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ORIGINAL RESEARCH

Variations in Platelet Count Associated with the Occurrence of Infected Pancreatic Necrosis, Surgical Intervention, and Mortality in Acute Pancreatitis: A Retrospective Cohort Study

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Background: Acute pancreatitis (AP) is a common abdominal emergency, often associated with severe complications such as infected pancreatic necrosis (IPN) and the need for surgical intervention. Platelet count dynamics during the course of AP may be linked to disease progression and outcomes.

Purpose: This study aimed to identify clinically meaningful longitudinal platelet count patterns in AP.

Methods: Longitudinal platelet count patterns were derived using group-based trajectory modeling (GBTM). Generalized additive models were used to demonstrate the association between platelet counts and outcomes.

Results: 2225 AP patients are enrolled in the analysis and classified into 5 subclasses using GBTM. Class 1 (n=269) had a low initial platelet count, which increased slowly; Class 2 (n=983) and Class 4 (n=597) had different initial platelet count levels, but fluctuated within the normal range; Class 3 (n=225) and Class 5 (n=151) had different initial platelet count levels, but both increased beyond the normal range. A significantly decreased risk of infected pancreatic necrosis (IPN) is observed in classes 2 (OR 0.3, CI 0.16–0.55) and 4 (OR 0.14, CI 0.06–0.33), but the risk was comparable among classes 1 (ref), 3 (OR 1.25, CI 0.66–2.41), and 5 (OR 0.69, CI 0.28–1.56). The risks of the surgical interventions were similar. However, the 30-day and 90-day mortality rates were significantly lower in classes 2, 3, 4, and 5 than in class 1. Generalized additive models also demonstrated the lowest risk of IPN, surgical intervention, and in-hospital mortality as platelet counts remained within the normal range.

Conclusion: Patients with platelet counts within the normal range had the lowest risk of IPN, surgical intervention, and mortality. Both thrombocytopenia and thrombocytosis indicate an increased risk of IPN and surgical intervention; however, mortality is significantly increased only in patients with thrombocytopenia.

Keywords: acute pancreatitis, platelet count, infected pancreatic necrosis, mortality, trajectory model

Introduction

Acute pancreatitis (AP) is a common gastrointestinal inflammatory condition with an incidence of 34 per 100000 person-years.[1,2] The clinical course is mild in most patients, but approximately 20–40% of patients develop secondary infection complications and organ dysfunction. The overall mortality rate in these patients was as high as 20% in these patients.[3]

Platelets play a pivotal role in homeostasis and thrombosis. There is growing recognition that it also plays a critical role in the immune system and inflammation response.[4] Abnormal platelet count is associated with poor outcomes in critically illness patients.[5,6] In our previously published study, we found that an abnormal platelet count on admission

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was a predictor of a higher incidence of intra-abdominal infection and surgical intervention in AP.[7] As a routine biomarker, platelet counts are measured repeatedly during the disease process. The change in the blood platelet count could provide valuable insights into the pathophysiological condition of the patient, including but not limited to vascular leakage, potential bleeding, thrombosis formation, and disseminated intravascular coagulation. The dynamic change in platelet count might provide important insights into patient prognosis.[8] To our knowledge, no study has systematically analyzed the importance of dynamic changes in platelet counts during the disease process.

Here, we conducted a retrospective hospital-based cohort study to identify clinically meaningful longitudinal platelet count patterns for outcomes as well as the risk factors for thrombocytosis in patients with AP.

Methods

Participants

We included adult patients discharged with a diagnosis of acute pancreatitis according to the revised 2012 Atlanta guideline[9] who were admitted to Ruijin Hospital, Shanghai Jiaotong University School of Medicine between January 2012 and May 2022. The patient exclusion criteria were as follows: (1) age < 18 years, (2) pregnancy, (3) autoimmune diseases, (4) hematological diseases, (5) cirrhosis, (6) malignancy, (7) time from symptom onset to admission > 72 h, (8) length of hospital stay < 72 h, (9) discharge against medical advice, and (10) no multiple platelet count measurements within 14 days after admission. All enrolled patients were followed-up until discharge or death.

This study was approved by the Institutional Ethics Board of Ruijin Hospital, Shanghai Jiaotong University School of Medicine (2018CR004). As this was a retrospective analysis and all patient data were de-identified, individual patient consent was not required. We strictly adhered to the principles of patient data confidentiality to ensure the security and privacy of all personal information. The data analysis was performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Data Collection

Clinical variables were extracted from the electronic databases. Baseline demographic information included the time interval from onset to admission, age, sex, body mass index, comorbidities (hypertension, diabetes mellitus, and chronic kidney disease), and etiologies (biliary, hypertriglyceridemia, alcohol, or others). The first laboratory indicators measured after admission, including white blood cell count (WBC), alanine aminotransferase (ALT), blood urine nitrogen (BUN), creatinine, C-reactive protein (CRP), D-dimer, fibrinogen, and total bilirubin (Tbil), were collected. Longitudinal platelet count data within 14 days after admission were collected daily. If there were multiple measurements within one day, the mean value was calculated for the analysis. Thrombocytosis is defined as a maximal platelet count greater than 450×10^9/L within 14 days.[10,11] The Balthazar scores were evaluated on the first CT scan after admission. Severities were classified as mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP), according to the revised 2012 Atlanta guideline.[9] The clinical outcomes included the incidence of infected pancreatic necrosis (IPN), surgical intervention, and in-hospital mortality. An IPN is diagnosed according to the culture results of the peripancreatic collections or the bubble sign on the CT scan. Indications for surgical intervention include suspicion of infection, ongoing gastric outlet obstruction, biliary or intestinal obstruction due to an enlarged pseudocyst, or disconnected duct syndrome.

