Trajectories of Lymphocyte Counts in the Early Phase of Acute Pancreatitis Are Associated With Infected Pancreatic Necrosis

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INTRODUCTION: Infected pancreatic necrosis (IPN) is an important complication of acute pancreatitis (AP). Absolute lymphocyte count (ALC) was reported to be associated with immunosuppression and the development of IPN. The aim of this study was to describe the trajectory of ALC during the early phase of AP and assess its association with IPN.

METHODS: We retrospectively screened patients with AP admitted to our center between January 2016 and July 2019. The ALC levels for the first 7 days after admission were collected. Group-based trajectory modeling was performed to detect the trajectories. Cox proportional hazards regression model was adopted to identify potential risk factors of IPN.

RESULTS: Overall, 292 patients were enrolled for analysis. A triple-group trajectory model was developed, assigning 116 patients to the low-level ALC group, 133 to the medium-level ALC group, and 43 to the high-level ALC group. There was no overall significant difference regarding the incidence of IPN among the 3 groups ($P = 0.066$). In pairwise comparison, patients in the low-level ALC group had significantly higher incidence of IPN than those in the high-level ALC group (hazard ratio: 3.50; 95% confidence interval: 1.22–10.00, $P = 0.020$). Length of hospital stay and intensive care unit stay differed significantly among patients with different trajectories ($P = 0.042$ and 0.033, respectively).

DISCUSSION: Despite the fact that the trajectories of ALC is overall insignificant for the development of IPN, patients with persistent low ALC trajectories during the early phase of AP are more likely to develop IPN when compared with patients with high ALC trajectories.

Trajectories of lymphocyte counts in the early phase of acute pancreatitis are associated with infected pancreatic necrosis

Introduction: Absolute lymphocyte count (ALC) was reported to be associated with immunosuppression and the development of IPN.

Methods: Use group-based trajectory modeling to classify different trajectories of ALC during the early phase of acute pancreatitis (AP).

Results:
✓ Patients with persistent low ALC in the early phase are at high risk of developing infected pancreatitis necrosis.
✓ The length of hospital stay and ICU stay of patients differ significantly among patients with different ALC trajectories.

Conclusion:
Patients with persistent low ALC at the early phase of AP may have increased risk for IPN, preventive strategies should be considered in this population.

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INTRODUCTION

The local lesion of the pancreas during an episode of acute pancreatitis (AP) varies greatly, ranging from mild pancreatic edema and inflammation to severe pancreatic and peripancreatic necrosis (1). Infected pancreatic necrosis (IPN), an important late complication of AP, carries substantial morbidity and mortality despite progress in treatment made in the past 2 decades, such as the shift from open surgery to minimally invasive techniques (2–4).

Previous studies showed that early-stage immune deficiency was common in patients with AP and associated with increased susceptibility to IPN and related septic complications (5,6). However, in clinical practice, monitoring immune status with representative markers such as human leukocyte antigen DR (HLA-DR) and T-cell subsets usually requires specific expertise and instruments subject to technical heterogeneity and availability. Alternatively, measurement of absolute lymphocyte count (ALC), which is believed to be strongly associated with immune function (7,8), is readily available with uniform techniques.

The clinical implication of ALC in AP was repeatedly reported in the literature. Christophi et al. (9) first found that ALC had a predictive value for the severity of AP in 1985. In 2015, Shen et al. (10) demonstrated that reduced ALC (below 0.8×10^9/L) within 48 hours of AP onset was associated with the development of IPN. However, ALC fluctuates over time in various diseases (8,11,12); therefore, the trajectory of ALC rather than a single point may provide more information.

In this study, we aimed to describe the trajectory of ALC during the early phase of AP and assess its association with key clinical outcomes, especially for IPN.

METHODS

Patients

This retrospective cohort study screened patients with AP admitted to the Center of Acute Pancreatitis, Jinling Hospital, from January 2016 to July 2019. All data were extracted from an electronic database (AP database) with the approval of the database management committee (No.: 2019 JLAPDMC-011). Data were collected prospectively during hospitalization with the consent of the patients or their next of kin for academic use. All the patients were routinely followed up for at least 6 months after discharge unless rejected. The inclusion criteria were as follows: (i) patients with AP within 7 days of onset; (ii) aged between 18 and 75 years; (iii) length of hospital stay (LOS) longer than 7 days; and (iv) follow-up data were available. The exclusion criteria included the following: (i) patients during pregnancy; (ii) patients with malignant or bone marrow–related diseases; (iii) history of immunosuppressive drugs; and (iv) history of New York Heart Academy III–IV heart failure, end-stage renal disease, or long-term oral corticosteroids (more than a year).

