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Prediction of infected pancreatic necrosis in acute necrotizing pancreatitis by the modified pancreatitis activity scoring system

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Abstract

Objectives: Infected pancreatic necrosis (IPN) is a significant complication of acute necrotizing pancreatitis (ANP). Early identification of patients at high risk of IPN would enable appropriate treatment, but there is a lack of valid tools. This study aimed to assess the performance of the Pancreatitis Activity Scoring System (PASS) and its modifications (by removing or reducing the weight of opioid usage) in predicting IPN in a cohort of predicted severe ANP patients.

Methods: Data was prospectively collected in the TRACE trial (2017–2020) involving 16 sites across China. The predictive performance of PASS, modified PASS (mPASS), and conventional indices were assessed by the area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow Ĉ-test, Brier score, and Fagan's nomogram. Multivariate logistic regression analysis (MLRA) was used to define the relationship between the best-performing PASS/mPASS model and IPN.

Results: A total of 508 subjects were enrolled (median age, 43 years; 62.8% males) in the original trial, and 122 developed IPN (24%) within 90 days after randomization. Compared with non-IPN patients, the scores of PASS and its modified models were significantly higher in the IPN patients (all $p < 0.001$). Among the PASS and its modifications, mPASS-4 had the largest AUC, the lowest Brier score, and good calibration. The mPASS-4 model demonstrated an AUC of 0.752 in predicting IPN (the optimal cut-off for the mPASS-4 was 292.5) and outperformed the conventional indices. The MLRA results showed that mPASS-4 >292.5 was an independent risk factor of IPN (OR: 3.6, 95% CI: 2.1–6.3).

Conclusion: The PASS and its modifications during the first week of ANP onset predict the development of IPN, with mPASS-4 performing best. The mPASS-4

Wenjian Mao, Kang Li and Jing Zhou contributed equally to this work.

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model simplifies the original PASS, increasing the likelihood of clinical implementation.

KEYWORDS
acute necrotizing pancreatitis, infected pancreatic necrosis, modified pancreatitis activity scoring system, opioid, pancreatitis activity scoring system

INTRODUCTION

Infected pancreatic necrosis (IPN) is a significant complication of acute pancreatitis (AP), carrying substantial morbidity and mortality, and requires expert management.[1,2] Improvements in the management of IPN in recent years have reduced it as a determinant of mortality,[3,4] but it remains a significant cause of morbidity.[5] Early identification of patients with a substantial risk of IPN would help key decision-making, including early transfer to a tertiary center and/or admission to intensive care. However, current prediction tools have focused on mortality as the principal outcome, and their performance in predicting IPN is not known.[6]

The AP Activity Scoring System (PASS), developed by a group of international experts in 2015,[7] was designed to measure disease activity in AP patients. Previous studies have investigated the relationship between the PASS score and several key clinical outcomes, including the development of severe acute pancreatitis (SAP), readmission after discharge, and extended hospital stay.[8–11] In 2018, we investigated the predictive accuracy of PASS for IPN in a retrospective study and found that PASS score at admission outperformed the conventional acute physiology and chronic health evaluation II (APACHE II) score.[12]

However, the original PASS was considered flawed because of the dominating weight assigned to opioid usage.[10] Accordingly, Pedram Paragomi et al. generated four modified PASS (mPASS) models by removing or reducing the weight of the morphine equivalent dose (MED) component.[13] An international cohort study showed that the mPASS was a better predicted severe AP than PASS, but the prediction of IPN was not included because of the low event rate and limited follow-up.[13]

Recently, we published the results of a multicenter, double-blind, randomized trial (The TRACE trial),[14] which investigated the impact of immune enhancement on the incidence of IPN in patients with predicted severe acute necrotizing pancreatitis (ANP). Data required for calculating PASS were prospectively collected at enrollment. In this *post hoc* analysis, we aimed to investigate the relationship between the PASS/mPASS and IPN. In addition, we sought to identify optimal cut-off thresholds of the PASS/mPASS for predicting IPN to provide a framework for applying this instrument in future clinical practice and research.

Key summary

The established knowledge on this subject

- There is a lack of validated tools for predicting infected pancreatic necrosis (IPN)
- The Pancreatitis Activity Scoring System (PASS) has potential to predict IPN but requires validation
- Four modified PASS (mPASS) models have been developed by removing or reducing the weight of opioid usage

The significant and/or new findings of this study

- Among the PASS/mPASS models, the mPASS-4 had the largest area under the receiver operating characteristic curve, the lowest Brier score, and good calibration
- The mPASS-4 model outperformed the conventional indices in predicting IPN
- The mPASS-4 model simplifies the original PASS, increasing the likelihood of clinical implementation

METHODS

Study design

We conducted this *post hoc* analysis using data from the TRACE trial to assess the performance of the PASS and its modifications in predicting IPN. The TRACE trial (ClinicalTrials.gov identifier, NCT02473406) is a large multicenter randomized controlled trial enrolling predicted severe ANP patients.[14] The original protocol was approved by the ethics committee of Jinling Hospital (2015NZKY-004-02), and the final protocol was published in 2020.[15] The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The enrollment was between March 2017 and December 2021. Written informed consent was obtained from the patients or their next of kin.