Platelet Count Trajectory Identification

The subclasses were derived using group-based trajectory modeling (GBTM), which is a type of latent class analysis used to map the different developmental courses of indices and assess heterogeneity within the population on the basis of maximum likelihood estimation.[12] The optimal number of subclasses was determined using the Akaike information criterion (AIC), Bayesian information criterion (BIC), and average posterior probability (AvePP). Lower AIC and BIC values with AvePP>70% in each subclass indicated better model fitting and discriminatory power. The minimum size of each subclass was defined as 5%.

Data Analysis

Categorical data were described as frequencies or ratios. Continuous variables were described using the median and interquartile range (IQR). Categorical variables were compared using χ the 2 test or Fisher exact test. Continuous variables between subclasses were compared using Kruskal–Wallis test. Multiple comparisons were corrected using Bonferroni test. We implemented multiple imputations based on random forest using chained equations and created five independent datasets to compute missing data. Variables with more than 20% of missing data were excluded. No imputation process was performed for longitudinal platelet count trajectory data. The associations between subclasses and the incidence of IPN and surgical intervention were estimated using logistic regression with odds ratios (OR) reported after adjustment for confounders. Kaplan–Meier survival curves were used to compare survival differences between subclasses. Cox proportional hazards models were fitted to mortality and hazard ratios (HR). A smoothing spline was plotted using generalized additive models to demonstrate the associations between the outcomes of IPN, surgical intervention, and in-hospital mortality with the lowest platelet count level within 14 days (PLT_{min}) and the highest platelet count level within 14 days (PLT_{max}). Finally, multivariable logistic regression analysis was used to identify risk factors for thrombocytosis. The "lcmm", "survival", "mice" and "mgcv" packages are used. All statistical analyses were performed using the R software (version 4.2.1). Differences were considered statistically significant at a two-sided significance level of < 0.05.

Results

A total of 4392 patients diagnosed with AP between Jan 2012 and May 2022 were included, of which 2167 were excluded based on the exclusion criteria. Finally, 2225 patients are included in the analysis. A screening flowchart is shown in Figure 1.

Platelet Count Trajectory Subclasses

GBTMs have been developed with a number of classes ranging from one to six. AICs and BICs decrease as the number of classes increases. When the number was greater than six, the minimum size for Model 6 was less than 5% (Table S1). Model 5, with five subclasses 5 was chosen as the best model. Model 5 grouped patients with AP into five subclasses according to the different platelet count trajectories: class 1 (12.1%, N=269), class 2 (44.2%, N=983), class 3 (10.1%,

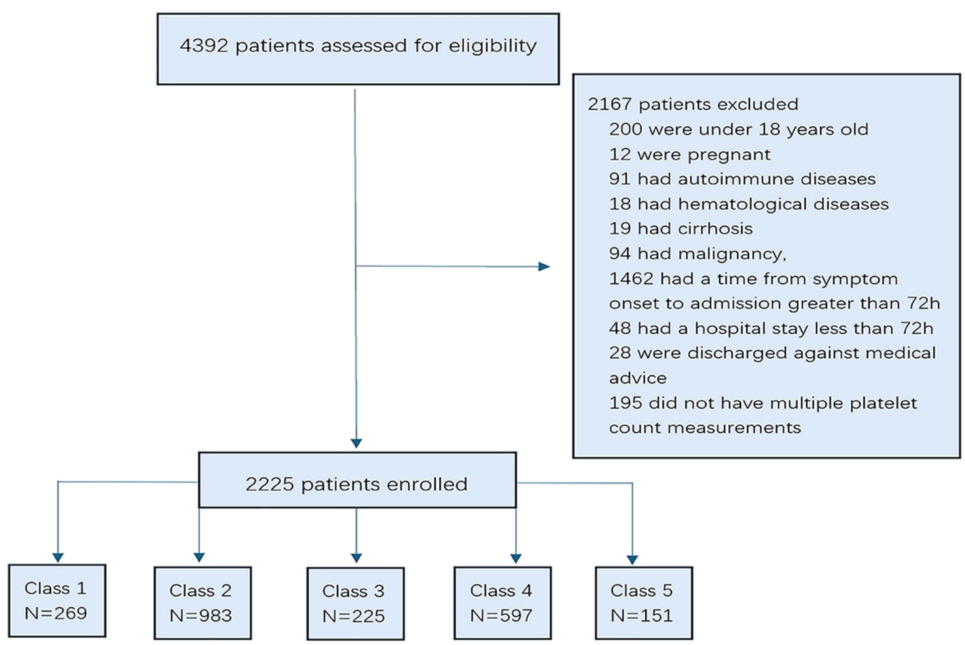

Figure 1 Screening flow chart.

N=225), class 4 (26.8%, N=597), and class 5 (6.8%, N=151). AvePP was greater than 70% in each subclass. The fixed effect coefficients for Model 5 are listed in Table S2.

Model 5 exhibited 5 different platelet count trajectory patterns. Class 1 had the lowest initial platelet count, close to the lower margin of the normal platelet count range (100x10^9/L), and increased slowly over 14 days. Class 2 had a moderate initial platelet count, which increased consistently but was within the normal range for 14 days. Class 3 patients had a moderate initial platelet count, increasing rapidly and out of the upper margin of the normal range (300x10^9/L) over 14 days. Class 4 patients had a high initial platelet count, with slight fluctuations, but was still within the normal range for 14 days. Class 5 had the highest initial platelet count, increasing rapidly and beyond the upper margin of the platelet count normal range for 14 days. The trajectories of platelet counts are depicted in Figure 2.

Patient Characteristics Between Subclasses

Among the 2225 enrolled AP patients with AP, significant differences in multiple variables were observed across the five subclasses (Table 1). Patients in class 1 were older (median, 57, IQR 42–69 years), with a relatively higher percentage of patients with SAP (18.6%). Patients in class 3 had the highest CRP level (median 192, IQR 121–282 mg/L) and the highest percentage of MSAP (55.1%) and SAP (23.6%) patients. Patients in class 4 had the lowest percentage of patients with SAP (1.8%) and the highest percentage of patients with MAP (66.3%). Patients had the lowest CRP levels (median 110, IQR 32–193 mg/L) in class 2 and were younger in class 5 (median 43, IQR 33–58 years). The percentage of patients is moderate in these two subclasses (7.1% and 9.3%, respectively).