Definitions

The diagnosis of AP required at least 2 of the following 3 features: upper abdominal pain, increased serum levels of lipase (or amylase) activity >3 times the upper limit of the normal range, and imaging findings (2). The severity of AP was evaluated based on the presence of transient organ failure, persistent organ failure, and local complications, namely, mild, moderate, and severe AP, respectively (2).

The diagnosis of IPN was made when there were confirmatory imaging findings and/or bacterial culture results: either the presence of extraluminal gas in the pancreatic and/or peripancreatic tissues on computed tomography or positive bacterial culture of the necrotic tissue from the fine-needle aspiration or drainage (2). The date of infection for each study subject was defined as the day when the IPN diagnosis was made. Organ dysfunction was evaluated for 3 organ systems (respiratory, renal, and cardiovascular) based on the Modified Marshall score (13). The local complications, including splanchnic vein thrombosis, intra-abdominal hypertension, abdominal bleeding, and gastrointestinal fistula, were judged by the treating physicians according to the records in the database (2).

Outcomes

The primary outcome was the incidence of IPN within 90 days after the onset of symptoms. The secondary outcomes included a 90-day mortality, LOS and intensive care unit stay, and incidence of systemic and local complications.

Data collection

The demographic characteristics (age, sex, body mass index [BMI], etc), clinical features (disease severity, organ functions, complications, mortality, length of stay, etc), laboratory results, interventions, and clinical outcomes of each patient were extracted from the database. BMI and disease severity scores such as the Acute Physiologic Assessment and Chronic Health Evaluation II, sequential organ failure assessment, and computed tomography severity index scores were evaluated on admission. The ALC levels were measured in the central laboratory of Jinling Hospital according to the standard protocols.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of quantitative data. The normally distributed continuous variables were tested by the Student *t* test and an analysis of variance test. The non-normally distributed continuous variables were tested by the Mann-Whitney *U* test and the Kruskal-Wallis test. The mean values with SD and median with interquartile range were used to describe continuous variables, whereas the frequency with percentage was used to describe categorical variables. The Fisher exact test was used for comparing categorical variables.

The trajectory analysis model was used to assess the association between changes of ALC over time and designated clinical outcomes. Group-based trajectory modeling (GBTM) was performed using the Proc Traj macro in SAS (14). The selection process of the optimal model was based on previous studies (15,16). The following parameters were used to assess the optimal number of trajectories: model fit statistics (tested using the significance of polynomial terms that describe the within-person shape of the longitudinal changes in ALC as a function of time [linear, quadratic, or cubic—to allow for curvilinear development patterns of ALC]), the Bayesian information criterion, values of mean posterior trajectory group membership probabilities, clinical usefulness, and the average posterior probability of group membership (17). The recommendation that each group should hold a minimum 5% group membership was taken into consideration (18).

For each of the models, intercept and slope(s) variance (i.e., random effects) were considered to permit interpersonal heterogeneity in ALC. The final model was able to be successfully estimated when the covariances of all random effects were constrained to zero. Each category was allocated names based on visual inspection of trajectory plots.

Univariable Cox proportional hazards regression model was performed for identifying potential risk factors of IPN. Cox proportional hazards regression models were adopted after stepwise adjustments for confounders to investigate the difference in efficacy among the different trajectories. Hazard ratio (HR) and 95% confidence interval (CI) were calculated, and missing data in multivariable analysis for categorical variables were coded as an unknown class to regress. The proportionality of hazards assumption was evaluated by Schoenfeld residuals. The Kaplan-Meier plots and log-rank tests were used to compare the rate of IPN within 3 trajectory groups. Two-tailed $P < 0.05$ is considered statistically significant. All analyses were conducted using SPSS, version 26.0 (IBM Analytics, Armonk, NY) and SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the study population

In total, 1,818 patients were screened, and 292 were included for analysis (Figure 1). The demographic and baseline characteristics of the study subjects are summarized in Table 1. During the 90 days after disease onset, 60 patients (20.5%) developed IPN, of whom 23 patients died. For patients without IPN, 8 died during the same period. Among these patients, 19 patients died due to septic shock, 9 died due to uncontrolled abdominal bleeding, and 3 died due to irreversible respiratory failure.

