International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Nucleotide-Bound Oligomeric Domain-Like Receptor Protein 3 as a Serological Biomarker in Relation to Disease Severity and Delirium After Acute Pancreatitis: A Two-Center Prospective Cohort Study

Zihao Tang[1], Xinwen Zhou[1], Yujun Rao[2], Jianye Wu[1]

[1]Department of Gastroenterology, Lishui City Hospital of Traditional Chinese Medicine, Lishui, Zhejiang Province, People's Republic of China; [2]Department of Gastroenterology, Lishui Hospital of Wenzhou Medical University, Lishui People's Hospital, Lishui, Zhejiang Province, People's Republic of China

Correspondence: Jianye Wu, Department of Gastroenterology, Lishui City Hospital of Traditional Chinese Medicine, Lishui, Zhejiang Province, People's Republic of China, Email equest@163.com

International Journal of General Medicine downloaded from https://www.dovepress.com/
For personal use only.

Objective: Acute pancreatitis (AP) is a very common infectious diseases, with delirium as a conventional complication. Nucleotide-binding oligomeric structural domain-like receptor protein 3 (NLRP3) is involved in inflammatory response after AP. We set out to determine whether serum NLRP3 levels are related to severity and delirium in patients with AP.

Methods: In this two-center prospective cohort study, a total of 311 patients with AP were divided to study group and validation group according to the ratio of 2:1, and serum NLRP3 levels were measured in all patients and healthy controls. To assess disease severity, Acute Physiology and Chronic Health Evaluation II (APACHE II), Ranson and Sequential Organ Failure Assessment (SOFA) scores were recorded. Delirium was observed as an outcome variable. Multifactorial analysis was performed to discern severity correlations and outcome correlations. Prediction model containing independent predictors of delirium was constructed in study group and validated in validation group.

Results: Serum NLRP3 levels were significantly higher in patients with AP than in controls, and were independently associated with three traditional indicators of AP severity, that is APACHE II scores, Ranson scores, and SOFA scores. When compared with the preceding traditional predictors, serum NLRP3 levels had comparable predictive ability for post-AP delirium. The four predictors were incorporated to create the predictive model of nomogram presentation. The model displayed significantly higher predictive capability than their use alone. In addition, the model was similarly effective for delirium prediction in validation group.

Conclusion: Elevated serum NLRP3 levels after AP, in firm correlation with AP severity, independently predict in-hospital delirium, solidifying serum NLRP3 as a candidate for severity assessment and delirium anticipation after AP.

Keywords: acute pancreatitis, NLRP3, severity, delirium, serum

Introduction

Acute pancreatitis (AP), one of the most common acute inflammatory digestive diseases, apparently, is an unpredictable and potentially fatal disease characterized by sudden onset, rapid progression, variable clinical course, and variable severity.[1] The pathophysiological processes of this entity mainly involve local and systemic inflammatory reactions, with multiple etiological factors leading to auto-digestion of pancreatic tissues, and consequent pancreatic oedema, hemorrhage, and necrotic injuries.[2,3] Acute physiology and chronic health evaluation II (APACHE II), Ranson and sequential organ failure assessment (SOFA) are preferably applied for appraisal of AP severity.[4,5] Delirium is an acute cerebral dysfunction that is mainly triggered by central nervous system disorders, drug overdose or withdrawal reactions, poisoning, metabolic

Received: 9 May 2025
Accepted: 19 June 2025
Published: 26 June 2025

© 2025 Tang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

disorders, and infections.[6,7] It has been found that the systemic inflammatory response after AP can cause delirium, and early recognition of delirium can help in the clinical management of AP patients.[8,9] In recent decades, the role of biomarkers in the assessment of disease severity and prediction of complications has been gradually emphasized.

Hyperactivation of inflammasome, a multiprotein complex assembled with the participation of intracytoplasmic pattern recognition receptors as the core of the inflammatory response, is involved in the development of several diseases.[10–12] Nucleotide-binding oligomeric structural domain-like receptor protein 3 (NLRP3) is one of the important members of the inflammatory vesicle family, which can mediate the production of a variety of inflammatory factors, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, and plays an important role in the process of inflammatory response.[13–16] Expression of NLRP3 was significantly elevated in pancreatic tissues of AP rats, while NLRP3 -/- mice showed reduced pancreatic edema, decreased inflammatory cell infiltration, and reduced tissue necrosis and hemorrhage.[17] In addition, high expression of NLRP3 in brain tissue of ischemia/reperfusion mice further aggravated brain tissue injury.[18] Inhibition of NLRP3 expression significantly reduced neuroinflammation, neuronal apoptosis and thus attenuated early brain injury in subarachnoid hemorrhage rats.[19] Also, serum NLRP3 levels were significantly elevated in patients with cerebral infarction and aneurysmal subarachnoid hemorrhage and were strongly associated with disease severity and poor prognosis of the patients.[20,21] Therefore, NLRP3, as a deleterious factor, may be a biomarker of brain injury. The aim of this study was to assess serum NLRP3 in relation to AP severity, as well as to further explore the ability of serum NLRP3 to predict delirium after AP.

Materials and Methods

Study Design and Participant Selection

In this two-center prospective cohort study, we included consecutively enrolled patients with first-in-life AP, who were admitted to Lishui Traditional Chinese Medicine Hospital and Lishui People's Hospital between March 2020 and July 2024, and all patients were classified into study and validation subgroups based on the ratio of 2:1 according to a randomized numerical table method. The exclusion criteria were as follows: (1) age <18 years; (2) preexisting severe systemic diseases or other specific conditions, such as uremia, cardiac failure, cirrhosis, myocardial infarction, pregnancy, last month's infections, and recent surgeries; (3) history of neuropsychiatric disorders, such as stroke (eg, cerebral infarction, aneurysmal subarachnoid hemorrhage, and cerebral hemorrhage, etc)., moderate to severe traumatic brain injury, and depression, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and cranial tumors. In addition, a control group consisting of people without other diseases was recruited for this study through a health screening program at the Physical Examination Center of Lishui Chinese Medicine Hospital.

The study was conducted in accordance with the principles set forth in the Declaration of Helsinki, and the study protocol was approved by the Ethics Committees of Lishui City Hospital of Traditional Chinese Medicine and Lishui City People's Hospital (Opinion No.: LLW-FO-403, LW-2024081). We informed the AP patients themselves or their legal representatives about study details and later they was authorized to sign written informed consent forms. And the controls by themselves provided written informed consent forms for indicating their willingness to participate in the study.

Data Acquisitions

Patients or their legal representatives as well as healthy controls themselves were asked to complete a comprehensive and detailed inquiries including age, gender, height, body weight, etc. Body mass index (BMI) was computed using the following equation: body weight (kg) divided by height squared (m^2). AP etiologies were of four types, that is bilious, alcoholic, hypertriglyceridemic and others. Severity of AP was classified using Revised Atlanta classification standard, that is severe AP (SAP), moderately severe AP (MSAP) and mild AP (MAP). In addition, the interval from pain onset to admission and the duration from pain onset to blood collection were recorded as two temporal parameters. Systemic severity of disease was assessed using APACHE II, Ranson and SOFA. Some pathophysiological complications, such as multiple organ dysfunction syndrome (MODS), peripancreatic effusion, pancreatic necrosis, sepsis, acute respiratory failure and acute renal injury, were documented. Using the confusion assessment method, patients were assessed by trained nurses twice a day until discharge to identify delirium via observing certain characteristic symptoms during the

patient's hospitalization, such as the acute onset and fluctuating process of symptoms, inattention, impaired consciousness level and cognitive deficits, as well as other features that support the diagnosis of delirium, including changes in the sleep-wake cycle, perceptual deficits, delusions, and inappropriate or unsafe behaviors.[22,23] Clinical assessors were unaware of serum NLRP3 levels in patients.

Immune Analysis

Peripheral venous blood samples were collected from AP patients at the time of admission to the hospital and from healthy controls at the time of routine physical examination. Routine laboratory markers, eg, blood leukocyte count, blood C-reactive protein (CRP) level, blood glucose level, and blood potassium level were measured using the conventional methods. The blood samples were naturally coagulated at room temperature for 10–20 minutes, followed by centrifugation at 3000 × g for 20 minutes at 4°C. Supernatant was cautiously extracted and then transferred to Eppendorf tubes for storage in a −80°C refrigerator awaiting testing. Serum NLRP3 levels were measured using the enzyme-linked immunosorbent assay (ELISA) kit (Catalog No. CSB-E15885H; yi-pu Biotech Co., Ltd). with a detection range of 0.156–10.0 ng/mL and a sensitivity of 0.039 ng/mL. Both intra-batch coefficient of variance and inter-batch coefficient of variance were lower than 10%. To ensure accuracy and reliability, the procedure was repeated twice for all samples. The technicians performing the tests were unclear about the clinical information to assure the impartiality of the tests and analyses.

Statistical Analysis

Graphical plots and statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA), GraphPad Prism 9.0 (GraphPad Software Inc., La Jolla, CA, USA), R 3.5.1 (https://www.r-project.org) and MedCalc 17.4 (MedCalc Software, Mariakerke, Belgium). G-Power 3.1.9.4 (Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, Düsseldorf, Germany) was applied to estimate the required sample size. Normality of the quantitative data was assessed using the Kolmogorov–Smirnov test. Normally distributed data were expressed as mean ± standard deviation, whereas non-normally distributed data, as median (upper and lower quartiles). Qualitative data were presented as counts (proportions). For comparisons between two groups, the $\chi 2$ test or Fisher's exact test was used for qualitative data, and the Mann–Whitney *U*-test or *t* test, for quantitative data. Correlations of continuous variables were analyzed using the Spearman correlation test, and correlations of categorical variables with continuous variables were analyzed using the Pearson correlation test. Multiple linear regression model was developed to identify variables independently associated with serum NLRP3 levels. To compare the differences between delirious and non-delirious patients, one-way logistic regression model was developed to analyze the relationship of each variable with delirium in patients with AP. The binary logistic regression model was configured to unveil variables, which were independently associated with delirium following AP. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to show associations. Subsequently, subject work characteristic (ROC) curves were constructed to explore the predictive value of serum NLRP3 levels for the development of delirium in patients with AP. The area under the curve (AUC) was estimated and the AUC was compared using a z-test. In addition, a restricted cubic spline method was taken to make sure that there was the linear correlation between serum NLRP3 levels and risk of delirium. A column-line graphical model, also termed as nomogram, was graphed to predetermine the risk of delirium. Calibration curve was plotted to verify model stability. Decision curve was drawn as a confirmation of clinical benefit of the model. A two-sided P value of <0.05 was considered statistically significant.