Associations Between Subclasses and Clinical Outcomes

The incidence of IPN was significantly higher in classes 1, 3, and 5 (7.8%, 9.3%, and 5.3%, respectively) than that in classes 2 and 4 (2.4% and 1.2%, respectively). The same pattern is shown that the incidence of surgical intervention is

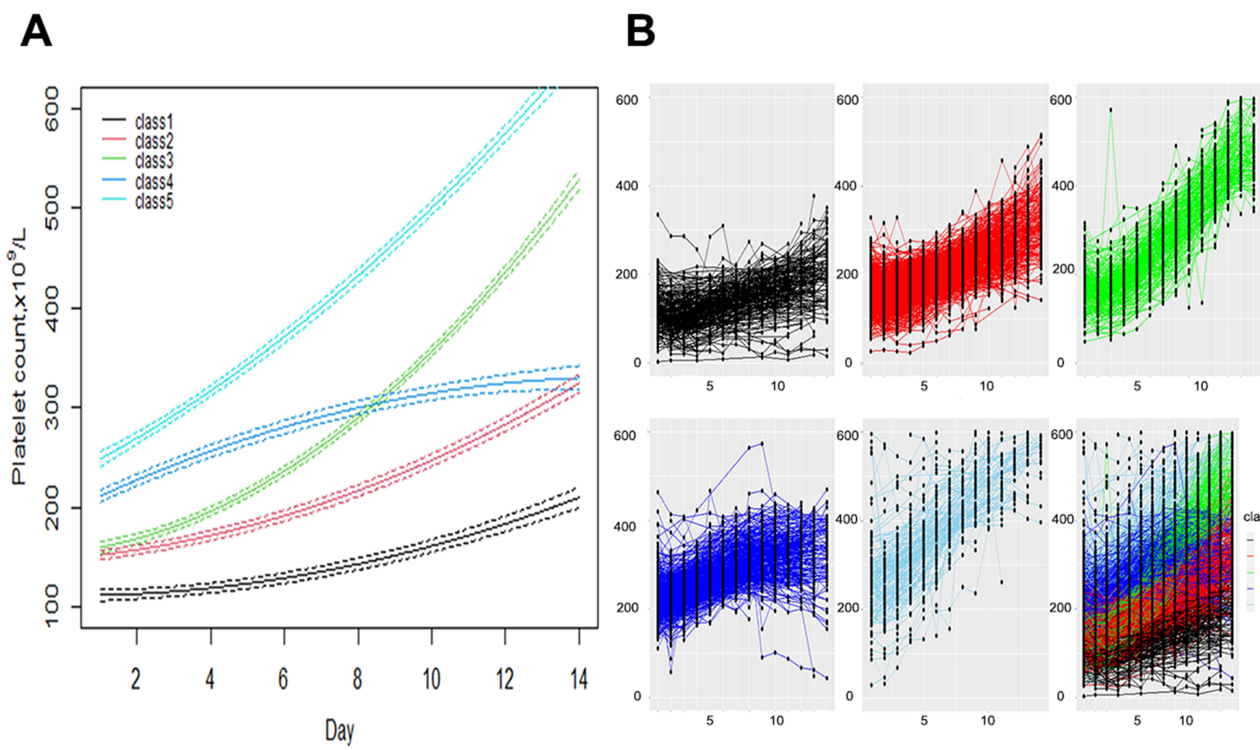

Figure 2 Trajectories of the platelet count during 14 days. (**A**) group-based trajectory modeling for the platelet count. (**B**) individual trajectory for the platelet count. The first five plots represent specific subclass from 1–5 and the last plot combines all the trajectories together. Each black point represented a single platelet count observation on each day, and longitudinal observations are linked by line individually. x-axis: represents the number of days. x-axis: represents the platelet count (x10^9/L). Class 1 is colored black; Class 2 is colored red; Class 3 is colored green; Class 4 is colored blue; Class 5 is colored skyblue.