Trajectories of ALC in AP

Posterior probabilities and goodness of fit of GBTM by the number of groups (2–5) and shapes (linear, quadratic, and cubic) are presented in Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A688 (see Supplementary data). The selected triple-group trajectory model with linear shapes had higher Bayesian information criterion values than the other models. Given the clinical usefulness (18) and the discriminating capacity for baseline ALC levels, the triple-group trajectory model with linear shapes was selected for analysis (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A688). The best fit of the triple-group models involved 3 linear trajectories (Figure 2; see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A688), with 39.7% patients categorized into group 1 (low-level ALC, L-ALC), 45.5% into group 2 (medium-level ALC, M-ALC), and 14.8% into group 3 (high-level ALC, H-ALC).

The demographic and clinical data of the 3 groups are summarized in Table 2. Patients in the L-ALC group were significantly older than those in the other 2 groups ($P < 0.001$). For clinical outcomes, LOS and length of intensive care unit stay differ significantly among patients with different trajectories ($P = 0.042$ and 0.033, respectively). For systemic and local complications, only abdominal bleeding showed a significant difference among groups ($P = 0.013$).

Results of the Cox proportional hazards model

By the 90th day after the onset of AP, 31 patients (10.6%) had died. The incidence of IPN in patients with different trajectories (L-ALC, M-ALC, or H-ALC) is presented in Figure 3. Trajectory groups had no significant impact on the overall risk of IPN during the study period ($P = 0.071$). In pairwise comparisons, patients in the L-ALC group were significantly more likely to develop IPN
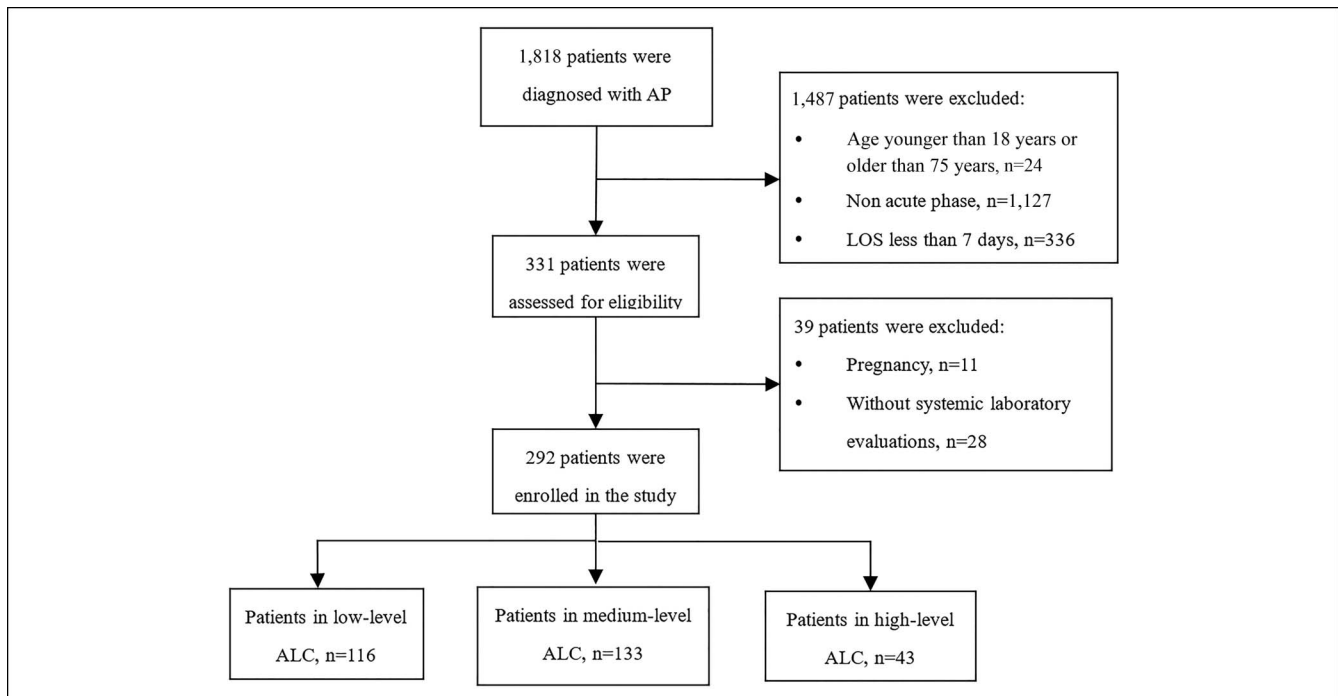