Results

Characteristics of the Study Population

An initial appraisal was done in a cumulative of 382 patients with AP, and following removal of 71 patients owing to the exclusion criteria, a collective of 311 patients awaited clinical analysis; in total, 211 and 100 patients were respectively allocated to the study group and validation group (Figure 1). In addition, 100 healthy volunteers were recruited as controls. Table 1 shows age, gender and BMI of all patients and all controls, with nonsignificant distinctions in these parameters between the two groups. The baseline characteristics of all patients, study group and validation group are

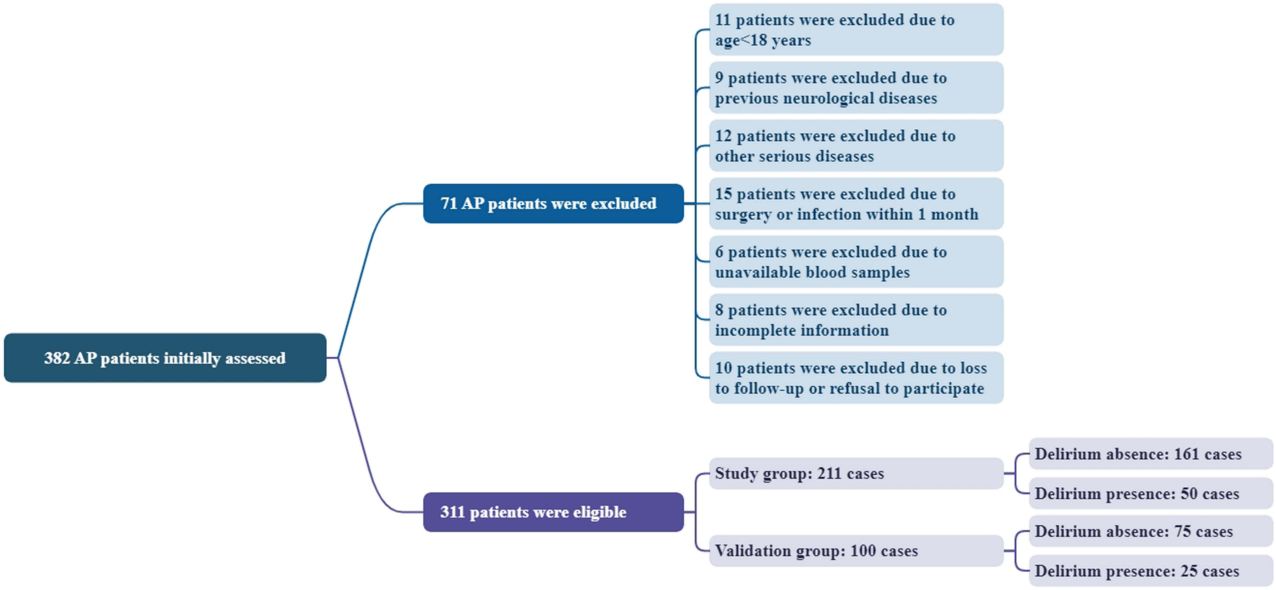

Figure 1 Flowing-chart for selecting eligible patients with acute pancreatitis. Initially, a total of 382 patients were assessed and ultimately, 311 patients were analyzed after excluding 71 patients in compliance with the exclusion criteria, of whom 211 constituted the study group and 100 were assigned to the validation group.
Abbreviation: AP, acute pancreatitis.

outlined in Table 2, and a revelation was not existent about significant differences in these baseline characteristics between study group and validation group (all P > 0.05; Table 2).

Correlation Analysis Between Serum NLRP3 Levels and Disease Severity

As shown in Figure 2, serum NLRP3 levels were significantly higher in AP patients, and patients in study group and in validation group, as compared with healthy controls (all P < 0.001); and there were no statistically significant differences in serum NLRP3 levels between the total patients, the study group, and the validation group (all P > 0.05). In the study group, serum NLRP3 levels were substantially highest in patients with SAP, followed by MSAP, and were significantly lowest in those suffering from MAP (all P< 0.05, Figure 3). Serum NLRP3 levels showed a strongly positive correlation with APACHE II scores (P< 0.001; Figure 4A), Ranson scores (P< 0.001; Figure 4B), and SOFA scores (P< 0.001; Figure 4C). In addition, serum NLRP3 levels were significantly correlated with other variables, such as blood leukocyte counts, blood C-reactive (CRP) protein levels, blood procalcitonin levels, blood calcium levels, blood glucose levels, blood creatinine levels and others (all P< 0.05; Table 3 and Table 4). Those significantly correlated variables were integrated into the multivariable model, leading to a finding that APACHE II scores, Ranson scores, and SOFA scores were independently correlated with serum NLRP3 levels (all P<0.05; Table 5).

Table 1 Comparisons of Demographic Data Between Controls and Patients with Acute Pancreatitis

	All Patients (n=311)	Controls (n=100)	Z/χ^2	P value
Age (years)	48 (39–58)	45 (38–56)	−1.707	0.088
Gender (male/female)	186/125	57/43	0.247	0.619
Body mass index (kg/m^2)	25.6 (22.5–27.6)	25.5 (23.9–27.0)	−0.521	0.603

Notes: Quantitative data were reported as medians with upper and lower quartiles. Qualitative data were presented as counts (proportions). Intergroup comparisons of various variables were performed using the chi-square test for qualitative data, and Mann–Whitney *U*-test for quantitative data.

Table 2 Baseline Characteristics of All Patients and Basic Features Between Study Group and Validation Group in Patients with Acute Pancreatitis

	All Patients	Two-Group Comparison		
		Study Group	Validation Group	P value
Number	311	211	100	
Age (years)	48 (39–58)	49 (39–58)	48 (39–61)	0.822
Gender (male/female)	186/125	123/88	63/37	0.625
Body mass index (kg/m^2)	25.6 (22.5–27.6)	25.6 (22.7–28.0)	25.2 (22.0–27.0)	0.073
Time between pain and admission (h)	14.0 (9.0–19.0)	14.0 (10.0–19.0)	14.5 (8.0–18.8)	0.774
Sample-collecting time after pain (h)	17.2 (12.4–20.9)	17.3 (12.6–20.8)	16.5 (10.7–21.1)	0.277
Revised Atlanta classification				0.664
MAP	169	118	51	
MSAP	90	60	30	
SAP	52	33	19	
MODS	61 (19.6%)	40 (19.0%)	21 (21.0%)	0.672
Peripancreatic effusion	182 (58.5%)	128 (60.7%)	56 (56.0%)	0.435
Pancreatic necrosis	62 (19.9%)	41 (19.4%)	21 (21.0%)	0.746
Sepsis	63 (20.3%)	40 (19.0%)	23 (23.0%)	0.407
Acute respiratory failure	60 (19.3%)	39 (18.5%)	21 (21.0%)	0.599
Acute renal injury	27 (9.7%)	19 (9.0%)	8 (8.0%)	0.769
APACHE II scores	11 (4–15)	11 (5–15)	10 (4–15)	0.502
Ranson scores	4 (2–5)	4 (3–5)	3 (2–5)	0.221
SOFA scores	5 (3–8)	6 (3–8)	5 (3–8)	0.349
Etiologies				0.749
Biliary	97	69	28	
Alcoholic	115	75	40	
Hypertriglyceremic	69	48	21	
Others	30	19	11	
Blood CRP levels (mg/L)	31.2 (21.3–54.9)	32.9 (22.0–55.0)	30.1 (20.1–48.3)	0.327
Blood leucocyte count (×10^9/L)	12.7 (9.4–16.2)	12.8 (9.7–16.2)	12.1 (8.7–15.4)	0.224
Blood PCT levels (ng/mL)	2.31 (1.48–3.42)	2.33 (1.52–3.52)	2.14 (1.29–3.32)	0.151
Blood calcium levels (mmol/L)	2.0 (1.9–2.2)	2.0 (1.9–2.2)	2.0 (1.9–2.1)	0.575
Blood glucose levels (mmol/L)	9.5 (7.4–14.4)	9.8 (7.5–14.7)	8.9 (7.1–13.1)	0.067
Blood creatinine levels (μmol/L)	110.4 (89.9–137.8)	113.1 (88.4–136.1)	109.5 (90.3–139.8)	0.425
Blood urea nitrogen levels (mg/dL)	12.3 (9.4–15.0)	12.3 (9.4–15.1)	12.5 (9.4–14.8)	0.981
Serum NLRP3 levels (ng/mL)	2.00 (1.71–2.66)	2.02 (1.69–2.66)	1.92 (1.76–2.67)	0.546

Notes: Qualitative variables were presented as counts (percentages) or medians (25th-75th) as applicable. The statistical methods included the chi-square test, Fisher exact test and Mann–Whitney *U*-test.

Abbreviations: APPACH II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; CRP, C-reactive protein; PCT, procalcitonin; RIP3, receptor-interacting protein kinase 3; MP, mild pancreatitis; MSP, moderately severe pancreatitis; SP, severe pancreatitis; MODS, multiple organ dysfunction syndrome.

Relationship Between Serum NLRP3 Levels and Delirium After AP

A total of 50 patients (23.7%) had the development of in-hospital delirium. In Figure 5, serum NLRP3 levels were significantly higher in patients with delirium than in those without delirium (P<0.001). Under the restricted triple spline, serum NLRP3 levels were linearly correlated with the likelihood of delirium during AP hospitalization (P nonlinearly >0.05; Figure 6). Table 6 shows that APACHE II scores, Ranson scores, SOFA scores, blood leukocyte count, blood CRP levels, blood procalcitonin levels, blood calcium levels, blood glucose levels, blood creatinine levels, revised Atlanta classification, pancreatic necrosis, sepsis, multiple organ dysfunction syndrome, acute respiratory failure, and acute kidney injury were presented as significantly distinct variables between patients with delirium and those without (all P<0.05). By subsequent univariate and multifactorial logistic regression analyses, APACHE II scores, Ranson scores, SOFA scores and serum NLRP3 levels appeared as independent predictors of delirium post-AP (all P<0.05; Table 7).

