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Platelet-to-lymphocyte ratio as a predictive index for delirium in critically ill patients

A retrospective observational study

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Abstract

Delirium is a neuropsychiatric syndrome commonly encountered in critically ill patients, and systemic inflammation has been strongly implicated to underlie its pathophysiology. This study aimed to investigate the predictive value of the platelet-to-lymphocyte ratio (PLR) for delirium in the intensive care unit (ICU).In this retrospective observational study, we analyzed the clinical and laboratory data of 319 ICU patients from October 2016 to December 2017. Using the Locally Weighted Scatterplot Smoothing technique, a PLR knot was detected at a value of approximately 100. Logistic regression was used to investigate the association between the PLR and delirium.Of the 319 patients included in this study, 29 (9.1%) were diagnosed with delirium. In the delirium group, the duration of mechanical ventilation was significantly longer than that in the no-delirium group (40.2±65.5 vs. 19.9±26.5 hours, respectively; $P < .001$). A multiple logistic regression analysis showed that PLR > 100 (odds ratio [OR]: 1.003, 95% confidence interval [CI]: 1.001–1.005), age (OR: 2.76, 95% CI: 1.110–6.861), and the ratio of arterial oxygen partial pressure to the inspired oxygen fraction (OR: 0.996, 95% CI: 0.992–0.999) were independent predictors of delirium.In our study, a high PLR value on ICU admission was associated with a higher incidence of delirium. Owing to easy calculability, the PLR could be a useful delirium predictive index in ICUs, thereby enabling early interventions to be implemented.

Abbreviations: APACHE II = acute physiology and chronic health evaluation II, CI = confidence interval, ICU = intensive care unit, IL = interleukin, LOS = length of stay, OR = odds ratio, PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to the inspired oxygen fraction.

Keywords: critically ill, delirium, inflammation, platelet-to-lymphocyte ratio

1. Introduction

Delirium is a common neuropsychiatric syndrome in the intensive care unit (ICU) that presents as impaired consciousness, cognition, and attention,[1,2] with a reported incidence that varies from 11% to 87%.[3] Previous studies indicated that delirium could contribute to prolonged mechanical ventilation duration and ICU length of stay (LOS), as well as a higher mortality rate.[4–6] However, effective therapies for delirium, including pharmacologic and nonpharmacologic, remain limited. Thus, identifying patients who are at high risk of delirium is critical.

According to recent findings, neuroinflammation[7] is a potential underlying mechanism for delirium. Nonetheless, its pathophysiology remains unclear. Studies have confirmed that inflammatory markers, such as interleukin (IL)-1, IL-8, cortisol, and tumor necrosis factor α, were significantly elevated in patients with delirium.[8–10]

Recently, the platelet-to-lymphocyte ratio (PLR) was reported as a marker for the inflammatory response in various diseases, including coronary artery disease,[11–13] acute kidney injury,[14] and various cancers.[15,16] However, whether a similar association exists between PLR and delirium in critically ill patients remains unclear. Therefore, we performed a retrospective analysis to explore the predictive effect of PLR in delirium.

2. Methods

2.1. Study design and patients

This was a retrospective, observational study performed from October 2016 to December 2017 in a tertiary teaching hospital that has a 20-bed general ICU. The study was approved by the Ethical Committee of Dongyang People's Hospital. Informed consent was waived because of the study's observational nature. All patients in the ICU received the standard treatment to prevent delirium—the 'ABCDE' bundle,[17] including Awake, Breathing coordination, Choice of sedation, Delirium monitoring and treatment, and Early mobility and exercise. All adult patients

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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admitted to the ICU were screened. The exclusion criteria were as follows:

(1) inability to communicate (coma, profound dementia);
(2) a history of schizophrenia or Parkinson's disease;
(3) brain injury; and
(4) stay in the ICU of less than 24 hours.