Table 1 Patient Characteristics Between Subclasses

Variables	Class 1 (N=269)	Class 2 (N=983)	Class 3 (N=225)	Class 4 (N=597)	Class 5 (N=151)	p value
Age, y	57 (42–69)	53 (39–65)	46 (35–60)	44 (35–57)	43 (33–58)	<0.001
Sex (male%)	175 (65.1)	649 (66.0)	137 (60.9)	360 (60.3)	90 (59.6)	0.123
Body mass index, kg/m^2	24.1 (21.5–26.3)	25.0 (22.5–27.9)	25.1 (22.9–27.7)	25.2 (23.0–28.2)	24.8 (22.6–27.6)	<0.001
Time interval from onset to admission, days	1 (1–2)	1 (1–2)	2 (1–2)	2 (1–2)	2 (1–3)	<0.001
Comorbidities (%)						
Hypertension	101 (37.5)	357 (36.3)	71 (31.6)	162 (27.1)	38 (25.2)	<0.001
Diabetes mellitus	62 (23.0)	247 (25.1)	44 (19.6)	128 (21.4)	29 (19.2)	0.194
Chronic kidney diseases	6 (2.2)	17 (1.7)	1 (0.4)	3 (0.5)	1 (0.7)	0.086
Etiologies (%)						
Biliary	142 (52.8)	465 (47.3)	96 (42.7)	236 (39.5)	61 (40.4)	0.001
Hypertriglyceridemia	67 (24.9)	308 (31.3)	88 (39.1)	223 (37.4)	54 (35.8)	0.001
Alcoholic	18 (6.7)	62 (6.3)	26 (11.6)	49 (8.2)	16 (10.6)	0.044
Others	42 (15.6)	148 (15.1)	15 (6.7)	89 (14.9)	20 (13.2)	0.018
Laboratory indicators						
Platelet count, x10^9/L	113 (90–142)	161 (138–187)	173 (146–206)	220 (196–247)	263 (214–305)	<0.001
WBC, x10^9/L	8.9 (6.0–12.3)	10.1 (7.2–13.6)	12.3 (8.8–15.6)	11.2 (8.3–14.1)	14.0 (10.2–17.8)	<0.001
ALT, IU/L	32 (16–87)	29 (17–78)	28 (17–66)	24 (16–66)	26 (15–68)	0.244
BUN, mmol/L	5.4 (4.0–8.2)	4.5 (3.3–6.3)	5.8 (3.9–7.8)	3.8 (2.9–4.9)	3.8 (2.8–5.3)	<0.001
Creatinine, μmol/L	74 (61–92)	69 (57–84)	68 (55–85)	65 (53–76)	64 (51–77)	<0.001
CRP, mg/L	118 (37–234)	110 (32–193)	192 (121–282)	126 (46–203)	157 (92–226)	<0.001
D-dimers, mg/L	2.8 (0.8–5.0)	1.6 (0.7–3.7)	3.9 (2.3–6.1)	1.5 (0.8–3.3)	3.0 (1.3–4.9)	<0.001
Fibrinogen, g/L	3.7 (2.7–5.5)	4.1 (3.0–5.6)	5.1 (3.8–6.4)	4.8 (3.4–6.2)	5.3 (4.4–6.2)	<0.001
Tbil, mmol/L	24.5 (16.0–35.2)	21.5 (15.4–29.8)	23.2 (15.8–35.4)	19.4 (14.5–27.4)	20.0 (14.4–31.0)	<0.001
Balthazar score	3 (1–4)	2 (1–4)	4 (3–4)	2 (1–3)	3 (2–4)	<0.001
Severity (%)						
MAP	136 (50.6)	640 (65.1)	48 (21.3)	396 (66.3)	64 (42.4)	<0.001
MSAP	83 (30.9)	273 (27.8)	124 (55.1)	190 (31.8)	73 (48.3)	<0.001
SAP	50 (18.6)	70 (7.1)	53 (23.6)	11 (1.8)	14 (9.3)	<0.001
Outcomes						
IPN (%)	21 (7.8)	24 (2.4)	21 (9.3)	7 (1.2)	8 (5.3)	<0.001
Surgical intervention (%)	28 (10.4)	38 (3.9)	26 (11.6)	9 (1.5)	12 (7.9)	<0.001
In-hospital mortality (%)	21 (7.8)	12 (1.2)	7 (3.1)	6 (1.0)	2 (1.3)	<0.001

Notes: Continuous data are presented as median (IQR); categorical data are represented as count (percentage). First measured laboratory indicators after admission are shown.

Abbreviations: WBC, white blood cell count; ALT, alanine aminotransferase; BUN, blood urine nitrogen; CRP, C-reactive protein; Tbil, total bilirubin; MAP, mild acute pancreatitis; MASP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; IPN, infected pancreatic necrosis.

significantly higher in class 1, class 3, and class 5 (10.4%, 11.6%, and 7.9%, respectively) compared with class 2 and class 4 (3.9% and 1.5%) (Table S3 and Figure 3). The associations between subclasses and the incidence of IPN and surgical intervention were estimated using logistic regression, with adjustment for the demographic variables of age and sex, and class 1 as reference. The results revealed that a significantly decreased risk of IPN was observed in classes 2 (OR 0.3, CI 0.16–0.55, p<0.001) and 4 (OR 0.14, CI 0.06–0.33, p<0.001), but the risk was not decreased in classes 3 (OR 1.25, CI 0.66–2.41, p=0.48) and 5 (OR 0.69, CI 0.28–1.56, p=0.39). A significantly decreased risk of surgical intervention was also observed in classes 2 (OR 0.34, CI 0.21–0.58, p<0.001) and 4 (OR 0.13, CI 0.06–0.28, p<0.001), but the risk did not decrease in classes 3 (OR 1.14, CI 0.64–2.04, p=0.63) and class 5 (OR 0.76, CI 0.36–1.53, p=0.46).

As shown in the survival curves, patients in class 1 had the highest 30-day and 90-day mortality rates compared with those in the other subclasses (Figure 4). The associations between subclasses and 30-day and 90-day mortality