Study participants and data collection

The original trial recruited 508 patients with predicted severe ANP (APACHEII≥8) admitted within 7 days of the advent of abdominal

pain. The complete eligibility criteria and full details on data collection can be found in the published protocol.[15] All the data required in this *post hoc* analysis were extracted from the electronic database of the TRACE trial.[14]

The data required for calculating the PASS were collected prospectively within the first 12 h of enrollment. The original PASS consists of five separately weighted parameters, including Organ failure (OF) (100 points per organ), oral feeding intolerance (40 points), systemic inflammatory response syndrome (SIRS) (25 points per criterion), morphine equivalent dose or MED (5 points per equivalent), and pain score (5 points per scale).[7,8] The PASS was calculated based on the worst or extreme findings at each time point. OF, including respiratory, cardiovascular, or renal failures, was defined according to the modified Marshal score ≥2 for each individual organ system.[7] Multiple organ dysfunction syndrome (MODS) is defined as two or more failures of different organ systems.

The changes of the MED component from PASS to the mPASS are shown in Figure 1 as follows.

1. mPASS-1: MED was deleted;
2. mPASS-2: no opioid administration received a score of 0, and any opioid administration received 50;
3. mPASS-3: no opioid received a score of 0, low opioids (<17 MED) 25, and high opioids (≥17 MED) 50;
4. mPASS-4: no opioid received a score of 0, low opioid (<17) 25, high opioid (≥17) 75.

Clinical outcomes

The primary outcome was the development of IPN during the 90 days after randomization. The diagnostic criteria of IPN were: gas bubbles within the pancreas and/or peripancreatic necrosis on CT; a positive culture from pancreatic and/or peripancreatic necrosis obtained by fine-needle aspiration, drainage, or necrosectomy.[1] The diagnoses were made by the treating physician according to the standard protocol.

To assess the PASS/mPASS in relation to other clinical outcomes, patients were divided into two groups based on the optimal cut-off value of the best-performing model in predicting IPN. The clinical outcomes (SAP, OF, major complications, mortality, et al.) besides IPN were compared between groups.

Statistical methodology

Continuous data are reported as medians and interquartile ranges and analyzed by Mann-Whitney's test. Categorical data are expressed as frequencies and percentages. The comparison of categorical data between groups was performed using the Chi-square test or Fisher's exact test.

Predictive performance was assessed by the area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow Ĉ-test (H-L), and Brier score to determine the best-performing scoring system. The Youden's Index of receiver operator characteristic (ROC) analysis was used to define the optimal cut-off point and corresponding sensitivity and specificity for each scoring system to predict 90-day IPN. The DeLong test, a nonparametric approach developed by Elizabeth R. DeLong et al.[16] was then used to compare the differences in AUC. The positive LR (Likelihood Ratio) was calculated and the Fagan's nomogram was constructed to help clinicians use different scoring system results to estimate a patient's probability of having a disease.[17]

Univariate logistic regression was used to assess the relationship between PASS/mPASS (as dichotomous variables using the optimal cut-off values) and 90-day IPN. The other clinical parameters and severity scores were also evaluated. We then introduced the most significant PASS/mPASS in the univariate logistic regression analyses, potential confounders ($p < 0.1$), and several a priori variables (age, gender and etiology) into the multivariate logistic regression model to assess the relationship between PASS/mPASS and 90-day IPN.

Statistical tests were two-sided, and p values <0.05 were considered significant unless otherwise stated. All data processing was done in SPSS 25.0 software and R 4.1.1 software (R Foundation for Statistical Computing).

RESULTS

Characteristics of the study population

Between March 2017 and December 2020, 508 patients with predicted severe ANP were randomized. The most frequent etiology was hyperlipidemia (49.4%), and 62.8% of participants were male. The demographic and baseline characteristics of the study subjects are summarized in Table 1. During the 90 days after randomization, 122 patients (24.0%) developed IPN. Compared with non-IPN patients, all the scores of PASS and mPASS were significantly higher in the IPN patients (all $p < 0.001$).

Predictive performance of the scoring systems

The results of the ROC analysis are shown in Figure 2. Among the PASS/mPASS models, the mPASS-4 had the largest AUC (0.752). Compared to the conventional indices, the mPASS-4 had a significantly higher AUC than the APACHE II score ($Z = 2.95$, $p = 0.003$), BISAP score ($Z = 4.13$, $p < 0.001$), and C-reactive protein (CRP) ($Z = 5.25$, $p < 0.001$) in the DeLong test. Among the seven scoring systems, all models except the original PASS and the APACHE II showed good calibration for predicting 90-day IPN according to the H-L test ($p > 0.05$). Precision, as measured by the Brier score, ranged from 0.154 for the mPASS-4 score to 0.175 for the BISAP score. Among the PASS/mPASS models, the mPASS-4 had the lowest Brier score (0.154) (Table 2). The optimal cut-off values and the positive LR values of the PASS and its modifications, APACHE II and BISAP are also shown in Table 2.

