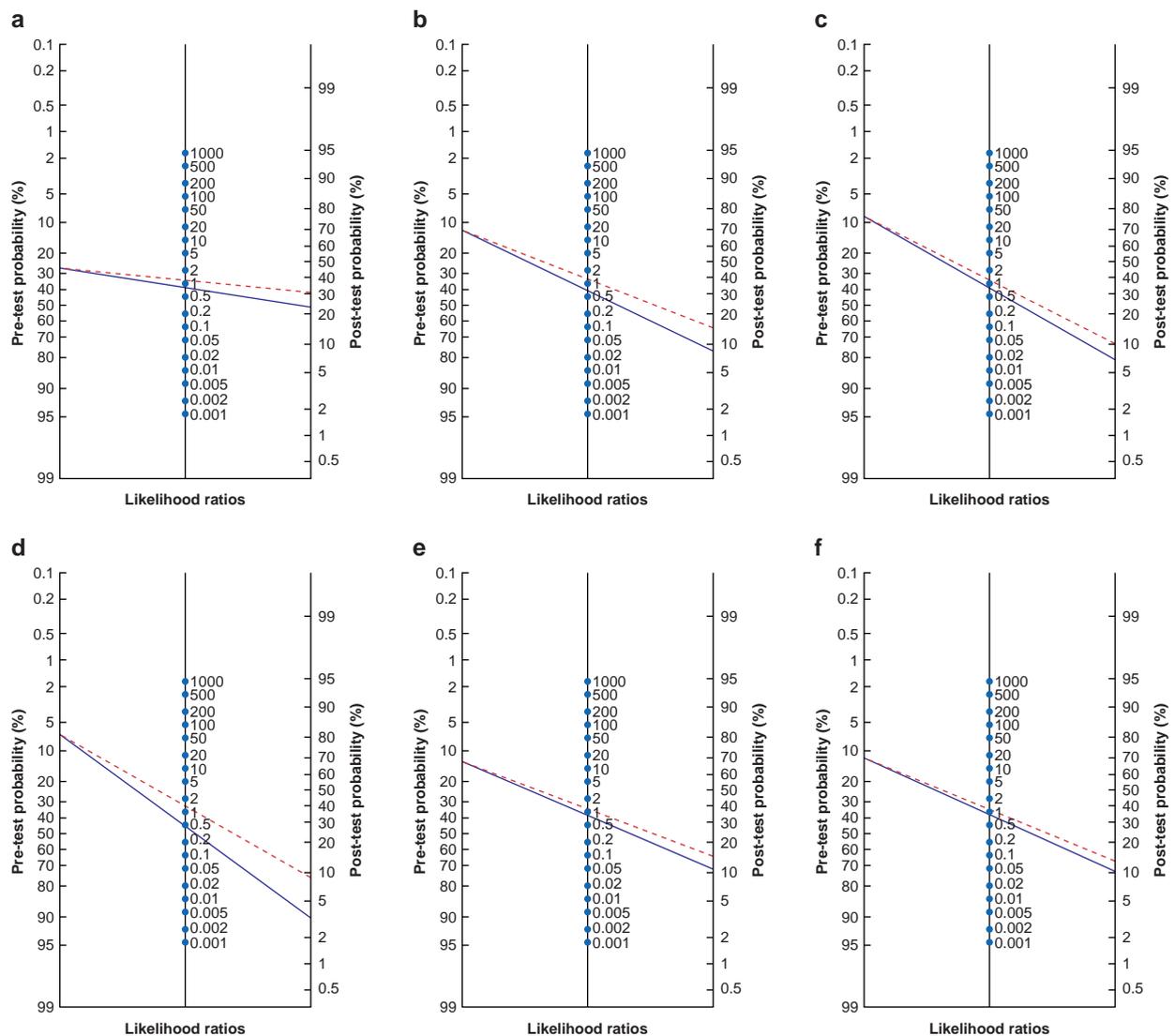
Fig. 2 Nomograms of pre- and post-test probabilities and likelihood ratios of an NRS greater than or equal to seven

a For predicting AP severity according to the revised Atlanta classification. **b** For predicting organ failure. **c** For predicting respiratory organ failure. **d** For predicting renal organ failure. **e** For predicting pancreatic necrosis. **f** For predicting fluid collections. NRS, numeric rating scale; AP, acute pancreatitis.

a more precise evaluation of the relationship between pain, disease severity, and prognosis.

The primary strength of the present study was the multicentred, prospective, international design, including the large study cohort, enhancing generalizability and the completeness of data, which were validated after initial data collection. Pain intensity was self-reported and, therefore, subject to significant inter-individual variation, as the pain experience is subjective and can vary considerably between individuals. The analyses did not account for pre-admission analgesia. However, as all patients were directly admitted to one of the inclusion centres and not transferred from other centres, any pre-admission analgesia would have been self-administered and the use of strong analgesics before admission was likely minimal. Another limitation was the snapshot design of the database, which only recorded pain intensity on admission. Repeated pain assessments over time would have allowed for an analysis of its temporal evolution, potentially offering further insight into the relationship between pain and prognosis. In this

study, strong associations were found between severe pain on admission and several clinical outcomes of AP. However, the discriminatory performance of severe pain in predicting these outcomes was poor. This is likely because some patients recover spontaneously, despite experiencing severe pain on presentation. Nevertheless, the higher negative predictive values suggest that the absence of severe pain on admission may help rule out certain adverse outcomes, particularly renal failure.

The present study showed that severe pain was associated with worse outcomes of AP, but the discriminatory performance of using severe pain to predict outcomes of AP was poor. Future research is warranted to refine the assessment of AP pain and clarify the underlying mechanisms. A more comprehensive understanding of pain in AP could improve its prognostic value, guide more personalized treatment strategies, and optimize pain management. This, in turn, may aid in monitoring treatment response, informing analgesic dose adjustments, and determining the timing of different analgesic strategies, ultimately improving both clinical and patient-centred outcomes.

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The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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