Figure 1. Process of patient selection

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Table 1. Baseline and clinical characteristics of AP patients with or without IPN (n = 292)

Parameter	Non-IPN group (N = 232)	IPN group (N = 60)	*P* value
Age, yr	44.40 (12.11)	45.47 (12.72)	0.548
Sex, M/F	149/83	40/20	0.764
BMI, kg/m^2	26.55 (3.76)	27.59 (3.31)	0.052
APACHE II score	7 (5.11.5)	12 (9.15)	<0.001
SOFA score	3 (1.6)	8 (5.12)	<0.001
CT severity index score	6 (6.7)	10 (8.10)	<0.001
Etiology, n (%)			0.541
Biliary	90 (38.8)	24 (40.0)	
Hyperlipidemic	130 (56.0)	36 (60.0)	
Alcoholic	7 (3.0)	0	
Others	5 (2.2)	0	
History, no. (%)			
Smoke	68 (29.3)	16 (26.7)	0.751
Alcohol	72 (31.0)	25 (41.7)	0.127
Diabetes	70 (30.2)	12 (20.0)	0.147
Laboratory indexes			
ALC on admission	0.95 (0.45)	0.83 (0.41)	0.061
CRP, mg/L	203.79 (78.19)	193.71 (75.37)	0.371
PCT, μg/L	6.63 (21.79)	14.44 (22.22)	0.016
IL-6, ng/L	228.08 (295.00)	224.31 (251.58)	0.931

ALC, absolute lymphocyte count; AP, acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Enquiry II; BMI, body mass index; CT, computed tomography; CRP, C-reactive protein; IL-6, interleukin-6; SOFA, sequential organ failure assessment.

than patients in the H-ALC group during the study period (HR: 3.02; 95% CI: 1.07–8.58, *P* = 0.038).

After adjustment for patient characteristics (age, sex, BMI, and etiology) (Table 3), the L-ALC group still had a significantly higher risk of IPN compared with the H-ALC group (HR: 3.50; 95% CI: 1.22–10.00, *P* = 0.020) but not for the M-ALC group (HR: 2.31; 95% CI: 0.80–6.62, *P* = 0.120). Apart from trajectories, BMI higher than 30 kg/m^2 was found to be associated with a higher probability of developing IPN. The remaining variables (age, sex, and etiology) were not associated with increased IPN risk.

DISCUSSION

In this study, 3 distinct patterns of ALC trajectories were identified in patients with acute-phase AP (H-ALC, M-ALC, and L-ALC groups). The incidence of IPN showed a trend from high to low in the 3 groups from L-ALC to H-ALC groups. These findings were in accordance with several previous studies, suggesting that lymphocytopenia is a clinically relevant phenomenon in patients with AP (5,9,10), especially when it persists. Moreover, the L-ALC trajectory was found to be an independent risk factor of infection within 90 days in reference to the H-ALC group.

GBTM is a statistical technique widely acknowledged for analyzing longitudinal data, identifying distinct subgroups of individuals following a particular pattern of change over time on a given variable (16). Jiang et al. (19) used GMTM in patients with

inflammatory bowel disease to identify overall disease severity by financial charges. This study is the first to apply GBTM to classify different trajectories of ALC during the early phase of AP. The results identified a group of patients characterized by persistent low ALC with a significantly higher risk of the development of IPN.

The proportion of hypertriglyceridemia acute pancreatitis (HTG-AP) in this study is much higher than that in the literature (20). A similar phenomenon was reported repeatedly in Chinese cohorts, and possible explanations include genetic background and change in lifestyle (21–23). In addition, several studies have shown that patients with HTG-AP were more likely to develop severe courses (21,24). This study included only patients hospitalized for more than 7 days, which means we almost excluded all the mild cases. The high proportion of severe cases may also contribute to the significantly high proportion of HTG-AP in our study subjects.