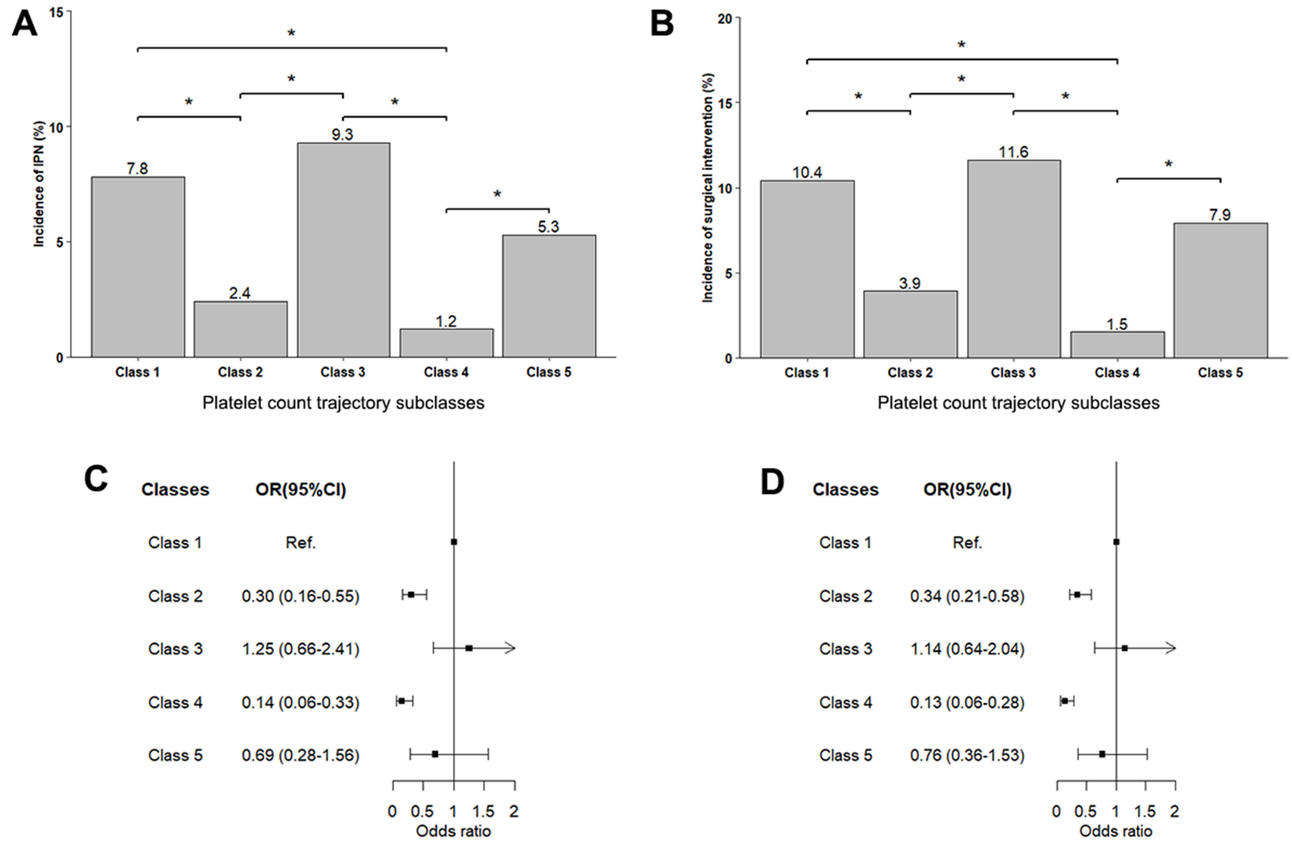

Figure 3 Comparisons of the incidence of IPN and surgical intervention among subclasses. (**A**) Comparisons of the incidence of IPN among subclasses; (**B**) Comparisons of the incidence of surgical intervention among subclasses. *Multiple comparisons are corrected with Bonferroni test. A corrected significance level less than 0.005 is defined as statistical significance. (**C**) OR and 95% CI for the risk of IPN across subclasses estimated by Logistic regression. (**D**) OR and 95% CI for the risk of surgical intervention across subclasses estimated by Logistic regression.

Abbreviations: IPN, infected pancreatic necrosis; OR, odds ratio; CI, confidence interval.

rates were estimated using Cox regression, with class 1 as a reference. The 30-day mortality rate was significantly lower in classes 2 (HR 0.17, CI 0.06–0.49, $p<0.001$), 3 (HR 0.22, CI 0.06–0.79, $p=0.019$), and 4 (HR 0.32, CI 0.11–0.93, $p=0.036$) and marginally lower in class 5 (HR 0.16, CI 0.02–1.26, $p=0.083$). The associations between subclasses and the 90-day mortality rate showed similar results, with a more significant decrease in class 5 (HR 0.22, CI 0.05–0.95, $p=0.043$).

Associations Between PLT_{min} and PLT_{max} with Clinical Outcomes

PLTmin represents the lowest platelet count within 14 days, and PLTmax is the highest. The PLT_{min} and PLT_{max} among 5 subclasses are listed in Table S4. PLT_{min} was lowest in class 1, with a median value of $92x10^9$/L. PLT_{max} was highest in classes 5 and 3, with median values of $511x10^9$/L and $456x10^9$/L, respectively. The PLT_{min} event could occur any day after the onset of AP, but PLT_{max} events usually occurred during the second week (Figure S1). The associations between PLT_{min} and PLT_{max} and the clinical outcomes of IPN, surgical intervention, and in-hospital mortality were generated using generalized additive models and plotted with smoothing splines. The results showed that the risks of IPN, surgical intervention, and in-hospital mortality decreased as platelet count increased to the normal range. However, when the platelet count increased beyond the normal range, the risks of IPN and surgical intervention increased; however, there was no change in the risk of in-hospital mortality (Figure 5).