As shown in Figure 3, with the pre-test probability of 24% (122/508), the probability that a patient had 90-day IPN would rise to

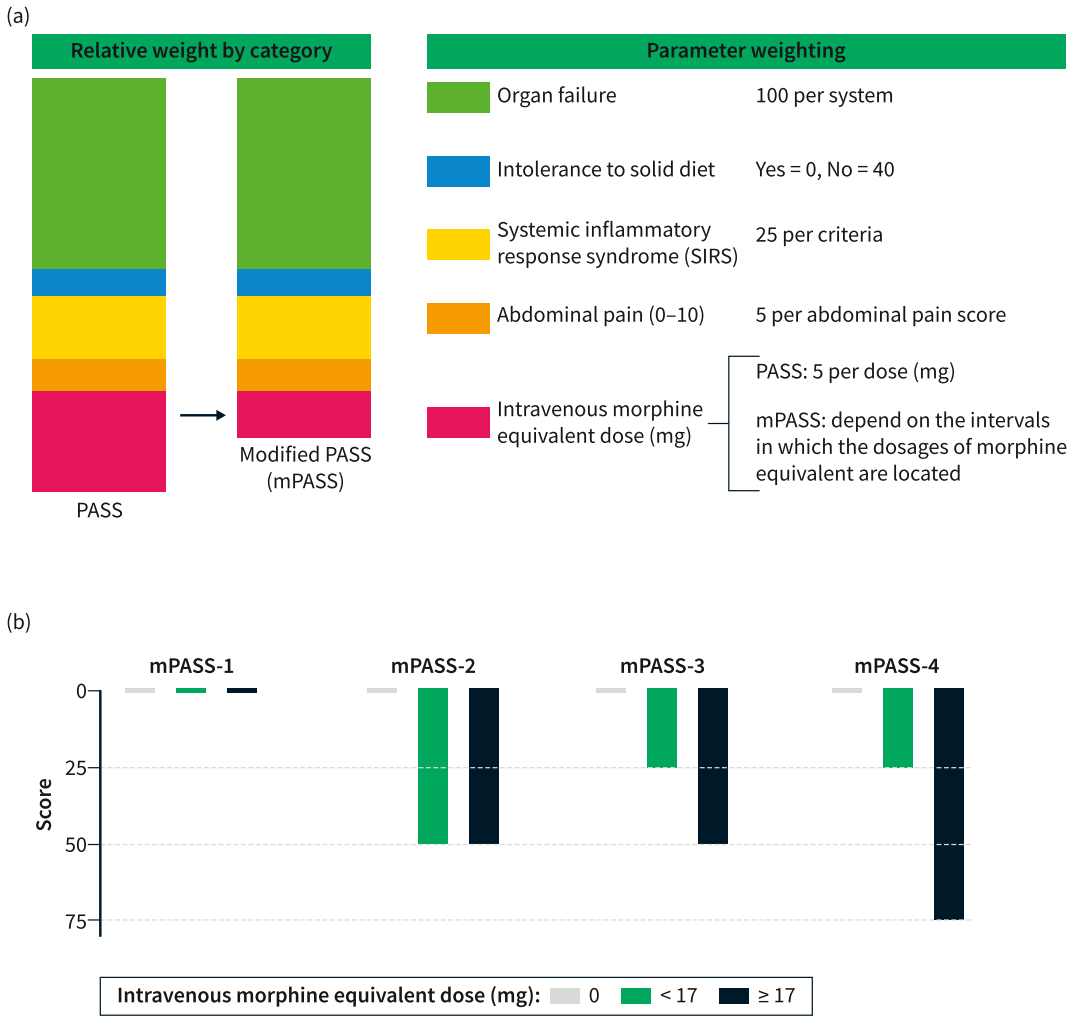

FIGURE 1 The changes from the original Pancreatitis Activity Scoring System (PASS) to the mPASS scores. (a) main differences between the original PASS and mPASS models, (b) scores of morphine equivalent dose (MED) component in the four mPASS scores. PASS denotes PASS. mPASS denotes modified PASS.

46.7% if the patient had an mPASS-4 above the cut-off. In the same way, post-test probabilities for the positive PASS, mPASS-1, mPASS-2, mPASS-3, APACHE II and BISAP scores were 41.4%, 39.4%, 39.4%, 40.0%, 33.1% and 45.8%, respectively.

The association between the PASS/mPASS and 90-day IPN

In the univariate analysis, the PASS and its modifications (dichotomous variables), baseline lymphocyte count, presence of MODS, age, and the extent of pancreatic necrosis were all associated with 90-day IPN. The most significant mPASS-4 was then introduced into the multivariate analysis. After controlling for the confounders found in the univariate analysis (lymphocyte count at enrollment, presence of MODS, age, and the extent of pancreatic necrosis) and the a priori factors (gender and etiology), mPASS-4 >292.5 remained an independent risk factor for 90-day IPN (odds ratio (OR): 3.6, 95% CI: 2.1–6.3) (Table 3).

Clinical outcomes in patients with mPASS4 above 292.5 or not

The optimal cut-off value of 292.5 for enrolment mPASS-4 (the best performing predictor of 90-day IPN) was used to divide the patients into two groups (≤292.5, $n = 341$; >292.5, $n = 167$). The enrollment mPASS-4 score of >292.5 was associated with higher incidences of SAP, renal failure, intraperitoneal hemorrhage, and gastrointestinal fistula, more requirement of invasive interventions, prolonged hospital and intensive care unit stay, and increased hospital costs and mortality (all $p < 0.05$) (Table 4).