Recent studies have shown that immunosuppression could occur early in some patients with AP and was an independent risk factor of IPN (6,25). Rapidly strengthening compensatory anti-inflammatory response syndrome after initial systemic inflammation, which could be excessive in some patients, is characterized by a decrease in the monocyte surface expression of HLA-DR antigens, thereby making the host vulnerable to secondary infections (6,26,27), leading to poor outcomes (28,29). Therefore, an early and reliable biomarker, which can help identify these high-risk patients and facilitate treatment, should be of great clinical value.
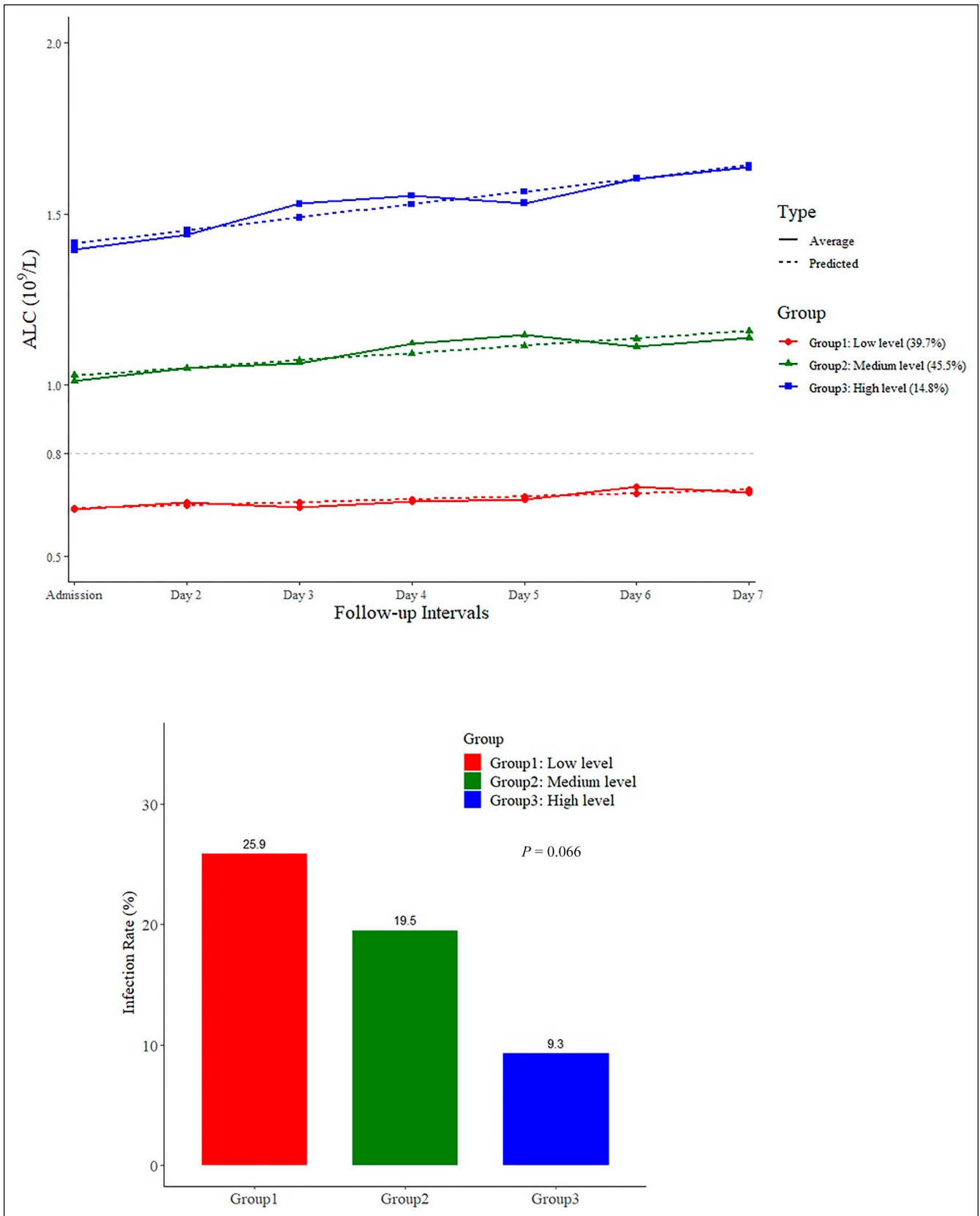
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Figure 2. Trajectories of ALC in the first week after AP admission and IPN rate in each group

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Table 2. Baseline and clinical data of patients with AP in 3 trajectory groups (n = 292)