2.2. Data collection

We collected the data from the electronic medical records system within the first 24 hours after ICU admission. We obtained the patients' demographic data, including sex, age, education level, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, surgical types, comorbidities, tracheal intubation, and drinking and smoking status. Laboratory measurements included the ratio of arterial oxygen partial pressure to the inspired oxygen fraction (PaO_2/FiO_2), hemoglobin, platelet, lymphocyte, white blood cell, neutrophil, hematocrit, serum potassium, sodium, total protein, albumin, glucose, creatinine, and C-reactive protein levels. The PLR was calculated by dividing the platelet count by the lymphocyte count on ICU admission. The primary outcome was delirium diagnosed after ICU admission. The secondary outcomes included the hospital LOS, ICU LOS, and mechanical ventilation duration.

2.3. Definition of delirium

Diagnosis of delirium was made according to the Confusion Assessment Method for ICU by nursing staff who had undergone specialist training to make diagnoses of delirium, which included acute onset or fluctuating course of inattention, disorganized thinking, and an altered level of consciousness. All patients were evaluated for delirium twice daily until ICU discharge.

2.4. Grouping methods for PLR in the logistic models

The locally weighted scatterplot smoothing technique was used to detect the cutoff values of the PLR that predicted delirium. Thus, in the multivariate logistic regression, PLR was divided into 2 groups ($\leq$100 and >100).

2.5. Statistical analyses

Continuous data were presented as means ± standard deviation or medians (interquartile range) and count data were presented as proportions. The Student's t-test was applied for normally distributed continuous variables and the $\chi 2$ test for categorical variables. For non-normally distributed continuous variables, the Mann–Whitney *U*-test was used. A univariate 1-way analysis of variance was performed to assess significant differences in the demographic data and laboratory measurements. Predictive variables from the univariate analysis with a $P < .1$ were included in the multivariate models, which were constructed using the stepwise backwards method. Finally, the age, APACHE II score, serum glucose level, surgery, serum albumin level, respiratory disease, PaO2/FiO2, and PLR were included in the logistic models. The STATA 11.2 software (College Station, TX) was used for all statistical analyses. A 2-tailed test was used and $P < .05$ was considered statistically significant.

3. Results

In total, 319 patients were included in this study after screening. The baseline comparisons are shown in Table 1. The mean age was 62.6 ± 16.8 years and 49.5% were males. Twenty-nine patients (9.1%) were diagnosed with delirium. In total, 278 patients (87.1%) were admitted to the surgical services and the most common diagnoses were cardiac disease (31.7%) and orthopedic diseases (17.2%). There were 84 patients (26.3%) with a history of cigarette smoking and 63 (19.7%) with a history of alcohol drinking. Significant differences were found between the delirium and no-delirium groups in age, APACHE II score, history of respiratory diseases, history of surgery, PaO2/FiO2, serum glucose level, albumin level, platelet count, and PLR.

Regarding the clinical outcomes, a longer duration of mechanical ventilation was observed in the delirium group compared to the no-delirium group (40.2 ± 65.5 vs 19.9 ± 26.5 hours, respectively; $P < .001$). The differences in the ICU LOS (7.9 ± 7.8 vs 5.3 ± 9.4 days, respectively; $P = .11$) and hospital LOS (25.7 ± 13.2 vs 29.3 ± 30.3 days, respectively; $P = .50$) were not significant.

In the locally weighted scatterplot smoothing curve between the PLR and delirium, a knot was detected at a PLR value of approximately 100, on ICU admission (Fig. 1). Thus, in the multivariable logistic regression model (Table 2), the linear spline function was applied using the cutoff value of 100. The results showed that a PLR >100 (odds ratio [OR]: 1.003, 95% confidence interval [CI]: 1.001–1.005), age (OR: 2.76, 95% CI: 1.110–6.861), and PaO2/FiO2 (OR: 0.996, 95% CI: 0.992–0.999) were significantly correlated with a risk of delirium.