DISCUSSION

In this study, it was found that a higher PASS/mPASS score during the first week of predicted severe ANP was associated with the development of IPN. Among the PASS and four modified PASS models, the mPASS-4 had the largest AUC, the lowest Brier score (a

TABLE 1 Baseline characteristics of the study subjects

Characteristics	Total (*N* = 508)	IPN (*N* = 122)	Non-IPN (*N* = 386)
Age, median (IQR), y	43 (35–53)	48 (37–56)	42 (34–52)
Gender			
Women, *n* (%)	189 (37.2)	43 (35.2)	146 (37.8)
Men, *n* (%)	319 (62.8)	79 (64.8)	240 (62.2)
BMI, median (IQR), kg/m^2	26.4 (24.0–28.4)	26.4 (24.2–28.7)	26.4 (24.0–28.4)
Etiologies, *n* (%)			
Alcoholic	32 (6.3)	11 (9.0)	21 (5.4)
Biliary	201 (39.6)	56 (45.9)	145 (37.6)
Idiopathic	24 (4.7)	4 (3.3)	20 (5.2)
Hypertriglyceridemia	251 (49.4)	51 (41.8)	200 (51.8)
Interval between onset and enrollment, d	4 (2.5–6)	5 (2.2–6)	4 (2.5–6)
Organ failure at admission, *n* (%)	323 (63.6)	98 (80.3)	225 (58.3)
MODS at admission, *n* (%)	107 (21.1)	56 (45.9)	51 (13.2)
The extent of pancreatic necrosis, *n* (%)			
<30%	316 (62.2)	50 (41.0)	266 (68.9)
30%–50%	127 (25.0)	43 (35.2)	84 (21.8)
>50%	65 (12.8)	29 (23.8)	36 (9.3)
Use of antibiotics, *n* (%)	434 (85.4)	107 (87.7)	327 (84.7)
Use of Tα1, *n* (%)	254 (50)	57 (46.7)	197 (51.0)
Disease severity at enrollment			
CRP, median (IQR), g/L	165.1 (100.1–236.2)	184.3 (115.6–249.7)	162.4 (96.7–227.0)
Lymphocyte count, median (IQR) unit, 10^9/L	0.9 (0.6–1.2)	0.8 (0.6–1.1)	0.9 (0.7–1.2)
APACHE II score, median (IQR)	10 (8–13)	12 (9–15)	9 (8–12)
BISAP, median (IQR)	2 (1–2)	2 (2–3)	2 (1–2)
PASS, median (IQR)	235 (190–537)	490 (249–1059)	225 (160–430)
mPASS1, median (IQR)	230 (180–295)	298 (235–376)	215 (155–270)
mPASS2, median (IQR)	230 (180–295)	298 (235–376)	215 (155–270)
mPASS3, median (IQR)	230 (180–295)	298 (234–376)	215 (155–266)
mPASS4, median (IQR)	230 (180–315)	315 (235–396)	215 (155–290)

Abbreviations: APACHE II, acute physiology and chronic health evaluation II, which ranges from 0 to 71, with higher scores indicating more severe disease, BISAP, bedside index for severity in acute pancreatitis; BMI, body mass index; CRP, C-reactive protein; IPN, infected pancreatic necrosis; IQR, interquartile range; mPASS, modified pancreatitis activity scoring system; MODS, multiple organ dysfunction syndromes; PASS, pancreatitis activity scoring system; Tα1, thymosin α1.

lower Briers score indicates better accuracy), and good calibration. The mPASS-4 outperformed the conventional indices in predicting IPN. Our results suggest that an mPASS-4 greater than 292.5 was independently associated with the development of IPN after adjustment for potential confounders.

The PASS was initially introduced in 2015 and assessed in two studies conducted in central and southern California.[7,8] Wu et al.[7] identified several distinct patterns of disease activity related to disease progression and duration of illness. They found early and persistent elevation of disease activity among patients with SAP. Buxbaum et al.[8] validated the score's ability to forecast important clinical events at different time points in another cohort, suggesting that it is a valid measure of activity in AP. Furthermore, Paragomi et al.[10] analyzed repeated PASS measurements using a generalized estimating equations model, and significant differences in PASS trajectories were found in patients with different severity and length of hospital stay.