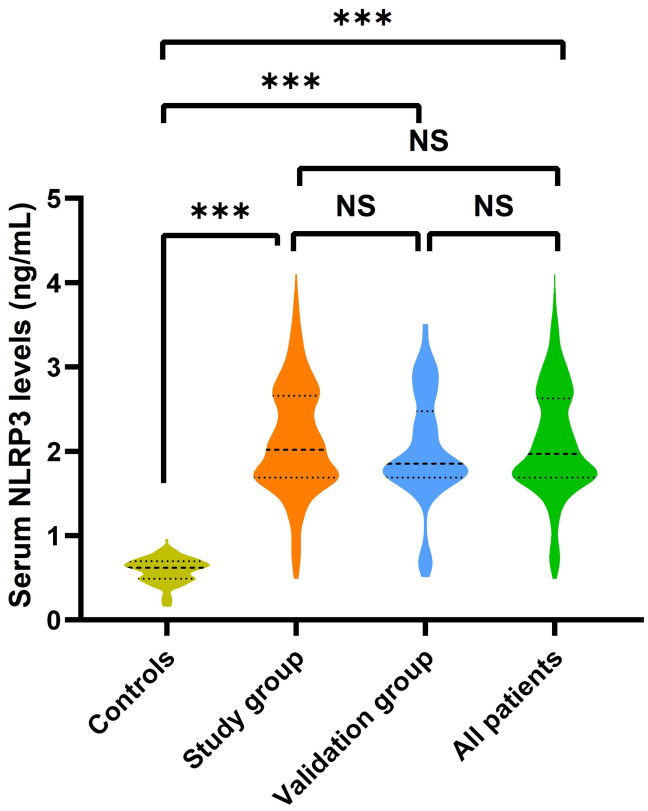

Figure 2 Boxplot illustrating serum nucleotide-bound oligomeric domain-like receptor protein 3 levels between patients with acute pancreatitis and controls. No significant distinctions were found in terms of serum nucleotide-bound oligomeric domain-like receptor protein 3 levels among the three groups, namely, the whole group, study group, validation group (all P>005). The levels were substantially lower in the controls than in any of the three groups (all P<0.001). ***P<0.001.
Abbreviations: NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3; NS, non-significant.

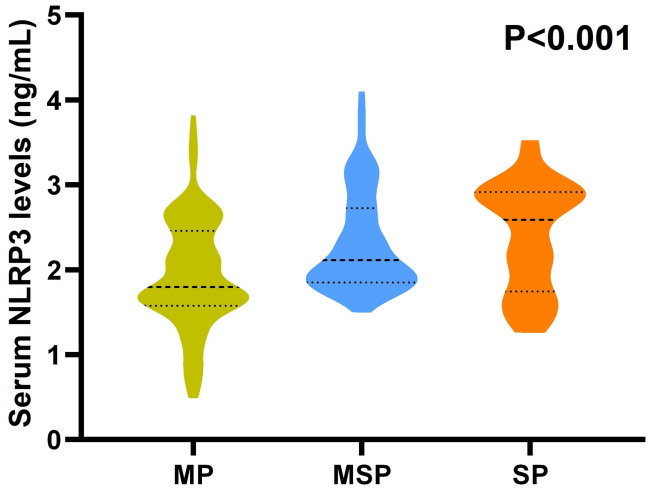

Figure 3 Boxplot illustrating serum nucleotide-bound oligomeric domain-like receptor protein 3 levels in patients with acute pancreatitis of different severity. Serum nucleotide-bound oligomeric domain-like receptor protein 3 levels were significantly higher in patients with severe acute pancreatitis than in patients with moderately severe acute pancreatitis and in those with mild acute pancreatitis (P<0.001).
Abbreviations: NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3; SAP, severe acute pancreatitis; MSAP, moderately severe acute pancreatitis; MAP, mild acute pancreatitis.

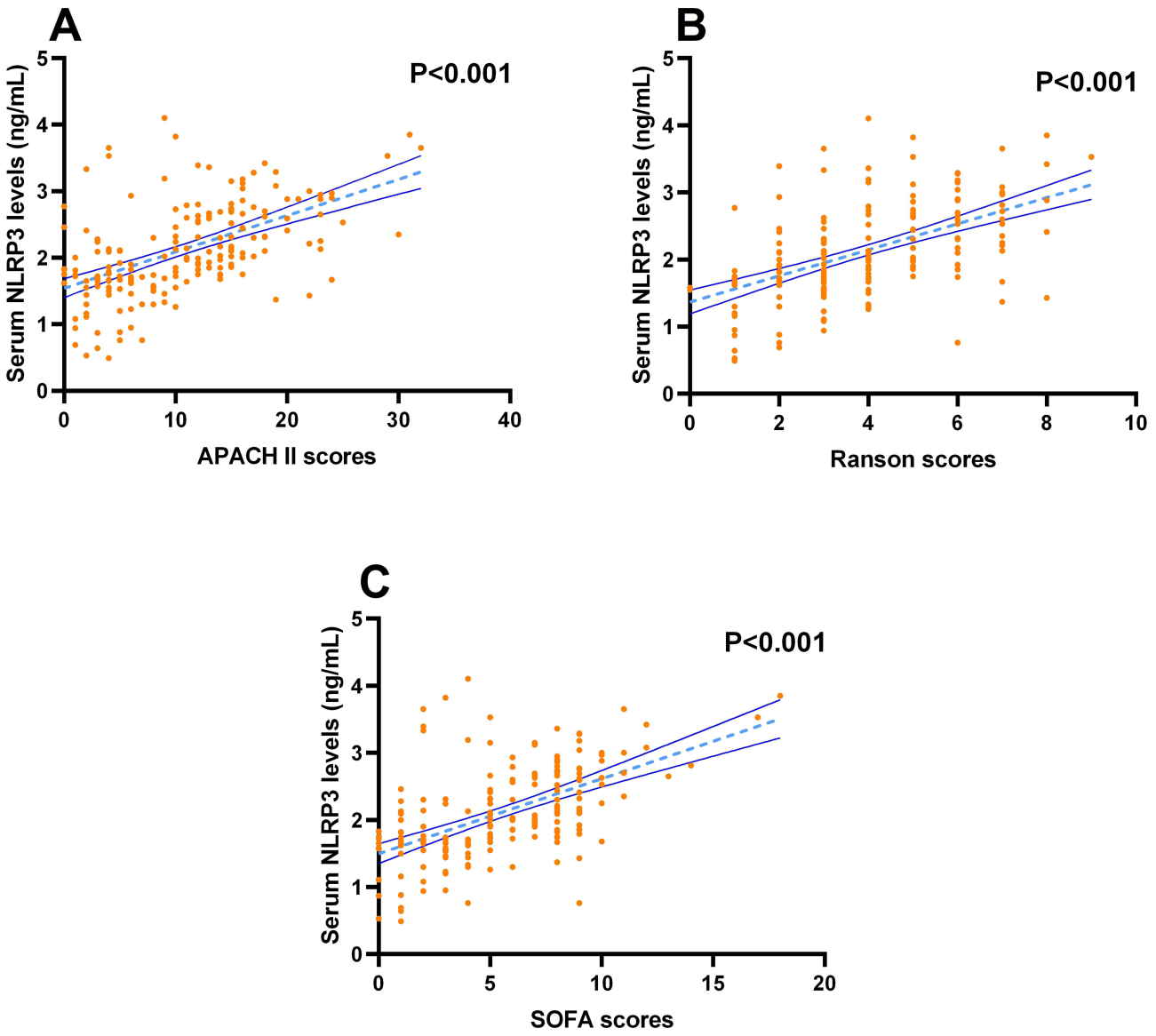

Figure 4 Correlogram delineating the relationship between serum nucleotide-bound oligomeric domain-like receptor protein 3 levels and conventional severity scores after acute pancreatitis. Serum nucleotide-bound oligomeric domain-like receptor protein 3 levels were positively correlated with acute physiology and chronic health evaluation II scores (P<0.001; (**A**), Ranson scores (P<0.001); (**B**) and Sequential Organ Failure Assessment scores (P<0.001); (**C**) after acute pancreatitis.
Abbreviations: NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

Based on the background of ROC curve analysis, serum NLRP3 level were significantly predictive of delirium via AUC above 0.750 and maximum Jordon J index was set at 0.543 by using the cutoff value of 2.32 ng/mL (Figure 7A). In Figure 7B, its predictive power was comparable to APACHE II scores (AUC=0.825; 95% CI, 0.766–0.873; P=0.319), Ranson scores (AUC=0.831; 95% CI, 0.774–0.879; P=0.274), and SOFA scores (AUC=0.821; 95% CI, 0.763–0.870; P=0.405). Subsequently, A prediction model was created of integrating APACHE II scores, Ranson scores, SOFA scores, and serum NLRP3 levels. As plotted in Figure 7B, the predictive ability of the model (AUC, 0.868; 95% CI, 0.814–0.910) was significantly higher than those of APACHE II scores (P=0.032), Ranson scores (P=0.048), SOFA scores (P=0.044) and serum NLRP3 levels (P=0.005). In addition, the predictive ability of serum NLRP3 levels were not significantly different between the study group and validation group (ACU=0.793; 95% CI, 0.700–0.867; P=0.907; Figure 7C). The model was pictorially delineated via the nomogram for predicting associated risk of delirium occurrence (Figure 8). The points corresponding to the three variables were summed to calculate a total score; the higher the total

https://doi.org/10.2147/IJGM.S534284

Table 3 Factors Correlated with Serum Nucleotide-Binding Oligomeric Structural Domain-Like Receptor Protein 3 Levels After Acute Pancreatitis Using Spearman Test

	Spearman Test		Univariate Linear Regression Analysis	
	ρ	P value	β (95% CI)	P value
Age (years)	0.099	0.152	4.979 (−0.480–10.437)	0.074
Body mass index (kg/m^2)	0.032	0.646	1.453 (−20.649–23.544)	0.897
Time between pain and admission (h)	0.113	0.101	11.153 (−0.911–23.217)	0.070
Sample-collecting time (h)	0.104	0.211	11.748 (−0.491–23.988)	0.060
APACHE II scores	0.591	<0.001	38.939 (31.082–46.796)	<0.001
Ranson scores	0.575	<0.001	138.486 (109.734–167.239)	<0.001
SOFA scores	0.592	<0.001	79.525 (63.598–95.453)	<0.001
Blood CRP levels (mg/L)	0.361	<0.001	3.813 (1.837–5.790)	<0.001
Blood leucocyte count (×10^9/L)	0.363	<0.001	35.254 (21.219–49.289)	<0.001
Blood PCT levels (ng/mL)	0.243	<0.001	67.943 (26.30–109.156)	0.001
Blood calcium levels (mmol/L)	−0.151	0.028	−313.609 (−576.375–50.842)	0.020
Blood glucose levels (mmol/L)	0.142	0.039	18.248 (4.876–31.621)	0.008
Blood creatinine levels (μmol/L)	0.292	<0.001	3.147 (1.402–4.892)	<0.001
Blood urea nitrogen levels (mg/dL)	−0.048	0.488	−8.737 (−25.825–8.352)	0.315

Abbreviations: APPACH II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; MODS, multiple organ dysfunction syndrome; CRP, C-reactive protein; PCT, procalcitonin; β, beta; 95% CI, 95% confidence interval.