4. Discussion

The results of this study show that the PLR was significantly higher in the ICU patients with delirium. A high PLR value (>100) on ICU admission was associated with a higher incidence rate of delirium. In addition, age and PaO2/FiO2 were also determined to be independent risk factors for delirium. In our study, 9.3% of the patients developed delirium, which is less than the reported incidences in previous studies.[3,4,18] This discrepancy could be caused by the fact that we applied a quality control circle to reduce the occurrence of delirium. Additionally, the delirium incidence rate was significantly lower among surgical patients than among medical patients. We found that the proportion of patients with diabetes mellitus was 13.2%; however, it is likely that there were undiagnosed cases. There were significant differences between those with delirium, no-delirium, and serum glucose level, but not with diabetes. Our results are similar to those reported by van et al.[19]

The neuroinflammatory hypothesis is a popular hypothesized mechanism underlying the development of delirium.[20] It is theorized that acute peripheral inflammatory stimulation, brain parenchymal cell activation, as well as proinflammatory cytokine expression could lead to neuronal cell apoptosis and synaptic dysfunction,[21–26] promoting the development of delirium. It is well known that delirium is common in end organ dysfunction after sepsis. Martin et al found that sepsis-induced delirium is the most common cause of delirium in the ICU and that sepsis and delirium are closely related. Furthermore, systemic inflammation could be an important trigger,[27] there is increasing evidence indicating that proinflammatory factors, such as procalcitonin,[28] IL-8,[9] IL-6, and S100 beta,[29] have important roles in the development of delirium. In addition, C-reactive protein

Table 1

Comparisons of baseline characteristics between delirium and no-delirium.

	No-delirium N=290	Delirium N=29	Total N=319	*P*
Age (yr)	61.6±16.8	72.4±13.4	62.6±16.8	.001
Male [n (%)]	143 (49.3%)	15 (51.7%)	158 (49.5%)	.804
Alcohol drinking [n (%)]	57 (19.7%)	6 (20.7%)	63 (19.7%)	.894
Smoking [n (%)]	75 (25.9%)	9 (31.0%)	84 (26.3%)	.547
Diabetes [n (%)]	38 (13.1%)	4 (13.8%)	42 (13.2%)	1.000
Hypertension[n (%)]	100 (34.5%)	13 (44.8%)	113 (35.4%)	.267
APACHE-II	13.6±3.7	15.6±2.7	13.9±3.7	.006
Type of medical condition				
Respiratory diseases [n (%)]	11 (3.8%)	6 (20.7%)	17 (5.3%)	.002
Orthopedic diseases [n (%)]	50 (17.2%)	5 (17.2%)	55 (17.2%)	1.000
Cardiac disease [n (%)]	96 (33.1%)	5 (17.2%)	101 (31.7%)	.080
Post-surgery[n (%)]	259 (89.3%)	19 (65.5%)	278 (87.1%)	.001
Clinical outcomes				
Ventilation duration (hours)	19.9±26.5	40.2±65.5	21.8±32.5	.001
ICU length of stay (days)	5.0±9.5	7.9±7.8	5.3±9.4	.110
duration of hospital stays (d)	29.7±31.4	25.7±13.2	29.3±30.3	.502
Biochemical indexes on ICU admission				
PaO2/FiO2 (mmHg)	347.4±124.1	266.8±113.2	340.1±125.1	.001
Serum sodium (mmol/L)	138.3±4.0	137.4±7.5	138.2±4.4	.216
Serum glucose (mmol/L)	8.1±2.7	9.9±3.8	8.2±2.8	.006
Serum albumin (g/L)	32.5±6.2	30.3±4.0	32.3±6.1	.026
C-reactive protein (mg/L)	86.7±56.5	100.5±54.7	87.9±56.4	.164
Serum osmolarity (mmol/L)	283.8±14.0	287.0±10.4	294.1±13.7	.230
Serum creatinine (mmol/L)	76.1±71.2	70.4±34.0	75.6±68.6	.669
Red blood cell (x10^9/L)	4.0±6.9	3.6±0.7	4.0±6.6	.736
White blood cell (x10^9/L)	11.7±4.9	12.3±5.4	11.8±4.9	.544
Neutrophil count (x10^9/L)	10.0±4.6	10.9±4.6	10.1±4.6	.330
Lymphocyte count (x10^9/L)	1.0±0.7	1.0±0.9	1.0±0.7	.840
Platelet count (x10^9/L)	158.0±78.8	195.8±87.8	161.5±80.3	.015
PLR	202.2±144.9	306.5±240.5	211.7±158.4	.001
NLR	13.6±10.9	17.1±12.7	13.9±11.1	.108

APACHE-II = acute physiology and chronic health evaluation, ICU = intensive Care Unit, NLR = neutrophil to lymphocyte ratio, PaO2/FiO2 = ratio of arterial oxygen partial pressure to fraction of inspired oxygen, PLR = platelet to lymphocyte ratio.