Parameter	L-ALC (N = 116)	M-ALC (N = 133)	H-ALC (N = 43)	Total (N = 292)	P value
Age, yr	49.69 (11.91)	42.59 (11.30)	37.21 (10.26)	44.62 (12.22)	<0.001
Sex, M/F	76/40	81/52	32/11	189/103	0.269
BMI, kg/m²	26.23 (3.20)	26.91 (3.83)	27.74 (4.32)	26.76 (3.69)	0.060
APACHE II score	9.5 (5.14)	8 (5.12)	7 (3.12)	8 (5.13)	0.031
SOFA score	5 (3.8)	4 (1.7)	3 (2.5)	4 (2.7)	0.022
CT severity index score	6.5 (6.8)	6 (6.8)	6 (6.6)	6 (6.8)	0.086
Admission day[a]	3.82 (1.89)	3.63 (1.80)	4.23 (1.97)	3.80 (1.87)	0.183
Etiology, no. (%)					<0.001
Biliary	60 (51.7)	46 (34.6)	8 (18.6)	114 (39.0)	
Hyperlipidemic	51 (44.0)	86 (64.7)	29 (67.4)	166 (56.8)	
Alcoholic	2 (1.7)	0	5 (11.6)	7 (2.4)	
Others	3 (2.6)	1 (0.8)	1 (2.3)	5 (1.7)	
History, no. (%)					
Smoke	30 (25.9)	38 (28.6)	16 (37.2)	84 (28.8)	0.378
Alcohol	31 (26.7)	53 (39.8)	13 (30.2)	97 (33.2)	0.088
Diabetes	42 (36.2)	31 (23.3)	9 (20.9)	82 (28.1)	0.046
Severity of AP, no. (%)					0.296
Mild	5 (4.3)	12 (9.0)	3 (7.0)	20 (6.8)	
Moderate	48 (41.4)	65 (48.9)	21 (48.8)	134 (45.9)	
Severe	63 (54.3)	56 (42.1)	19 (44.2)	138 (47.3)	
Organ failure, no. (%)					
ARDS	55 (47.4)	56 (42.1)	20 (46.5)	131 (44.9)	0.696
AKI	44 (38.3)	35 (26.3)	13 (30.2)	92 (31.5)	0.133
Shock	27 (23.3)	25 (18.8)	6 (14.0)	58 (19.9)	0.425
Complication, no. (%)					
SVT	7 (6.0)	4 (3.0)	3 (7.0)	14 (4.8)	0.419
IAH	14 (12.1)	16 (12.0)	6 (14.0)	36 (12.3)	0.941
Bleeding	22 (19.0)	11 (8.3)	2 (4.7)	35 (12.0)	0.013
Fistula	7 (6.0)	10 (7.5)	1 (2.3)	18 (6.2)	0.573
IPN	30 (25.9)	26 (19.5)	4 (9.3)	60 (20.5)	0.066
Hospital stay, d	27.41 (32.16)	21.45 (21.47)	16.88 (14.20)	23.14 (25.72)	0.042
ICU stay, d	20.14 (25.37)	14.75 (16.58)	12.05 (12.94)	16.49 (20.32)	0.033
Mortality, no. (%)	15 (12.9)	14 (10.5)	2 (4.7)	31 (10.6)	0.316

AKI, acute kidney injury; ALC, absolute lymphocyte count; AP, acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Enquiry II; ARDS, acute respiratory distress syndrome; BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; H-ALC, high-level ALC; IAH intra-abdominal hypertension; ICU, intensive care unit; IL-6, interleukin-6; IPN, infected pancreatic necrosis; L-ALC, low-level ALC; M-ALC, medium-level ALC; SOFA, sequential organ failure assessment SVT, splanchnic vein thrombosis.
[a]Days from onset to admission.

Peripheral blood lymphocytes play an essential role in the immune system. Many studies have shown that lymphocytes are involved in the inflammatory response of AP (25,27). Ueda et al. studied 101 patients and found that their immune-related indicators, such as CD4+, CD8+, and CD20 + T lymphocytes, decreased significantly in patients developing IPN (6). Moreover, Oiva et al. showed that lymphocytes of patients with immune suppression had impaired NFκB activation, which enhanced p38 activation and sustained inflammation, increasing infection risk (30). The findings partly explain why immunosuppressed patients are prone to infection.