To make the PASS easier to calculate and address concerns regarding overweighing opioid usage, Paragomi et al.[13] proposed

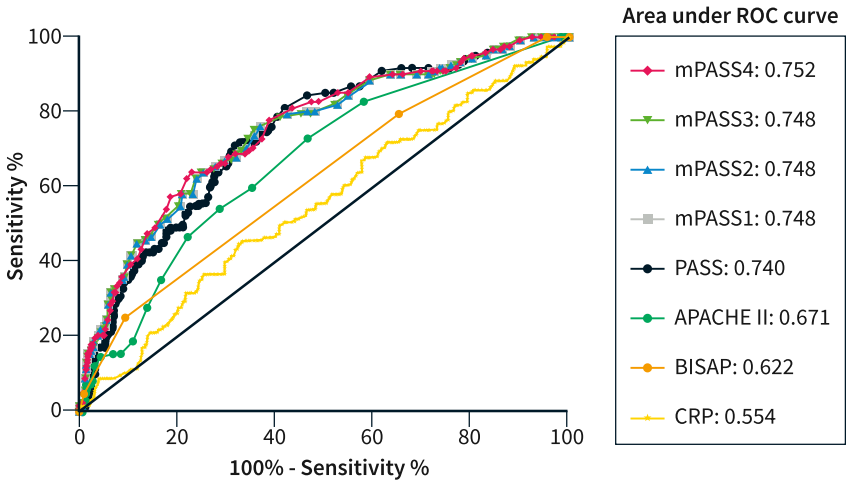

FIGURE 2 Receiver operator characteristic (ROC) analysis for pancreatitis activity scoring system (PASS)/mPASS scores, APACHE II score, BISAP score, and C-reactive protein (CRP) at enrollment in predicting 90-day infected pancreatic necrosis (IPN). mPASS denotes modified PASS. APACHE II denotes acute physiology and chronic health evaluation II, which ranges from 0 to 71, with higher scores indicating more severe disease. BISAP denotes bedside index for severity in acute pancreatitis (AP).

TABLE 2 Scoring system performance for 90-day infected pancreatic necrosis (IPN)

	ROC			H-L		
Performance variable	AUC	95% CI	Cut-off	p-value[a]	Brier score[b]	Positive LR[c]
PASS	0.740	0.691–0.789	312.5	<0.001	0.173	2.24
mPASS-1	0.748	0.697–0.798	232.5	0.150	0.155	2.06
mPASS-2	0.748	0.697–0.798	232.5	0.150	0.155	2.06
mPASS-3	0.748	0.698–0.799	232.5	0.099	0.155	2.11
mPASS-4	0.752	0.703–0.802	292.5	0.061	0.154	2.77
APACHE II	0.671	0.617–0.725	9	0.050	0.175	1.57
BISAP	0.622	0.565–0.679	2	0.071	0.175	2.67

Abbreviations: APACHE II, acute physiology and chronic health evaluation II, which ranges from 0 to 71, with higher scores indicating more severe disease; AUC, area under the curve; BISAP, bedside index for severity in acute pancreatitis; CI, confidence interval; H-L, Hosmer-Lemeshow Ĉ-test; LR, likelihood ratio; mPASS, modified pancreatitis activity scoring system; PASS, pancreatitis activity scoring system; ROC, receiver operating characteristic curve.

[a]H-L *p*-values >0.05 indicates good calibration.

[b]The Brier score ranges from 0.0 (perfect) to 0.25 (worthless).

[c]Positive LR = Sensitivity/(1-Specificity).

several modified PASS models (mPASS) by removing or reducing the weight of the MED component. The mPASS could predict SAP with reasonable accuracy and differentiate between patients with different early trajectories in patients with different severities.[8] In contrast to the present study, the limitation of these studies was the inclusion of patients with mild AP with a very low incidence of IPN, making it very difficult to evaluate the predictive performance of the PASS/mPASS models for IPN.

Thiruvengadam et al.[11] performed a retrospective cohort study in a cohort of IPN patients and found that a higher PASS score was associated with worse outcomes and early readmission. However, they only included patients with confirmed IPN, precluding the possibility of evaluating the PASS in predicting IPN. The only study that investigated this was a single-center retrospective study conducted in 2018,[12] which evaluated the association between PASS during the early phase of AP and the development of IPN, which commonly occurs beyond two weeks of disease onset.[18] This *post hoc* analysis found that the mPASS-4 in the first week may be useful in predicting IPN. The findings from this retrospective study warranted prospective validation.

Several attempts had been made to predict IPN in a relatively early phase of AP, including increased blood urea nitrogen,

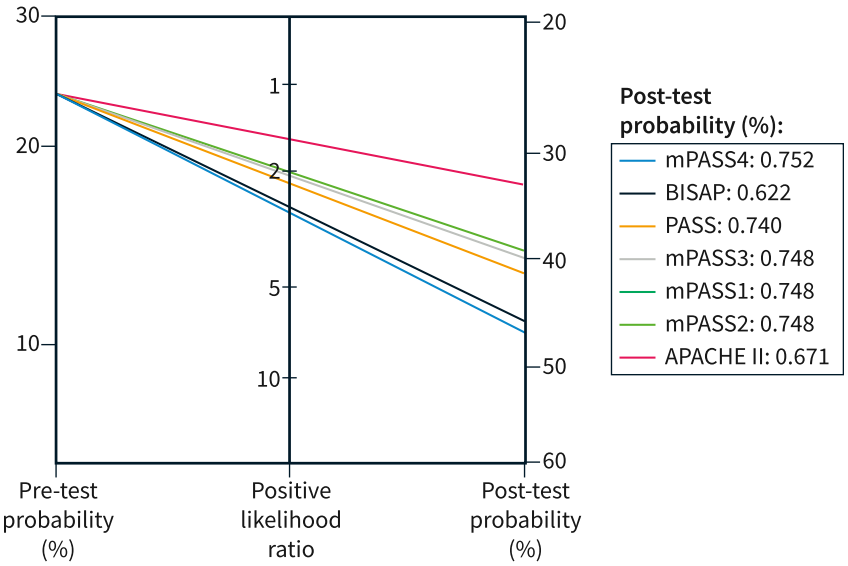

FIGURE 3 Fagan's nomogram for the calculation of the post-test probability that an individual has 90-day infected pancreatic necrosis (IPN) based on the seven scoring systems. PASS denotes pancreatitis activity scoring system. mPASS denotes modified PASS. APACHE II denotes acute physiology and chronic health evaluation II, which ranges from 0 to 71, with higher scores indicating more severe disease. BISAP denotes bedside index for severity in acute pancreatitis (AP).