Table 4 Factors Correlated with Serum Nucleotide-Binding Oligomeric Structural Domain-Like Receptor Protein 3 Levels After Acute Pancreatitis Using Pearson Test

	Pearson Test		Univariate Linear Regression Analysis	
	r	P value	β (95% CI)	P value
Gender (male/female)	−0.067	0.332	−66.352 (−200.860–68.155)	0.332
Revised Atlanta classification	0.289	<0.001	187.514 (102.758–272.270)	<0.001
MODS	0.193	0.005	237.387 (72.522–402.252)	0.005
Peripancreatic effusion	0.049	0.475	48.619 (−85.237–182.474)	0.475
Pancreatic necrosis	0.286	<0.001	349.325 (189.848–508.802)	<0.001
Sepsis	0.180	0.009	221.722 (56.541–386.992)	0.009
Acute respiratory failure	0.173	0.012	215.080 (47.976–382.184)	0.012
Acute renal injury	0.209	0.002	352.979 (128.009–577.949)	0.002
Etiologies (biliary/alcoholic/hypertriglyceremic/others)	0.035	0.616	17.584 (−51.478–86.646)	0.616

Abbreviation: MODS, multiple organ dysfunction syndrome.

score, the greater the risk of delirium. In addition, the calibration curve of the model confirmed that it had a medium-high stability (Figure 9). Decision curve analysis showed that the model had a significant clinical value (Figure 10).

Discussion

AP is a severe but reversible inflammation of pancreatic tissue that can progress to a systemic inflammatory response syndrome with high morbidity and mortality.[24] APACHE II scores, Ranson scores and SOFA scores are well-known as the three common indices, with frequent utilization for assessing disease severity and predicting AP patients' prognosis.[25–27] Moreover, the three metrics have been demonstrated to play an important role in predicting delirium episodes in AP patients.[9] During recent decades, biomarkers have been widely studied for their unique prognostic predictive value. However, no studies have reported changes in serum NLRP3 levels in patients with AP and their correlation with the acute severity of the patients. Early studies may have focused mainly on well-known inflammatory markers or general cytokines such as procalcitonin, CRP, and interleukin-6 and more.[28,29] These familiar biomarkers may

Table 5 Correlative Analysis of Serum Nucleotide-Binding Oligomeric Structural Domain-Like Receptor Protein 3 Levels Using Multivariate Linear Regression Analysis in Acute Pancreatitis

	β	95% CI	VIF	P value
Revised Atlanta classification	−0.133	−0.283–0.016	2.369	0.081
MODS	−0.160	−0.403–0.083	1.733	0.196
Pancreatic necrosis	0.077	−0.166–0.319	1.762	0.534
Sepsis	−0.127	−0.362–0.108	1.620	0.288
Acute respiratory failure	0.044	−0.186–0.275	1.525	0.705
Acute renal injury	−0.016	−0.314–0.281	1.380	0.913
APACHE II scores	0.027	0.003–0.050	5.1227	0.026
Ranson scores	0.075	0.004–0.147	3.577	0.039
SOFA scores	0.043	0.002–0.083	3.617	0.038
Blood CRP levels (mg/L)	0.001	−0.002–0.003	1.364	0.531
Blood leucocyte count ($\times 10^9$/L)	0.006	−0.015–0.026	1.571	0.593
Blood PCT levels (ng/mL)	0.010	−0.042–0.061	1.224	0.706
Blood calcium levels (mmol/L)	−0.277	−0.580–0.027	1.078	0.074
Blood glucose levels (mmol/L)	0.015	−0.001–0.030	1.082	0.062
Blood creatinine levels (μmol/L)	0.002	0.000–0.004	1.216	0.062

Abbreviations: APPACH II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; CRP, C-reactive protein; PCT, procalcitonin; β, beta; 95% CI, 95% confidence interval; VIF, variance inflation factor; MODS, multiple organ dysfunction syndrome.

have diverted attention from the study of more specific upstream inflammatory modulators such as NLRP3, resulting in scholars inadvertently overlooking NLRP3's central role. In this prospective cohort study of 311 patients with AP, we found that (1) serum NLRP3 levels were significantly higher in patients with AP compared with healthy controls and showed a significant positive correlation with disease severity; (2) serum NLRP3 levels were independently correlated with common indicators of severity such as the APACHE II scores, Ranson scores and SOFA scores; (3) serum NLRP3 levels were effective in predicting the onset of delirium with similar predictive ability as APACHE II scores, Ranson scores and SOFA scores; (4) the model combining serum NLRP3 levels, APACHE II scores, Ranson scores and SOFA scores performed satisfactorily. In conclusion, serum NLRP3 levels may be a potential biomarker of delirium onset in AP patients.

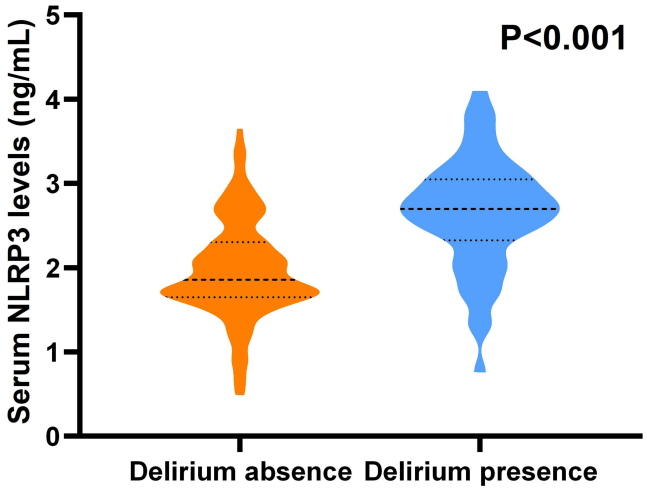

Figure 5 Boxplot portraying serum receptor-interacting protein kinase 3 levels across in-hospital delirium after acute pancreatitis. Serum nucleotide-bound oligomeric domain-like receptor protein 3 levels were notably higher in patients with in-hospital delirium after acute pancreatitis than in those without delirium (P<0.001).
Abbreviation: NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3.

https://doi.org/10.2147/IJGM.S534284

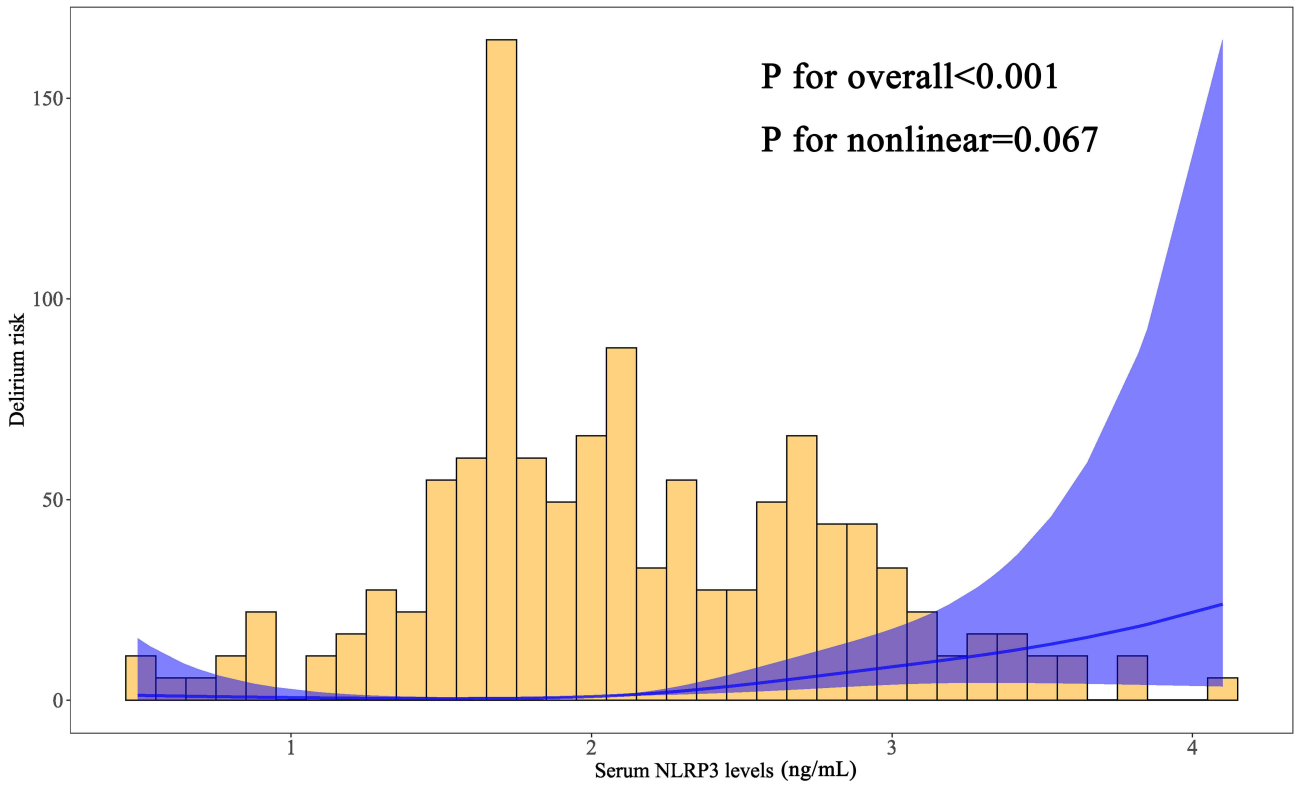

Figure 6 Restricted cubic spline depicting linear correlation of serum nucleotide-binding oligomeric structural domain-like receptor protein 3 levels with likelihood of development of in-hospital delirium after acute pancreatitis. There was a linear correlation between serum nucleotide-binding oligomeric structural domain-like receptor protein 3 levels and the probability of in-hospital delirium following acute pancreatitis (P>0.05).
Abbreviations: NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3.