ALC has been used as a remarkable index in sepsis and trauma to reflect immune function (31). In addition, it is a widely used index in patients with tumors and AIDS to prompt intervention and monitor the prognosis (32–34). During the current pandemic, lymphopenia was a common finding in patients with
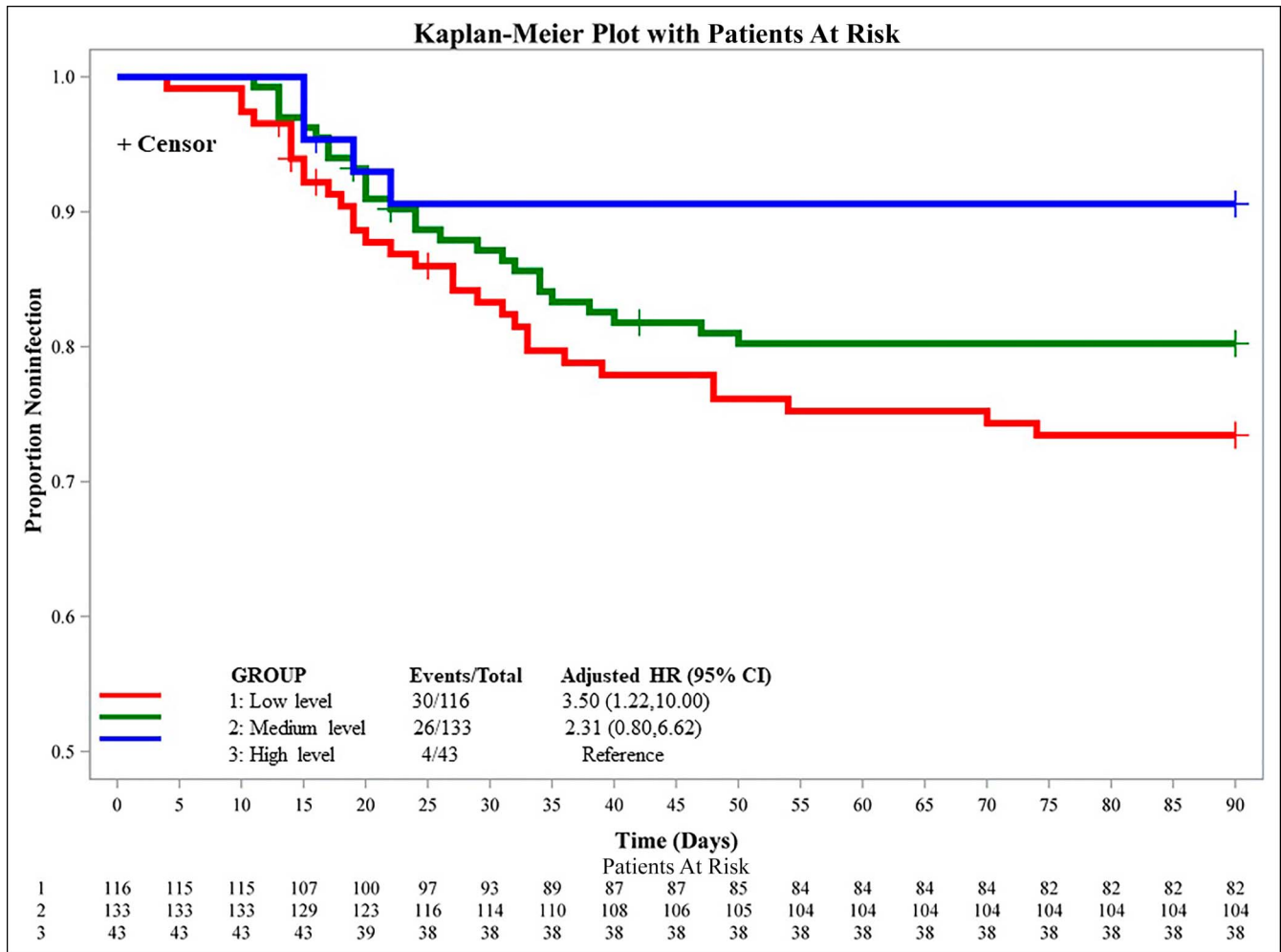
Figure 3. Kaplan-Meier Non-infection curves by ALC trajectory group

Table 3. Cox regression analysis for IPN based on the Cox proportional hazards model