TABLE 3 Predictors of 90-day infected pancreatic necrosis (IPN)

Clinical parameters	Univariate logistic regression OR (95% CI)	*p*	Multivariate logistic regression OR (95% CI)	*p*
Disease severity at enrollment				
mPASS4 > 292.5	5.92 (3.81–9.18)	<0.001	3.60 (2.07–6.27)	<0.001
MODS	5.57 (3.51–8.85)	<0.001	2.19 (1.18–4.06)	0.01
Lymphocyte count	0.66 (0.43–1.02)	0.06	0.78 (0.50–1.24)	0.30
The extent of pancreatic necrosis				
<30%	Reference 1.0	1.00	Reference 1.0	1.00
30%–50%	2.72 (1.69–4.38)	<0.001	2.13 (1.25–3.62)	0.01
>50%	4.29 (2.41–7.62)	<0.001	2.36 (1.23–4.54)	0.01
Age	1.02 (1.00–1.04)	0.02	1.02 (0.99–1.04)	0.07
Male	1.12 (0.73–1.71)	0.61	1.03 (0.61–1.74)	0.91
Etiologies				
Alcoholic	1.36 (0.61–2.99)	0.45	1.62 (0.63–4.17)	0.32
Biliary	Reference 1.0	1.00	Reference 1.0	1.00
Idiopathic	0.52 (0.17–1.58)	0.25	0.51 (0.14–1.83)	0.31
Hypertriglyceridemia	0.66 (0.43–1.02)	0.06	0.62 (0.35–1.08)	0.09

Abbreviations: CI, confidence interval; mPASS, modified pancreatitis activity scoring system; MODS, multiple organ dysfunction syndrome; OR, odd ratio.

procalcitonin (PCT), CRP, hematocrit (HCT),[19,20] hypotension in the first week,[21] reduced lymphocyte count,[22] APACHE II score at 24 h of hospital admission,[21] and early SIRS duration.[23] The problem was that all these studies included non-ANP patients who were unlikely to develop IPN. In contrast, the TRACE trial enrolled predicted severe ANP patients, 24% of whom developed IPN, consistent with that reported in previous large cohort studies,[24–26] which suggests that the findings of this study are generalizable.

The main differences between the PASS or its modifications and the other indices were that the PASS included the

TABLE 4 Clinical outcomes between mPASS4 above 292.5 and or not

Clinical outcomes	mPASS4 ≤292.5 (*N* = 341)	mPASS4 >292.5 (*N* = 167)	*p*
SAP, *n* (%)	192 (56.3)	144 (86.2)	<0.001
Organ failure, *n* (%)			
Respiratory	223 (65.4)	104 (62.3)	0.490
Renal	59 (17.3)	42 (25.1)	0.037
Cyclic	38 (11.1)	25 (15.0)	0.219
Major complications, *n* (%)			
Bleeding required interventions	4 (1.2)	21 (12.6)	<0.001
Fistula required interventions	2 (0.6)	9 (5.4)	<0.001
Requirement of invasive interventions, *n* (%)			
Catheter drainage[a]	23 (6.7)	52 (31.1)	<0.001
MI debridement[b]	7 (2.1)	22 (13.2)	<0.001
Open surgery	3 (0.9)	10 (6.0)	0.001
Length of hospital stay, median (IQR), *d*	12 (8–19)	22 (14–39)	<0.001
Length of ICU stay, median (IQR), *d*	7 (4–12)	16 (10–30)	<0.001
Log (hospitalization cost), median (IQR)	4.76 (4.53–4.97)	5.21 (4.97–5.51)	<0.001
90-day mortality, *n* (%)	11 (3.2)	35 (21.0)	<0.001
90-day IPN, *n* (%)	44 (12.9)	78 (46.7)	<0.001

Abbreviations: ICU, intensive care unit; IPN, infected pancreatic necrosis; IQR, interquartile range; mPASS, modified pancreatitis activity scoring system; MI, minimally invasive; SAP, severe acute pancreatitis.

[a]Both percutaneous and transluminal drainage were included.