To the best of our knowledge, the pathogenesis of AP is closely related to inflammatory responses as well as oxidative stress.[30] Therefore, targeted exploration of markers in relevance to inflammatory markers and oxidative stress in serum of AP patients may be useful for early prediction of delirium episodes in AP patients. Inflammatory vesicles are assembled multi-protein complexes with the participation of intracytoplasmic pattern recognition receptors, which are generally composed of nucleotide-binding oligomerization domain-like receptor (NLR), apoptosis-associated speck-like protein containing a CARD, and a CARD -like protein containing a CARD (ASC) and caspase.[31] Inflammasome, as an important participant in the inflammatory response, not only is expressed and functional in immune cells, such as neutrophils, but also is found to be distributed and regulated in pancreatic islet cells and podocytes, and its over-activation may participate in the development of varieties of inflammatory-responsive and autoimmune diseases.[32–34] When injury occurs, the conformation of inflammasome NLRP3 changes, and NLRP3 interacts with the N-terminal pyrimidine structural domain of ASC, recruits ASC and precursor caspase-1, assembles to form the NLRP3 inflammasome, and regulates the activation of caspase-1 to promote the maturation of precursors interleukin-1β and precursor interleukin-18 maturation, secretion and release, thereby mediating the inflammatory response.[35] Therefore, as the core part of the inflammatory response, NLRP3 inflammasome may provide a new target for the treatment of various inflammatory diseases.

Reportedly, NLRP3 expression is significantly elevated in pancreatic tissues of AP mice.[36] Increasing evidence suggests that NLRP3 may be deleterious, given that it could promote the progression of the inflammatory response, thereby exacerbating tissue and cellular damage. Specifically, upregulation of NLRP3 expression in mice notably exacerbated pancreatic and vesicular cell apoptosis after AP.[37] Concurrently, NLRP3 plays an important role in angiotensin II–induced pancreatic β-cell apoptosis.[38] Interestingly, inhibition of NLRP3 inflammatory vesicles resulted in a significant reduction in pyroptotic vesicular cell death, pancreatic necrosis, and systemic inflammation in AP mice, which may be mediated by inhibition of classical NLRP3 inflammatory vesicle-induced activation of gasdermin D (GSDMD), which attenuates pancreatic injury.[39,40] Furthermore, NLRP3 inflammatory vesicles play an important

Table 6 Factors Associated with in-Hospital Delirium After Acute Pancreatitis

	Presence (n=50)	Absence (n=161)	Z/χ^2	P value
Age (years)	51 (45–59)	48 (38–58)	−1.105	0.269
Gender (male/female)	24/26	99/62	2.856	0.091
Body mass index (kg/m^2)	26.4 (24.6–28.2)	27.0 (24.5–28.5)	−0.533	0.594
Time between pain and admission (h)	15.0 (13.8–18.0)	14 (9.0–19.0)	−1.458	0.145
Sample-collecting time (h)	18.4 (15.1–21.5)	16.7 (12.3–20.8)	−1.449	0.147
Revised Atlanta classification			17.560	<0.001
MAP	17 (34.0%)	101 (62.7%)		
MSAP	17 (34.0%)	43 (26.7%)		
SAP	16 (32.0%)	17 (10.6%)		
MODS	21 (42.0%)	19 (11.8%)	22.646	<0.001
Peripancreatic effusion	36 (72.0%)	89 (55.3%)	3.254	0.071
Pancreatic necrosis	17 (34.0%)	24 (14.9%)	8.884	0.003
Sepsis	18 (36.0%)	22 (13.7%)	12.388	<0.001
Acute respiratory failure	15 (30.0%)	24 (14.9%)	5.768	0.016
Acute renal injury	10 (20.0%)	9 (5.6%)	9.668	0.002
APACHE II scores	16 (14–21)	8 (4–14)	−6.939	<0.001
Ranson scores	6 (5–7)	3 (2–3)	−7.158	<0.001
SOFA scores	8 (7–10)	5 (2–8)	−6.886	<0.001
Etiologies			1.219	0.748
Biliary	15 (30.0%)	54 (33.5%)		
Alcoholic	19 (38.0%)	56 (34.8%)		
Hypertriglyceremic	13 (26.0%)	35 (21.7%)		
Others	3 (6.0%)	16 (9.9%)		
Blood CRP levels (mg/L)	40.1 (30.6–76.9)	28.1 (20.4–46.4)	−3.500	<0.001
Blood leucocyte count (×10^9/L)	15.2 (10.7–17.5)	12.0 (9.4–15.1)	−3.426	0.001
Blood PCT levels (ng/mL)	3.07 (1.79–4.94)	2.22 (1.49–3.29)	−2.782	0.005
Blood calcium levels (mmol/L)	2.0 (1.8–2.1)	2.1 (1.9–2.2)	−2.148	0.032
Blood glucose levels (mmol/L)	12.0 (8.0–17.7)	9.5 (7.1–13.0)	−3.104	0.002
Blood creatinine levels (μmol/L)	130.0 (103.4–143.3)	108.9 (87.7–135.3)	−2.051	0.040
Blood urea nitrogen levels (mg/dL)	13.0 (9.3–17.3)	12.2 (9.4–14.5)	−1.668	0.095
Serum NLRP3 levels (ng/mL)	1933.4 (1663.1–2175.1)	1326.6 (1178.7–1644.8)	−6.079	<0.001

Notes: Qualitative variables were presented as counts (percentages) and were compared for intergroup difference using chi-square test or Fisher exact test where appropriate. Quantitative variables were summarized as medians (25^{th}-75^{th}) and intergroup comparisons were done using the Mann–Whitney *U*-test.

Abbreviations: APPACH II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; MODS, multiple organ dysfunction syndrome; CRP, C-reactive protein; PCT, procalcitonin; NLRPP3, nucleotide-binding oligomeric structural domain-like receptor protein 3; OR, odds ratio; 95% CI, 95% confidence interval.

role in IL-1β maturation and inflammatory cascade response after SAP.[17] NLRP3 deficiency in mice attenuated pathological pancreatic injury and reduced amylase activation, as well as lessened interactions between pro-inflammatory cytokines, between anti-inflammatory cytokines, and between pro-inflammatory and anti-inflammatory cytokines, and consequently promoted recovery from AP.[17] In the present study, serum NLRP3 levels were significantly elevated after AP, and it was inferred that NLRP3 in the peripheral blood might partially originate from the injured pancreatic tissue. In the present study, we found that elevated serum NLRP3 levels had a significant positive correlation with traditional severity indicators of AP, such as APACHE II scores, Ranson scores, and SOFA scores. In conclusion, serum NLRP3 levels may reflect the severity of AP.

Brain injury is one of the major causes of delirium after severe illness. It has been found that microglia activation in the hippocampus of SAP rats was significantly enhanced and the expression of inflammatory factors such as interleukin-1β and tumor necrosis factor-α is significantly elevated in brain tissues, which aggravated brain tissue damage, thereby leading to cognitive impairment.[41,42] Previous studies have confirmed that biomarkers, such

Table 7 Multivariate Logistic Regression Analysis of Predictors of Delirium After Acute Pancreatitis

	Univariate Logistic Regression Analysis		Multivariate Logistic Regression Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.016 (0.989–1.043)	0.246	–	–
Gender (male/female)	0.578 (0.305–1.095)	0.093	–	–
Body mass index (kg/m^2)	0.953 (0.857–1.060)	0.378	–	–
Time between pain and admission (h)	1.045 (0.983–1.110)	0.159	–	–
Sample-collecting time (h)	1.046 (0.983–1.114)	0.159	-	-
Revised Atlanta classification		<0.001		0.195
MAP	1		1	
MSAP	2.349 (1.097–5.028)	0.028	0.352 (0.114–1.080)	0.068
SAP	5.592 (2.379–13.141)	<0.001	0.532 (0.103–2.752)	0.452
MODS	5.412 (2.587–11.320)	<0.001	1.985 (0.609–6.476)	0.256
Peripancreatic effusion	1.929 (0.966–3.852)	0.063	-	-
Pancreatic necrosis	2.941 (1.419–6.092)	0.004	0.323 (0.084–1.247)	0.101
Sepsis	3.554 (1.709–7.389)	0.001	1.613 (0.524–4.971)	0.405
Acute respiratory failure	2.446 (1.162–5.150)	0.018	1.503 (0.456–4.948)	0.535
Acute renal injury	4.222 (1.608–11.089)	0.003	0.572 (0.130–2.509)	0.419
APACHE II scores	1.228 (1.148–1.312)	<0.001	1.121 (1.035–1.206)	0.025
Ranson scores	2.162 (1.702–2.745)	<0.001	1.943 (1.019–3.706)	0.044
SOFA scores	1.602 (1.369–1.875)	<0.001	1.574 (1.067–2.322)	0.022
Etiologies		0.753	-	-
Biliary	1			
Alcoholic	1.481 (0.380–5.768)	0.571		
Hypertriglyceremic	1.810 (0.475–6.900)	0.385		
Others	1.981 (0.495–7.935)	0.334		
Blood CRP levels (mg/L)	1.013 (1.004–1.023)	0.006	1.001 (0.987–1.016)	0.855
Blood leucocyte count (×10^9/L)	1.134 (1.053–1.223)	0.001	0.955 (0.850–1.074)	0.444
Blood PCT levels (ng/mL)	1.422 (1.161–1.743)	0.001	1.200 (0.902–1.598)	0.211
Blood calcium levels (mmol/L)	0.244 (0.066–0.896)	0.034	0.349 (0.058–2.109)	0.252
Blood glucose levels (mmol/L)	1.104 (1.036–1.177)	0.002	1.084 (0.990–1.186)	0.083
Blood creatinine levels (μmol/L)	1.009 (1.000–1.017)	0.045	1.006 (0.993–1.019)	0.403
Blood urea nitrogen levels (mg/dL)	1.078 (0.993–1.169)	0.072	-	-
Serum NLRP3 levels (ng/mL)	5.531 (3.035–10.077)	<0.001	2.186 (1.004–4.760)	0.035