	Univariate Cox			Stepwise Cox		
Characteristics	HR	95% CI	P value	HR	95% CI	P value
Age	1.01	0.99, 1.03	0.489			
Sex	1.08	0.63, 1.84	0.787			
BMI[a] (kg/m^2)						
>30.0	2.08	1.03, 4.17	0.041	2.39	1.18, 4.85	0.015
25.0–30.0	1.30	0.68, 2.47	0.425	1.33	0.70, 2.52	0.386
<25.0	Reference			Reference		
Etiology[b]	0.93	0.55, 1.55	0.766			
Group						
L-ALC	3.02	1.07, 8.58	0.038	3.50	1.22, 10.00	0.020
M-ALC	2.16	0.76, 6.20	0.151	2.31	0.80, 6.62	0.120
H-ALC	Reference			Reference		

ALC, absolute lymphocyte count; BMI, body mass index; CI, confidence interval; H-ALC, high-level ALC; HR, hazard ratio, IPN, infected pancreatic necrosis; L-ALC, low-level ALC; M-ALC, medium-level ALC.
[a]BMI level was categorized by the WHO guidelines.
[b]Etiology was categorized as biliary and nonbiliary here because of the tiny number in the 2 groups.

severe coronavirus disease-19 (35,36), and ALC was therefore recommended as a marker for the classification of disease severity (37). In patients with AP, it was found that lymphocytes may be closely associated with infectious complications such as IPN and sepsis (6). Previous studies have demonstrated that early decreased levels of ALC could predict the severity of AP and the development of IPN (9,10), but neither observed continuous data. As a highly fluctuant parameter, a continuous monitor rather than a single-point sampling should reflect the underlying immune status more accurately.

From a technical perspective, ALC can be readily measured in most hospitals, and a great amount of data in infected patients is available (10). The WHO guidelines even recommend lymphocyte count more than CD4-cell percentage to initiate antiretroviral therapy in patients with HIV, considering its technical convenience (38). In most sites, measurement of ALC is involved in a white blood cell count, which is an indicator for inflammation routinely reported with complete blood counts. Hence, it could be an excellent marker in future AP trials to identify the appropriate study populations.

Picking out patients at high risk of developing IPN is of great clinical importance not only for early diagnosis but also for timely intervention (2), such as immunomodulation with octreotide, mesenchymal stem cells, or thymosin α1 (39). Several studies showed that mesenchymal stem cells transplantation in rats could reduce pancreatic necrosis and inflammatory cell infiltration and alleviate multiple organ damage (40,41). However, there is still a considerable gap between experimental results and clinical use. For thymosin α1, there was only 1 clinical study evaluating its effects in 24 patients with SAP (42). Nevertheless, the results suggested that early use of thymosin α1 enhanced immune function, thereby lowering infection rate. A multicenter, randomized, double-blind, placebo-controlled trial is currently underway to confirm the results (43).

Our findings are subject to several limitations. First, there were some missing data of ALC, which may bring in some inherent bias. Second, the overall difference among the 3 trajectories was not statistically significant. Thus, we should interpret the between-group difference cautiously. Moreover, because of the limited sample size, the relatively small number of patients assigned to the 3 groups may result in insufficient statistical power. Finally, the retrospective nature of the study precluded the possibility of causal relationship analysis, but the association we found warrant a larger prospective study.

In conclusion, among patients who were hospitalized for more than 7 days, overall, the trajectories during the early phase of AP were not significantly associated with the development of IPN. However, patients with persistent low ALC may have an increased risk of IPN. Preventive strategies should be considered in this population.

CONFLICTS OF INTEREST

Guarantor of the article: Lu Ke, PhD.
Specific author contributions: Jing Zhou, MSc and Wensong Chen, MSc, contributed equally to this work. J.Z, Y.L, C.Q, and B.Y contributed to the study concept and design. W.J, W.M, J.Y, and J.L were involved in literature search and data extracting. W.C and Y.L analyzed and interpreted the data. J.Z and L.K drafted the manuscript; all authors were involved in quality assessing of the articles. Z.T and W.L. supervised the study. All authors read and approved the final manuscript.

Study Highlights

WHAT IS KNOWN

✓ Absolute lymphocyte count (ALC) could reflect immune status.
✓ Measurement of ALC is readily available.
✓ ALC is associated with infected pancreatitis necrosis.

WHAT IS NEW HERE

✓ Group-based trajectory modeling was applied to classify different trajectories of ALC during the early phase of acute pancreatitis.
✓ Patients with persistent low ALC in the early phase are at high risk of developing infected pancreatitis necrosis.
✓ The length of hospital stay and intensive care unit stay of patients differ significantly among patients with different ALC trajectories.

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