[b]27 patients underwent exclusive percutaneous surgical MI debridement, one patient underwent exclusive endoscopic transluminal debridement, and one combined.

administration of opioid analgesics and the visual analog scale pain score into the calculation, implying the important role pain and analgesia played in the management of AP. In the early phase of AP, pain is ubiquitous, caused by the release of inflammatory mediators, arachidonic acid metabolites, bradykinins, and proteases, all of which may stimulate primary afferent sensory neurons.[27] Adequate analgesia is essential to AP patient management[28] and may reduce systemic inflammation. The MED score of the original PASS did not define a maximal upper limit, while the other four components have defined ranges, which may skew the composite PASS. In contrast, the mPASS models address this issue and weight MED by simplifying PASS, which enhances the likelihood of implementation in clinical practice. Taken together, the addition of pain and analgesia and the revised weight of the MED component may explain why the mPASS-4 appears to be superior to other indices, although it is not clear how this is related to IPN.

The main strength of our study was that the data was derived from a large multicenter randomized controlled trial that included standardized data collection and central monitoring. In addition, we only included patients with predicted severe ANP, who are at high risk for IPN. There are also several limitations. First, the PASS/mPASS scores were once rather than continuously calculated, precluding the possibility of trajectory analyses. In addition, hypertriglyceridemia-associated AP accounts for approximately 50% of the study subjects, significantly different from cohorts reported in other areas of the world.[29,30] The increase in hypertriglyceridemia-induced AP in the Chinese population might be attributed to dramatic changes in dietary habits[31] and genetic factors.[32] Although the performance of mPASS-4 in predicting IPN did not change after involving the etiologies as a confounder, the distinct etiological distribution may weaken the generalizability of our observed results.

CONCLUSION

In conclusion, the PASS and its modifications during the first week of ANP onset predict the development of IPN. Among the PASS/mPASS models, mPASS-4 had the largest AUC, the lowest Brier score, and good calibration. The modified PASS-4 simplifies the original PASS, increasing the likelihood of clinical implementation.

AUTHOR CONTRIBUTIONS

Study design: Lu Ke and Zhihui Tong; Data collection: Wenjian Mao, Kang Li, Jing Zhou, Miao Chen, Bo Ye, Gang Li and Xiaoyun Fu; Data analysis: Wenjian Mao and Jing Zhou; Drafting of the article: Wenjian Mao, Lu Ke, Vikesh Singh, James Buxbaum and John Windsor; Data

interpretation, review and/or revision of the manuscript: All authors; Study concept and study supervision: Weiqin Li, Yuxiu Liu, Zhihui Tong and Lu Ke. All authors approved this version to be published.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Deidentified individual participant data are available indefinitely in the electronic database. Data can be accessed through capctg.medbit.cn with the approval of the authors. Request for data can be made to the corresponding author (ctgkelu@nju.edu.cn) and will be discussed during a meeting of the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG).

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REFERENCES

1. 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(1):102–11. https://doi.org/10.1136/gutjnl-2012-302779
2. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400–15. https://doi.org/10.1038/ajg.2013.218
3. Shi N, Liu T, de la Iglesia-Garcia D, Deng L, Jin T, Lan L, et al. Duration of organ failure impacts mortality in acute pancreatitis. Gut. 2020;69(3):604–5. https://doi.org/10.1136/gutjnl-2019-318241
4. Hu W, Zhang Y, Hua T, Chen G, Song K, Pendharkar S, et al. IDDF2021-ABS-0134 Organ failure and infected pancreatic necrosis as determinants of mortality in patients with acute pancreatitis: an updated systematic review and meta-analysis. 2021;70(Suppl 2):A131-A.
5. Zubia-Olaskoaga F, Maraví-Poma E, Urreta-Barallobre I, Ramírez-Puerta MR, Mourelo-Fariña M, Marcos-Neira MP. 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(5):910–7. https://doi.org/10.1097/ccm.0000000000001565
6. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, et al. WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019;14(1):27. https://doi.org/10.1186/s13017-019-0247-0
7. Wu BU, Batech M, Quezada M, Lew D, Fujikawa K, Kung J, et al. Dynamic measurement of disease activity in acute pancreatitis: the pancreatitis activity scoring system. Am J Gastroenterol. 2017;112(7):1144–52. https://doi.org/10.1038/ajg.2017.114
8. Buxbaum J, Quezada M, Chong B, Gupta N, Yu CY, Lane C, et al. The Pancreatitis Activity Scoring System predicts clinical outcomes in acute pancreatitis: findings from a prospective cohort study. Am J Gastroenterol. 2018;113(5):755–64. https://doi.org/10.1038/s41395-018-0048-1
9. Lew D, Wu BU, Pandol SJ, Sugar CA, Senturk D, Afghani E. Disease course differences in acute pancreatitis based on etiology using the pancreatitis activity scoring system. Pancreas. 2018;47(7):e40–e1. https://doi.org/10.1097/mpa.0000000000001091
10. Paragomi P, Tuft M, Pothoulakis I, Singh VK, Stevens T, Nawaz H, et al. Dynamic changes in the pancreatitis activity scoring system during hospital course in a multicenter, prospective cohort. J Gastroenterol Hepatol. 2021;36(9):2416–23. https://doi.org/10.1111/jgh.15430
11. Thiruvengadam NR, Miranda J, Kim C, Behr S, Arain MA. The pancreatitis activity scoring system predicts clinical outcomes in patients with infected pancreatic necrosis. Pancreas. 2021;50(6):859–66. https://doi.org/10.1097/mpa.0000000000001838
12. Ke L, Mao W, Li X, Zhou J, Li G, Ye B, et al. The pancreatitis activity scoring system in predicting infection of pancreatic necrosis. Am J Gastroenterol. 2018;113(9):1393–4. https://doi.org/10.1038/s41395-018-0112-x
13. Paragomi P, Hinton A, Pothoulakis I, Talukdar R, Kochhar R, Goenka MK, et al. The modified pancreatitis activity scoring system shows distinct trajectories in acute pancreatitis: an international study. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterological Assoc. 2021;20(6):1334–42.e4. https://doi.org/10.1016/j.cgh.2021.09.014
14. Ke L, Zhou J, Mao W, Chen T, Zhu Y, Pan X, et al. Immune enhancement in patients with predicted severe acute necrotising pancreatitis: a multicentre double-blind randomised controlled trial. Intensive Care Med. 2022.
15. Zhou J, Mao W, Ke L, Chen T, He W, Pan X, et al. Thymosin alpha 1 in the prevention of infected pancreatic necrosis following acute necrotising pancreatitis (TRACE trial): protocol of a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial. BMJ Open. 2020;10(9):e037231. https://doi.org/10.1136/bmjopen-2020-037231
16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic