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; APPACH II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; CRP, C-reactive protein; PCT, procalcitonin; NLRP3, nucleotide-binding oligomeric structural domain-like receptor protein 3; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; MODS, multiple organ dysfunction syndrome.

as soluble fibrinogen-like protein 2, cold-inducible RNA-binding protein, have important roles in the prediction of delirium after AP.[9,43] Interestingly, the expression of NLRP3 was significantly increased in the brain tissue of SAP rats.[43] In addition, NLRP3 expression in brain tissue and peripheral blood was significantly elevated after acute brain injury, including intracerebral hemorrhage and aneurysmal subarachnoid hemorrhage, and was strongly correlated with disease severity and patient prognosis.[21,44,45] These data suggest that NLRP3 may be a potential prognostic biomarker of acute brain injury. Our study found that serum NLRP3 levels were independently associated with the emergence of in-hospital delirium after AP. Subsequent ROC curve analysis showed that serum NLRP3 levels had similar predictive power for delirium onset as APACHE II scores, Ranson scores and SOFA scores. Overall, the above data strongly support the potential ability of serum NLRP3 as a predictor of in-hospital delirium after AP. Moreover, the model incorporating the preceding three conventional variable and serum NLRP3 was built here. We then validated its reliability, clinical fit, and discriminatory efficiency using a series of statistical methods such as calibration, decision making, and ROC curves in both the study and validation groups. The results suggest that serum NLRP3 may have the ability to effectively discriminate risk of delirium during staying at hospital after AP.

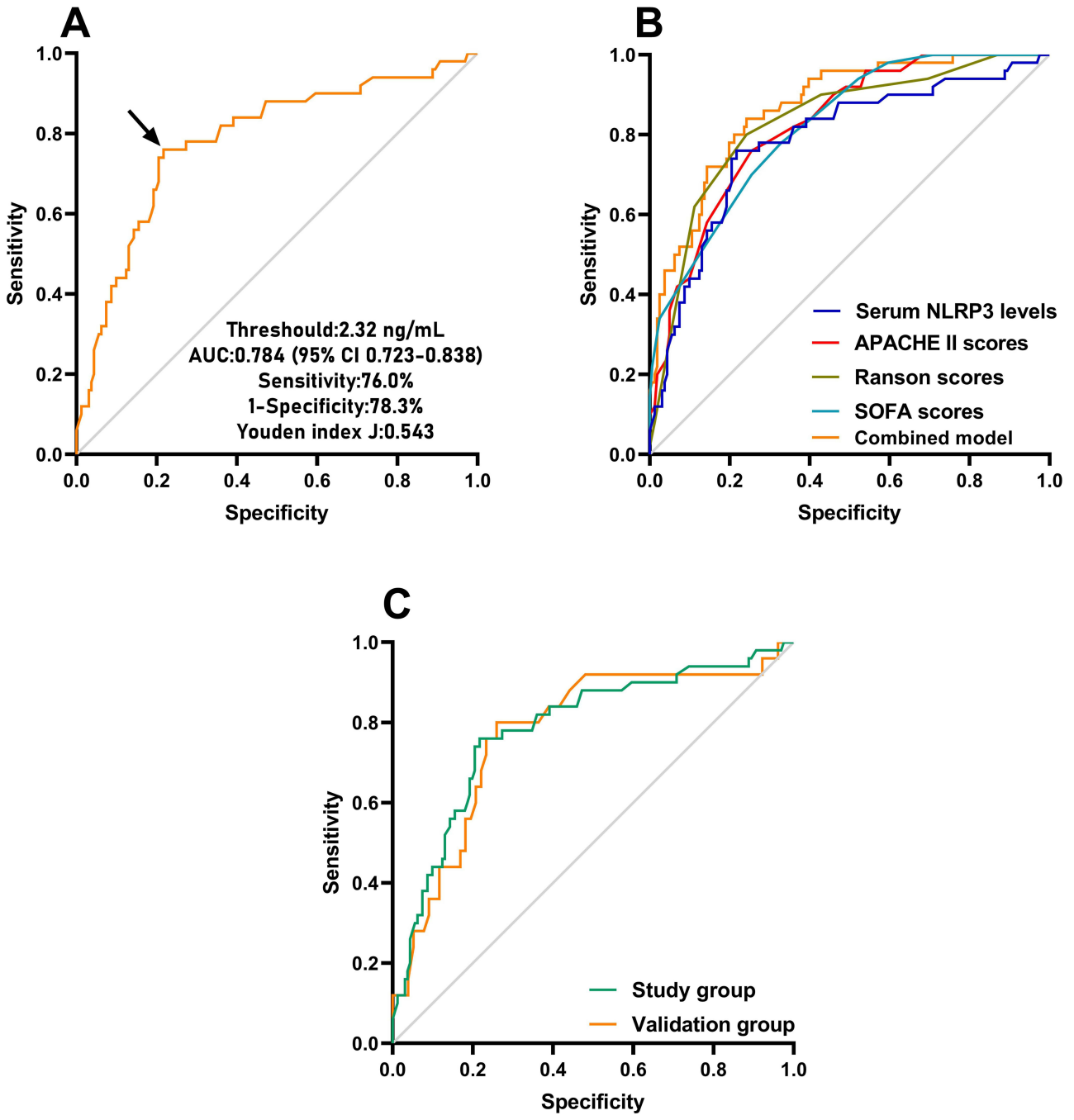

Figure 7 Receiver operating characteristic curve displaying relationship between admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and the presence of in-hospital delirium in patients with acute pancreatitis. The clinical metrics included the acute physiology and chronic health evaluation II, Ranson, and sequential organ failure assessment scores. Combined model encompassed the preceding scaling systems and serum nucleotide-binding oligomeric structural domain-like receptor protein 3 levels. Admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels efficiently predicted in-hospital delirium after acute pancreatitis (**A**); the prediction ability of the model was higher than the other four variables for in-hospital delirium following acute pancreatitis (**B**); prediction ability of serum nucleotide-binding oligomeric structural domain-like receptor protein 3 levels for in-hospital delirium following acute pancreatitis was similar between study group and validation group (**C**).

Abbreviations: AUC, area under curve; CI, confidence interval, NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

This study has several strengths and limitations. The strengths are that: (1) to the best of our knowledge, there are no studies reporting significantly elevated serum NLRP3 levels early in the disease in patients with AP and that these levels may be effective in assessing disease severity and predicting delirium, and (2) the relationship between serum NLRP3

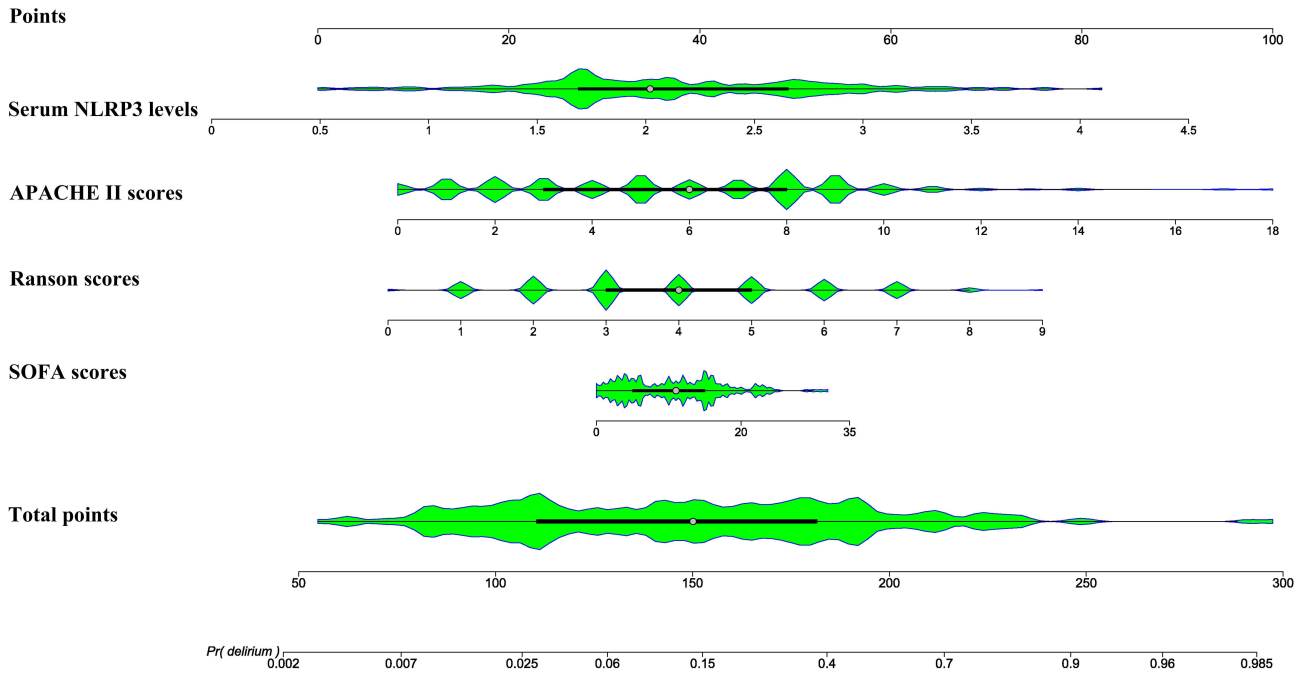

Figure 8 Nomogram outlining combination model of in-hospital delirium following acute pancreatitis. The nomogram provided an extensive in-hospital delirium prediction model including data from the acute physiology and chronic health evaluation II, Ranson, sequential organ failure assessment scores and serum nucleotide-binding oligomeric structural domain-like receptor protein 3 levels.