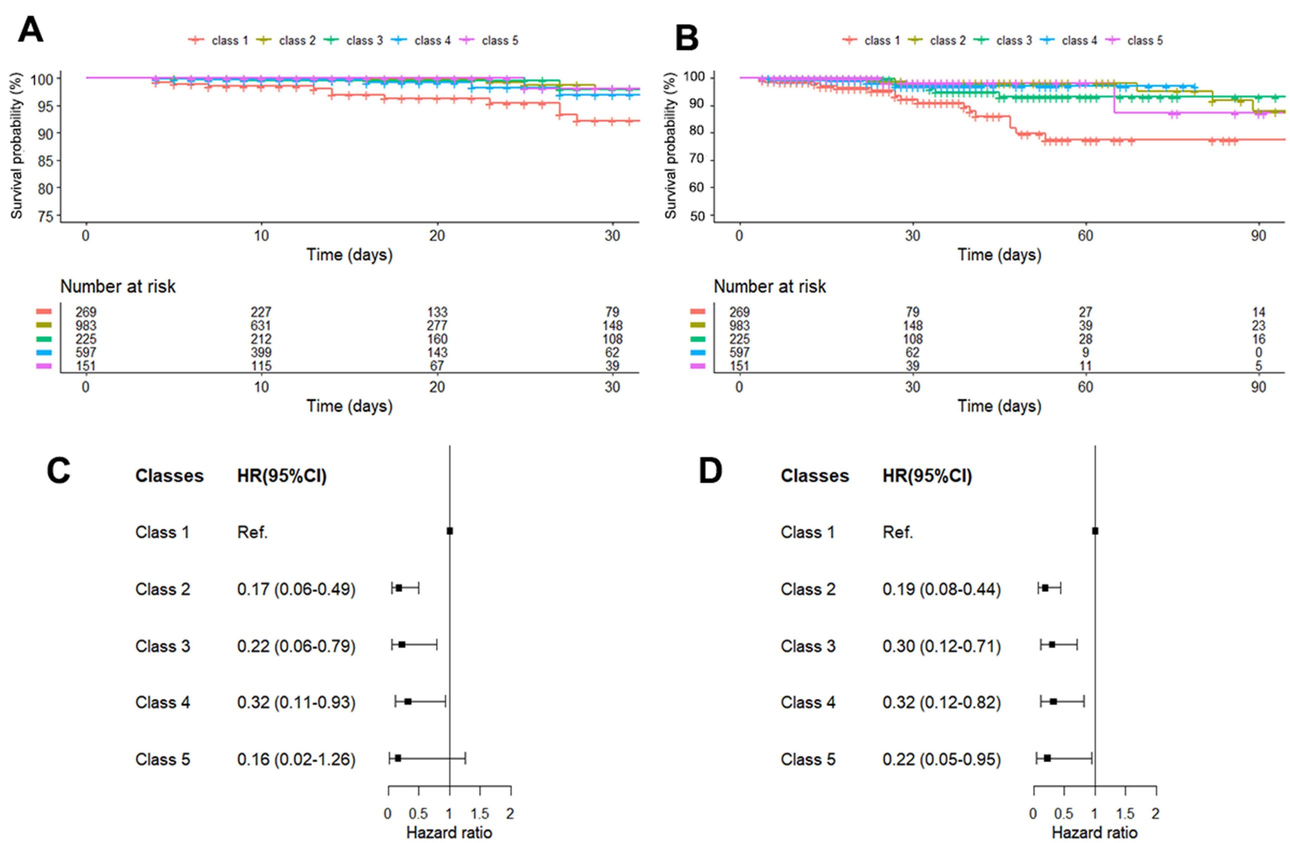

Figure 4 Comparisons of the 30-day and 90-day mortality rate among subclasses. (**A**) Kaplan–Meier survival curve of the 30-day mortality. (**B**) Kaplan–Meier survival curve of the 90-day mortality. (**C**) HR and 95% CI for the 30-day mortality rate across subclasses estimated by Cox regression. (**D**) HR and 95% CI for the 90-day mortality rate across subclasses estimated by Cox regression.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Risk Factors for Thrombocytosis in AP

Multivariable logistic regression analysis was used to identify the risk factors for thrombocytosis in AP. Factors including age, sex, body mass index, time interval from onset to admission, comorbidities, etiologies, first measured platelet count, WBC, ALT, BUN, creatinine, CRP, D-dimer, fibrinogen, Tbil, and Balthazar scores were adjusted. After adjustment, body mass index (OR 0.955, 95% CI 0.916–0.993, p=0.026), diabetes mellitus (OR 0.436, 95% CI 0.278–0.668, p<0.001), first measured platelet count (OR 1.011, 95% CI 1.008–1.014, p<0.001), WBC (OR 1.057, 95% CI 1.025–1.091, p<0.001), CRP (OR 1.002, 95% CI 1.000–1.004, p=0.031), D-dimers (OR 1.054, 95% CI 1.017–1.093, p=0.004), and Balthazar score (OR 2.642, 95% CI 2.158–3.287, p<0.001) are independent risk factors for thrombocytosis in AP (Table 2).

Discussion

In the present study, we analyzed platelet count trajectories within 14 days of AP onset. We applied GBTM to group five distinct subclasses, each characterized by a unique platelet count trajectory and different associations with prognoses. These subclasses included class 1, low platelet count, and a slow increase. Class 2 and class 4: moderate platelet count levels, increasing or fluctuating within the normal range. Class 3 and class 5: Moderate or high initial platelet count, increasing beyond the normal range. Our study highlights that in AP patients: (1) Patients with thrombocytopenia during the 14 days after the onset of AP exhibited a significantly higher risk of IPN, surgical intervention, and mortality. (2) Patients with thrombocytosis during the 14 days after the onset of AP exhibited a significantly higher risk of IPN and surgical intervention, but no change in the risk of mortality. (3) Patients who maintain the platelet count within the normal range during the 14 days after the onset of AP have the lowest risk of IPN, surgical intervention, and mortality.