curves: a nonparametric approach. Biometrics. 1988;44(3):837–45. https://doi.org/10.2307/2531595
17. Fagan TJ. Letter: nomogram for bayes theorem. N Engl J Med. 1975;293(5):257.
18. Garg PK, Zyromski NJ, Freeman ML. Infected necrotizing pancreatitis: evolving interventional strategies from minimally invasive surgery to endoscopic therapy-evidence mounts, but one size does not fit all. Gastroenterology. 2019;156(4):867–71. https://doi.org/10.1053/j.gastro.2019.02.015
19. Talukdar R, Nechutova H, Clemens M, Vege SS. Could rising BUN predict the future development of infected pancreatic necrosis? Pancreatol Off J Int Assoc Pancreatol (IAP). 2013;13(4):355–9. https://doi.org/10.1016/j.pan.2013.05.003
20. Chen HZ, Ji L, Li L, Wang G, Bai XW, Cheng CD, et al. Early prediction of infected pancreatic necrosis secondary to necrotizing pancreatitis. Medicine. 2017;96(30):e7487. https://doi.org/10.1097/md.0000000000007487
21. Thandassery RB, Yadav TD, Dutta U, Appasani S, Singh K, Kochhar R. Hypotension in the first week of acute pancreatitis and Apache II score predict development of infected pancreatic necrosis. Dig Dis Sci. 2015;60(2):537–42. https://doi.org/10.1007/s10620-014-3081-y
22. Zhou J, Chen W, Liu Y, Qu C, Jiang W, Yin J, et al. Trajectories of lymphocyte counts in the early phase of acute pancreatitis are associated with infected pancreatic necrosis. Clin Transl Gastroenterol. 2021;12(9):e00405. https://doi.org/10.14309/ctg.0000000000000405
23. Tan C, Yang L, Shi F, Hu J, Zhang X, Wang Y, et al. Early systemic inflammatory response syndrome duration predicts infected pancreatic necrosis. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2020;24(3):590–7. https://doi.org/10.1007/s11605-019-04149-5
24. Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. N Engl J Med. 2016;375(20):1972–81. https://doi.org/10.1056/nejmra1505202
25. Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut. 2019;68(6):1044–51. https://doi.org/10.1136/gutjnl-2017-314657
26. Garg PK, Madan K, Pande GK, Khanna S, Sathyanarayan G, Bohidar NP, et al. Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterological Assoc. 2005;3(2):159–66. https://doi.org/10.1016/s1542-3565(05)00485-4
27. Liddle RA, Nathan JD. Neurogenic inflammation and pancreatitis. Pancreatology Off J Int Assoc Pancreatology (Iap). 2004;4(6):551–9. discussion 9–60. https://doi.org/10.1159/000082180
28. Thavanesan N, White S, Lee S, Ratnayake B, Oppong KW, Nayar MK, et al. Analgesia in the initial management of acute pancreatitis: a systematic review and meta-analysis of randomised controlled trials. World J Surg. 2022;46(4):878–90. https://doi.org/10.1007/s00268-021-06420-w
29. Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, et al. Immediate versus postponed intervention for infected necrotizing pancreatitis. N Engl J Med. 2021;385(15):1372–81. https://doi.org/10.1056/nejmoa2100826
30. de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, et al. Aggressive or moderate fluid resuscitation in acute pancreatitis. N Engl J Med. 2022;387(11):989–1000. https://doi.org/10.1056/nejmoa2202884
31. Tian X, Huang Y, Wang H. Deviation of Chinese adults' diet from the Chinese food pagoda 2016 and its association with adiposity. Nutrients. 2017;9(9):995. https://doi.org/10.3390/nu9090995
32. Li XY, Pu N, Chen WW, Shi XL, Zhang GF, Ke L, et al. Identification of a novel LPL nonsense variant and further insights into the complex etiology and expression of hypertriglyceridemia-induced acute pancreatitis. Lipids Health Dis. 2020;19(1):63. https://doi.org/10.1186/s12944-020-01249-z

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