Abbreviations: NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

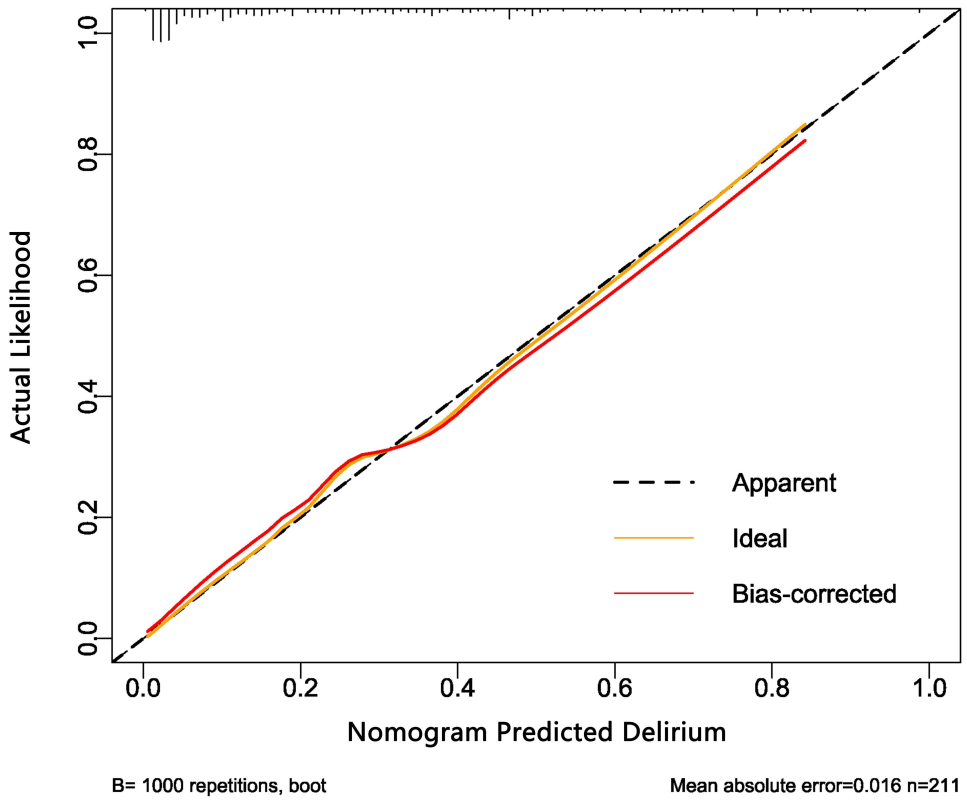

Figure 9 Calibration curve assessing the dependability of a model for predicting in-hospital delirium following acute pancreatitis. The model, in which acute physiology and chronic health evaluation II scores, Ranson scores, sequential organ failure assessment scores, and serum nucleotide-bound oligomeric domain-like receptor protein 3 levels were integrated, was comparatively stable for the prediction of in-hospital delirium after acute pancreatitis.

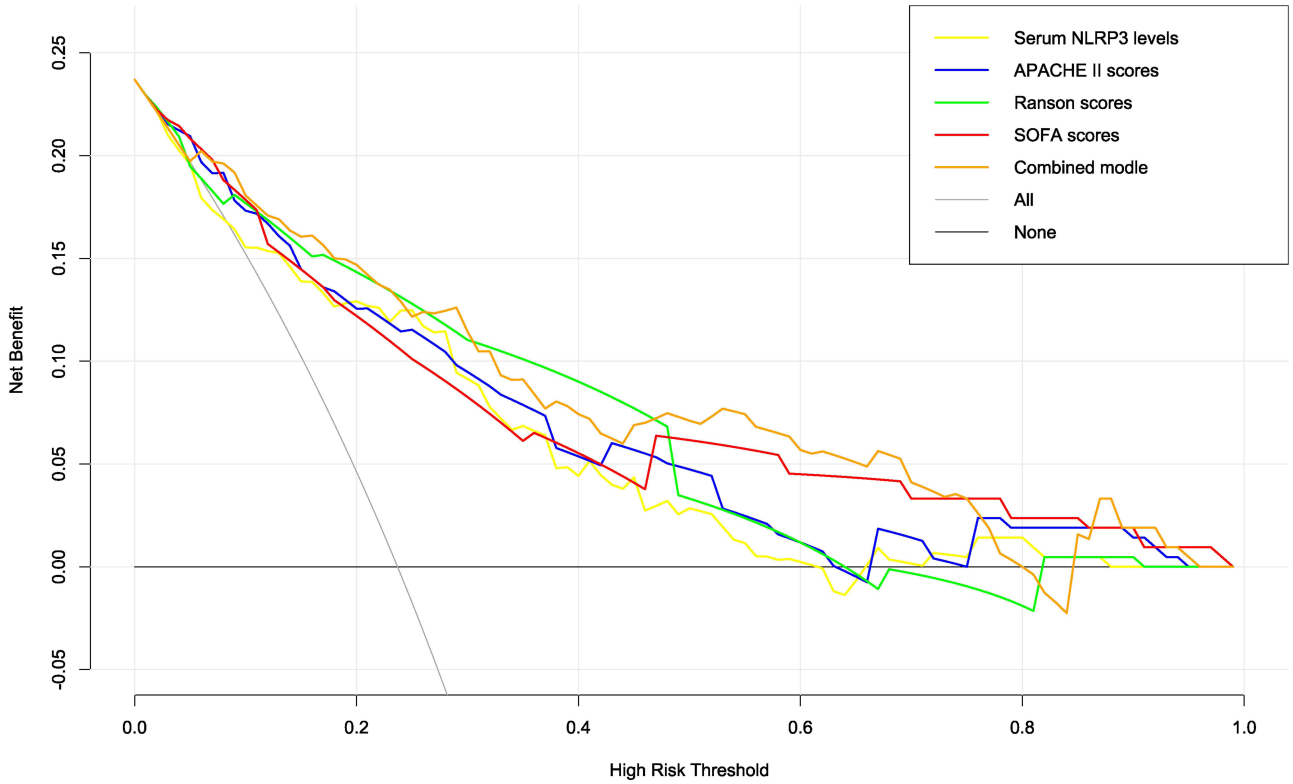

Figure 10 Decision curve displaying clinical fit of the model for predicting in-hospital delirium following acute pancreatitis. The decision curve analysis demonstrates the model was rather effective in predicting in-hospital delirium post-acute pancreatitis. Clinically, the model proved to be a reliable tool for forecasting in-hospital delirium within this timeframe.

Abbreviations: NLRP3, nucleotide-bound oligomeric domain-like receptor protein 3; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

levels and disease severity, and delirium after AP was validated by multivariate analysis, nomogram modeling, calibration curves, and decision curves relationship, supporting the reliability and scientific validity of the findings. The limitations are in the following. First, this study aimed to demonstrate the predictive role of serum NLRP3 levels on the onset of delirium after AP, but the sample size was statistically large enough, and a larger cohort study is needed at a later stage to validate the results of this study. Second, in this clinical study, serum NLRP3 was determined for its predictive value on delirium following AP, but further investigation of the specific mechanisms of NLRP3 in delirium episodes after AP may be helpful for further treatments of AP patients. Third, although the potential clinical utility of serum NLRP3 as a predictive biomarker of delirium post-AP may be acknowledged, in consideration of clinical implementation challenges regarding biomarker measurements, such as cost-effectiveness and assay standardization, the potential application of serum NLRP3 in guiding patient managements or therapeutic interventions warrants to be further schemed. Finally, measuring serum NLRP3 levels in AP patients at multiple time points will help to reveal the temporal trends of serum NLRP3 levels after AP, thus supporting clinical treatments.

Conclusion

In this two-center prospective cohort study, higher serum NLRP3 levels may be associated with higher APACHE II scores, Ranson scores, and SOFA scores in AP patients. In addition, elevated serum NLRP3 levels are strongly associated with the occurrence of delirium after AP, serum NLRP3 levels have effective prognostic power under the ROC curve, and the combination of serum NLRP3 with clinical scoring systems significantly enhances predictive accuracy compared to serum NLRP3 alone, altogether implying that serum NLRP3 may serve as a potential biomarker for predicting the occurrence of delirium in AP patients.

https://doi.org/10.2147/IJGM.S534284

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Statement

This study was carried out in accordance with the ethical guidelines of the Helsinki Declaration, and its protocol was approved by the Institutional Review Committee of Lishui City Hospital of Traditional Chinese Medicine and Lishui City People's Hospital (Opinion Nos. LLW-FO-403, LW-2024081). Legal representatives of patients and controls themselves gave written informed consent to participate in this study.

Acknowledgments

The authors thank all staff for their technical support.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

All authors report no conflicts of interest in this work.

References

1. van Dijk SM, Hallensleben NDL, van Santvoort HC, et al. Acute pancreatitis: recent advances through randomised trials. *Gut*. 2017;66(11):2024–2032. doi:10.1136/gutjnl-2016-313595
2. Das SL, Kennedy JI, Murphy R, Phillips AR, Windsor JA, Petrov MS. Relationship between the exocrine and endocrine pancreas after acute pancreatitis. *World J Gastroenterol*. 2014;20(45):17196–17205. doi:10.3748/wjg.v20.i45.17196
3. Dumnicka P, Maduzia D, Ceranowicz P, Olszanecki R, Drożdż R, Kuśnierz-Cabala B. The interplay between inflammation, coagulation and endothelial injury in the early phase of acute pancreatitis: clinical implications. *Int J Mol Sci*. 2017;18(2):354. doi:10.3390/ijms18020354
4. Chauhan R, Saxena N, Kapur N, Kardam D. Comparison of modified Glasgow-Imrie, Ranson, and apache II scoring systems in predicting the severity of acute pancreatitis. *Pol Przegl Chir*. 2022;95(1):6–12. doi:10.5604/01.3001.0015.8384
5. Tee YS, Fang HY, Kuo IM, Lin YS, Huang SF, Yu MC. Serial evaluation of the SOFA score is reliable for predicting mortality in acute severe pancreatitis. *Medicine*. 2018;97(7):e9654. doi:10.1097/MD.0000000000009654
6. Hübscher A, Isenmann S. Delir: konzepte, ätiologie und klinisches management [Delirium: concepts, etiology, and clinical management]. *Fortschr Neurol Psychiatr*. 2016;84(4):233–244. German. doi:10.1055/s-0042-104502
7. Ormseth CH, LaHue SC, Oldham MA, Josephson SA, Whitaker E, Douglas VC. Predisposing and precipitating factors associated with delirium: a systematic review. *JAMA Network Open*. 2023;6(1):e2249950. doi:10.1001/jamanetworkopen.2022.49950
8. Ye X, Li B, Xu F, Pan D, Wu J. Receptor-interacting protein kinase 3 as a serological biomarker in relation to disease severity and delirium after acute pancreatitis: a prospective cohort study. *Int J Gen Med*. 2024;17:5309–5323. doi:10.2147/IJGM.S488540
9. Xu WB, Hu QH, Wu CN, Fan ZK, Song ZF. Serum soluble fibrinogen-like protein 2 concentration predicts delirium after acute pancreatitis. *Brain Behav*. 2019;9(4):e01261. doi:10.1002/brb3.1261
10. Sharma BR, Kanneganti TD. NLRP3 inflammasome in cancer and metabolic diseases. *Nat Immunol*. 2021;22(5):550–559. doi:10.1038/s41590-021-00886-5
11. Noonin C, Thongboonkerd V. Exosome-inflammasome crosstalk and their roles in inflammatory responses. *Theranostics*. 2021;11(9):4436–4451. doi:10.7150/thno.54004
12. Kahlenberg JM, Kaplan MJ. The inflammasome and lupus: another innate immune mechanism contributing to disease pathogenesis? *Curr Opin Rheumatol*. 2014;26(5):475–481. doi:10.1097/BOR.0000000000000088
13. Prakash AV, Park IH, Park JW, Bae JP, Lee GS, Kang TJ. NLRP3 inflammasome as therapeutic targets in inflammatory diseases. *Biomol Ther*. 2023;31(4):395–401. doi:10.4062/biomolther.2023.099
14. Hu L, Chen H, Zhang X, Feng Z, Zhang H, Meng Q. Rosiglitazone ameliorates radiation-induced intestinal inflammation in rats by inhibiting NLRP3 inflammasome and TNF-α production. *J Radiat Res*. 2020;61(6):842–850. doi:10.1093/jrr/rraa062