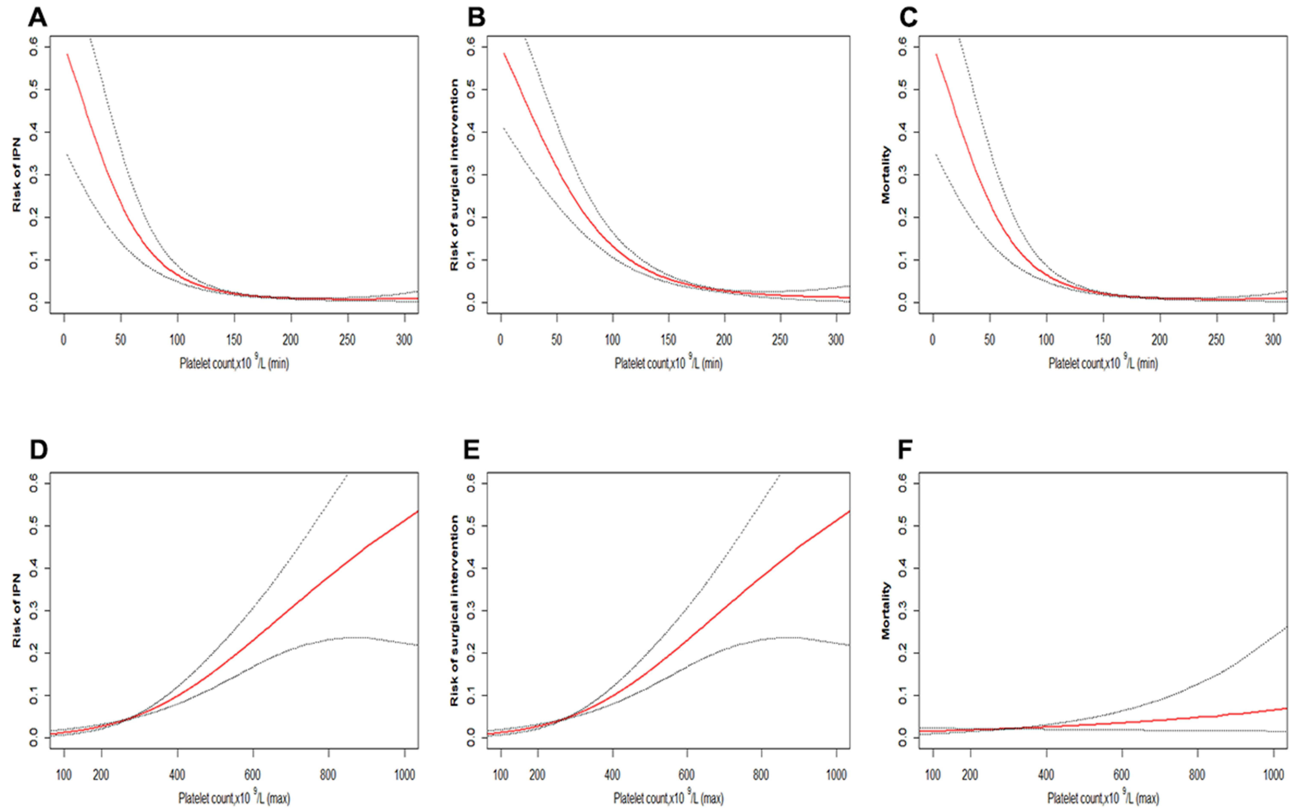

Figure 5 Associations between PLT_{min} and PLT_{max} with outcomes of IPN, surgical intervention, and in-hospital mortality. Smoothing splines were generated using generalized additive models. The red line indicates the estimated risk rate and the gray dotted line indicates the 95% confidence interval. (**A**) PLT_{min} with IPN risk (**B**) PLT_{min} with risk for surgical intervention. (**C**) PLT_{min} associated with risk of in-hospital mortality. (**D**) PLT_{max} at risk of IPN. (**E**) PLT_{max} with risk of surgical intervention. (**F**) PLT_{max} with risk of in-hospital mortality.

Abbreviations: HR, hazard ratio; CI, Confidence interval; IPN, Infected pancreatic necrosis; PLT_{min}, lowest platelet count in 14 days; PLT_{max}, highest platelet count over 14 days.

The platelet count is an easily accessible routine test for hospitalized patients. Quantitative or functional platelet abnormalities reflect coagulation, hematopoietic, and immune dysregulation. Accumulating evidence has proven that platelet counts vary during hospitalization in critical illnesses, and dynamic changes in platelet count could provide more insight into the pathophysiological condition of patients.[8,13] Thrombocytopenia is a well-recognized independent risk factor for poor prognosis.[5,14] In our previously published study, patients with AP and thrombocytopenia were more likely to develop SAP than those without. In the same study, we found that patients with thrombocytosis on admission were more likely to have intra-abdominal infections and surgical intervention.[7] Similar conclusions were also obtained in another study, which found that patients with thrombocytosis and thrombocytopenia during hospitalization had higher pancreatic necrosis and pancreatic-related infection levels than those with normal platelet levels.[15] However, the platelet counts reported in these studies were measured at different time points during different disease stages. As a time-sensitive indicator, platelet count levels fluctuate dynamically at different disease stages; therefore, it is necessary to study the trajectories of platelet counts in a longer process based on longitudinal data. The findings of this study have important implications for the clinical management of patients with AP. By identifying distinct platelet count trajectories and their associations with outcomes, clinicians can use platelet count dynamics as a simple and cost-effective tool for risk stratification. Patients with thrombocytopenia or thrombocytosis during the first 14 days of AP onset should be closely monitored for complications such as IPN and the need for surgical intervention. These patients may benefit from more aggressive monitoring and early interventions to prevent adverse outcomes.

The mechanism underlying thrombocytosis was not yet been clearly elucidated. The platelet life cycle begins with megakaryocytes in the bone marrow. Platelet maturation takes approximately 5 days, and released platelets circulate for 7–10 days in healthy humans.[16,17] Several clinical and laboratory findings support reactive thrombocytosis as an acute phase response caused by increased levels of inflammatory cytokines such as interleukin 6 (IL-6) and CRP.[18,19] The dynamic change patterns of

Table 2 Multivariable Logistic Regression for the Risk of Thrombocytosis in AP

Variables	OR (95% CI)	p value
Age, y	0.991 (0.977–1.005)	0.251
Sex	0.901 (0.627–1.297)	0.572
Body mass index, kg/m^2	0.955 (0.916–0.993)	0.026*
Time interval from onset to admission, days	1.112 (0.902–1.369)	0.319
Comorbidities		
Hypertension	0.879 (0.583–1.315)	0.535
Diabetes mellitus	0.436 (0.278–0.668)	<0.001*
Chronic kidney diseases	0.678 (0.084–3.287)	0.667
Etiologies		
Biliary	Ref.	
Hypertriglyceridemia	0.850 (0.538–1.341)	0.486
Alcoholic	1.183 (0.639–2.132)	0.583
Others	0.584 (0.288–0.994)	0.056
Laboratory indicators		
Platelet count, x10^9/L	1.011 (1.008–1.014)	<0.001*
WBC, x10^9/L	1.057 (1.025–1.091)	<0.001*
ALT, IU/L	0.999 (0.997–1.001)	0.408
BUN, mmol/L	0.978 (0.918–1.043)	0.503
Creatinine, µmol/L	1.001 (0.998–1.004)	0.432
CRP, mg/L	1.002 (1.000–1.004)	0.031*
D-dimers, mg/L	1.054 (1.017–1.093)	0.004*
Fibrinogen, g/L	1.007 (0.892–1.135)	0.904
Tbil, mmol/L	1.002 (0.998–1.007)	0.272
Balthazar score	2.642 (2.158–3.287)	<0.001*

Notes: Odds ratio (OR); confidence interval (CI). First measured laboratory indicators after admission are adjusted. *p<0.05.