15. Tangi TN, Elmabsout AA, Bengtsson T, Sirsjö A, Fransén K. Role of NLRP3 and CARD8 in the regulation of TNF-α induced IL-1β release in vascular smooth muscle cells. *Int J Mol Med*. 2012;30(3):697–702. doi:10.3892/ijmm.2012.1026
16. Ridker PM, Rane M. Interleukin-6 signaling and anti-interleukin-6 therapeutics in cardiovascular disease. *Circ Res*. 2021;128(11):1728–1746. doi:10.1161/CIRCRESAHA.121.319077
17. Fu Q, Zhai Z, Wang Y, et al. NLRP3 deficiency alleviates severe acute pancreatitis and pancreatitis-associated lung injury in a mouse model. *Biomed Res Int*. 2018;2018:1294951. doi:10.1155/2018/1294951
18. Minutoli L, Puzzolo D, Rinaldi M, et al. ROS-mediated NLRP3 inflammasome activation in brain, heart, kidney, and testis ischemia/reperfusion injury. *Oxid Med Cell Longev*. 2016;2016(1):2183026. doi:10.1155/2016/2183026
19. Chen S, Ding YH, Shi SS, Tu XK. Schisandrin B inhibits NLRP3 inflammasome pathway and attenuates early brain injury in rats of subarachnoid hemorrhage. *Chin J Integr Med*. 2022;28(7):594–602. doi:10.1007/s11655-021-3348-z
20. Wang Y, Huang H, He W, Zhang S, Liu M, Wu S. Association between serum NLRP3 and malignant brain edema in patients with acute ischemic stroke. *BMC Neurol*. 2021;21(1):341. doi:10.1186/s12883-021-02369-4
21. Xu B, Zhou Y, Zhang Z, Ma J, Lv K. Serum concentrations of NLRP3 in relation to functional outcome and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Clin Chim Acta*. 2022;536:61–69. doi:10.1016/j.cca.2022.09.004
22. Zhou C, Wang H, Wang L, Zhou Y, Wu Q. Diagnostic accuracy of the family confusion assessment method for delirium detection: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2024;72(3):892–902. doi:10.1111/jgs.18692
23. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286(21):2703–2710. doi:10.1001/jama.286.21.2703
24. Ge P, Luo Y, Okoye CS, et al. Intestinal barrier damage, systemic inflammatory response syndrome, and acute lung injury: a troublesome trio for acute pancreatitis. *Biomed Pharmacother*. 2020;132:110770. doi:10.1016/j.biopha.2020.110770
25. Pando E, Alberti P, Mata R, et al. Early changes in blood urea nitrogen (BUN) can predict mortality in acute pancreatitis: comparative study between BISAP score, APACHE-II, and other laboratory markers-A prospective observational study. *Can J Gastroenterol Hepatol*. 2021;2021:6643595. doi:10.1155/2021/6643595
26. Zhu J, Wu L, Wang Y, Fang M, Liu Q, Zhang X. Predictive value of the Ranson and BISAP scoring systems for the severity and prognosis of acute pancreatitis: a systematic review and meta-analysis. *PLoS One*. 2024;19(4):e0302046. doi:10.1371/journal.pone.0302046
27. Adam F, Bor C, Uyar M, Demırağ K, Çankayalı İ. Severe acute pancreatitis admitted to intensive care unit: SOFA is superior to Ranson's criteria and APACHE II in determining prognosis. *Turk J Gastroenterol*. 2013;24(5):430–435. doi:10.4318/tjg.2013.0761
28. Tarján D, Szalai E, Lipp M, et al. Persistently high procalcitonin and C-reactive protein are good predictors of infection in acute necrotizing pancreatitis: a systematic review and meta-analysis. *Int J Mol Sci*. 2024;25(2):1273. doi:10.3390/ijms25021273
29. Li J, Chen Z, Li L, et al. Interleukin-6 is better than C-reactive protein for the prediction of infected pancreatic necrosis and mortality in patients with acute pancreatitis. *Front Cell Infect Microbiol*. 2022;12:933221. doi:10.3389/fcimb.2022.933221
30. He J, Ma M, Li D, et al. Sulfiredoxin-1 attenuates injury and inflammation in acute pancreatitis through the ROS/ER stress/Cathepsin B axis. *Cell Death Dis*. 2021;12(7):626. doi:10.1038/s41419-021-03923-1
31. Fu J, Wu H. Structural mechanisms of NLRP3 inflammasome assembly and activation. *Annu Rev Immunol*. 2023;41(1):301–316. doi:10.1146/annurev-immunol-081022-021207
32. Wu D, Chen Y, Sun Y, et al. Target of MCC950 in inhibition of NLRP3 inflammasome activation: a literature review. *Inflammation*. 2020;43(1):17–23. doi:10.1007/s10753-019-01098-8
33. Münzer P, Negro R, Fukui S, et al. NLRP3 inflammasome assembly in neutrophils is supported by PAD4 and promotes NETosis under sterile conditions. *Front Immunol*. 2021;12:683803. doi:10.3389/fimmu.2021.683803
34. Yang S, Cao J, Wang Y, et al. Small intestinal endocrine cell derived exosomal ACE2 protects islet β-Cell function by inhibiting the activation of NLRP3 inflammasome and reducing β-Cell pyroptosis. *Int J Nanomed*. 2024;19:4957–4976. doi:10.2147/IJN.S450337
35. Sun L, Ma W, Gao W, et al. Propofol directly induces caspase-1-dependent macrophage pyroptosis through the NLRP3-ASC inflammasome. *Cell Death Dis*. 2019;10(8):542. doi:10.1038/s41419-019-1761-4
36. Shen Y, Yang H, Wu D, Yang H, Hong D. NLRP3 inflammasome inhibitor MCC950 can reduce the damage of pancreatic and intestinal barrier function in mice with acute pancreatitis. *Acta Cir Bras*. 2022;37(7):e370706. doi:10.1590/acb370706
37. Kanak MA, Shahbazov R, Yoshimatsu G, Levy MF, Lawrence MC, Naziruddin B. A small molecule inhibitor of NFκB blocks ER stress and the NLRP3 inflammasome and prevents progression of pancreatitis. *J Gastroenterol*. 2017;52(3):352–365. doi:10.1007/s00535-016-1238-5
38. Wang J, Feng Y, Huo H, et al. NLRP3 inflammasome mediates angiotensin II-induced islet β cell apoptosis. *Acta Biochim Biophys Sin*. 2019;51(5):501–508. doi:10.1093/abbs/gmz032
39. Sheng LP, Han CQ, Ling X, Guo XW, Lin R, Ding Z. Proanthocyanidins suppress NLRP3 inflammasome and M1 macrophage polarization to alleviate severe acute pancreatitis in mice. *J Biochem Mol Toxicol*. 2023;37(2):e23242. doi:10.1002/jbt.23242
40. Gao L, Dong X, Gong W, et al. Acinar cell NLRP3 inflammasome and gasdermin D (GSDMD) activation mediates pyroptosis and systemic inflammation in acute pancreatitis. *Br J Pharmacol*. 2021;178(17):3533–3552. doi:10.1111/bph.15499
41. Ou X, Hua Y, Liao X, Gong C, Kang Y. Cognitive impairments induced by severe acute pancreatitis are attenuated by berberine treatment in rats. *Mol Med Rep*. 2018;18(3):3437–3444. doi:10.3892/mmr.2018.9313
42. Cabral-França T, Cruz FF, Silva PC, et al. Hippocampal microglia activation induced by acute pancreatic injury in rats. *Dig Dis Sci*. 2024;69(1):148–160. doi:10.1007/s10620-023-08167-x
43. Gong JD, Qi XF, Zhang Y, Li HL. Increased admission serum cold-inducible RNA-binding protein concentration is associated with prognosis of severe acute pancreatitis. *Clin Chim Acta*. 2017;471:135–142. doi:10.1016/j.cca.2017.06.002
44. Wu X, Zhang Y, Zhang Y, et al. MST4 attenuates NLRP3 inflammasome-mediated neuroinflammation and affects the prognosis after intracerebral hemorrhage in mice. *Brain Res Bull*. 2021;177:31–38. doi:10.1016/j.brainresbull.2021.09.006
45. Gao F, Zeng S, Chao D, Wu L. Dl-3-n-Butylphthalide attenuates early brain injury and delayed neurological dysfunction by regulating NLRP3 inflammasome after subarachnoid hemorrhage. *Brain Res Bull*. 2024;217:111084. doi:10.1016/j.brainresbull.2024.111084

International Journal of General Medicine

Dovepress
Taylor & Francis Group

Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/international-journal-of-general-medicine-journal