Abbreviations: WBC, white blood cell count; ALT, alanine aminotransferase; BUN, blood urine nitrogen; CRP, C-reactive protein; Tbil, total bilirubin.

the platelet count in this study corresponded to the changes in the platelet count after inflammatory stimulation. Thrombocytosis occurred in the second week following admission. Typically, the initial platelet counts were comparable between class 3 (median 173 x10^9/L) and class 2 (median 161 x10^9/L), but CRP levels were significantly higher in class 3 (median 192 mg/L) than in class 2 (median 110 mg/L). The platelet count in the class 3 group increased rapidly and was outside the normal range in the second week. This evidence supports the hypothesis that inflammatory factors affect reactive thrombocytosis. Another explanation may be the activation of hematopoietic function. The white blood cell count is increased correspondingly with the high initial platelet counts in class 3 (median 12.3 x10^9/L) and class 5 (median 14.0 x10^9/L), but decreased correspondingly with the low initial platelet counts in class 1 (median 8.9 x10^9/L). It is important to acknowledge that platelet count alterations in AP patients may be influenced by factors other than the disease itself. For instance, the use of anticoagulants, such as heparin, can lead to heparin-induced thrombocytopenia, a condition characterized by a significant drop in platelet count due to immune-mediated platelet destruction. Additionally, splenic vein thrombosis, a complication occasionally observed in AP, can lead to splenic sequestration of platelets, resulting in thrombocytopenia. Other factors, such as infections, autoimmune disorders, or bone marrow suppression, may also contribute to platelet count fluctuations. While these factors were not explicitly analyzed in this study, their potential impact on platelet trajectories should be considered in future research to provide a more comprehensive understanding of platelet dynamics in AP.

IPN is a detrimental factor for mortality in patients with AP.[20] The early identification of risk factors and timely intervention could potentially improve patient outcomes. A series of scoring systems and biomarkers has been selected as early predictors of IPN.[21–23] However, most IPN occur 2 weeks after onset, which makes it difficult to predict IPN based solely on early indicators.[24] Routine blood testing is a simple and inexpensive approach that can be performed at almost all medical institutions. Our study aligns with existing evidence, indicating that continuous monitoring of platelet counts could provide valuable clinical information for IPN prediction. We found that patients maintaining the platelet count within the normal range during the 14 days after the onset of AP (classes 2 and 4) had the lowest risk of IPN as well as the lowest risk of surgical intervention and mortality. The risks of IPN and surgical intervention in patients with thrombocytosis (classes 3 and 5) were comparable with those in patients with thrombocytopenia (class 1). Spline curves showed that the risks of IPN and surgical intervention increased as platelet count decreased or increased beyond the normal range. This nonlinear relationship may explain why platelet counts were neglected in previously published linear prediction models for IPN.[25,26] Interestingly, even though the risks of IPN and surgical intervention are comparable between patients with AP with thrombocytopenia and thrombocytosis, mortality is significantly lower in patients with thrombocytosis. It seems that an increased platelet count is a protective factor against mortality in patients with AP and IPN. The mechanism is poorly understood but may be explained by the better hematopoietic function of the body in thrombocytosis. Moreover, platelets possess immune properties and can inhibit the spread of infection,[27] which may become a target for anti-infection treatment in the future.

This study is the first to investigate platelet count trajectories in patients with AP and identify five clinically meaningful AP subclasses based on platelet count. However, this study has some limitations. First, the retrospective nature of this study limits causal inferences. Second, the data size was large but collected from one center, and validation should be verified using other data sources. Third, the temporal development of subclasses may be modified by treatment within the trajectory window.

Conclusions

In conclusion, five distinct longitudinal platelet count trajectories and clinically meaningful AP subclasses were identified based on platelet counts within 14 days of disease onset. Patients who maintain a platelet count within the normal range have the lowest risk for IPN, surgical intervention, and mortality. Both the occurrence of thrombocytopenia and thrombocytosis indicate an increased risk of IPN and surgical intervention; however, mortality is significantly increased only in patients with thrombocytopenia.

Abbreviations

AP, acute pancreatitis; IPN, infected pancreatic necrosis; GBTM, group-based trajectory modeling; OR, odds ratio; CI, confidence interval; IQR, interquartile range; HR, hazard ratios; WBC, white blood cell; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; Tbil, total bilirubin; MAP, mild acute pancreatitis; MSAP,: moderately severe acute pancreatitis; SAP, severe acute pancreatitis; AIC, Akaike information criterion; BIC, Bayesian information criterion;, AvePP, average posterior probability; PLT_{min}, the lowest platelet count level within 14 days; PLT_{max}, the highest platelet count level within 14 days.

Data Sharing Statement

The data will be shared when asking for the corresponding author Zaiqian Che (chezaiqian@163.com).

Ethics Approval and Consent to Participate

This study was approved by the Institutional Ethics Board of Ruijin Hospital, Shanghai Jiaotong University School of Medicine (2018CR004). As this was a retrospective analysis and all patient data were de-identified, individual patient consent was not required. We strictly adhered to the principles of patient data confidentiality to ensure the security and privacy of all personal information. This study was conducted in accordance with the 1964 Declaration of Helsinki and its amendments.

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.

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Disclosure

The authors declare that they have no conflict of interest.

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