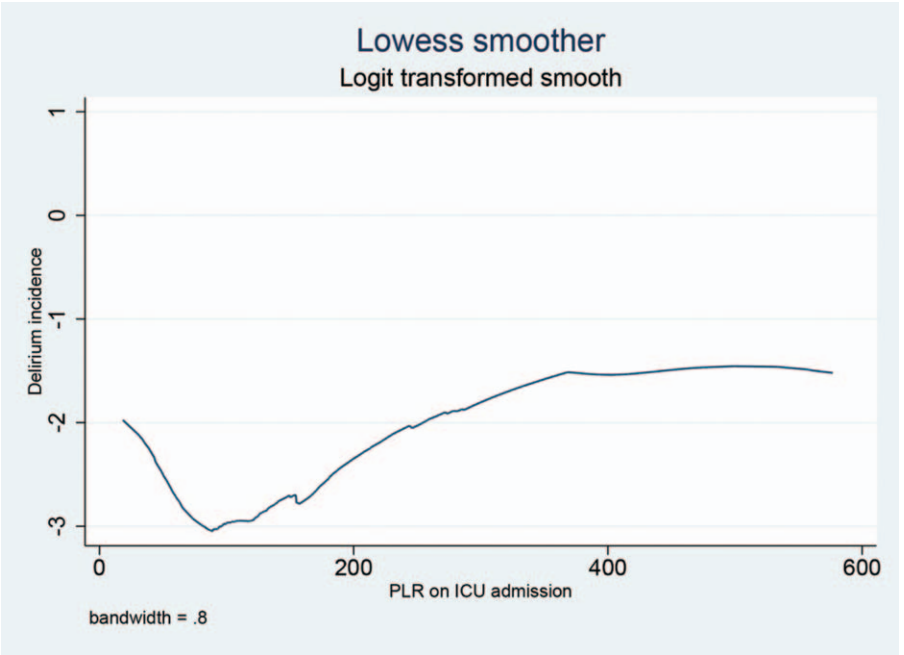

Figure 1. Crude relationship between PLR on ICU admission and delirium. ICU = Intensive Care Unit, PLR = platelet to lymphocyte ratio.

Table 2

Effects of variables on delirium in univariate and multivariate logistic regression.

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P*-Value**	**OR**	**95% CI**	***P*-Value**
PLR1	0.997	0.977–1.023	.788	0.979	0.954–1.005	.114
PLR2	1.003	1.001–1.005	.001	1.003	1.001–1.005	.012
PaO2/FiO2	0.994	0.991–0.998	.001	0.996	0.992–0.999	.026
Age	2.932	1.303–7.242	.013	2.760	1.110–6.861	.029
Post-surgery	0.227	0.098–0.549	.001	0.456	0.172–1.211	.115
Respiratory disease	6.617	2.119–19.119	.001			
APACHE-II	1.172	1.047–1.326	.008			
Serum glucose	1.188	1.063–1.334	.003			
Serum albumin	0.926	0.858–0.997	.046			

APACHE-II = acute physiology and chronic health evaluation, CI = confidence interval, OR = odds ratio, PaO2/FiO2 = Ratio of arterial oxygen partial pressure to fraction of inspired oxygen, PLR1 = platelet to lymphocyte ratio<100, PLR2 = platelet to lymphocyte ratio>100.

levels were found[30] to predict severity and duration of postoperative delirium. Overall, inflammation is a potential underlying mechanism of delirium.

In previous studies, it was reported that platelets may exhibit an important effect on inflammatory modulation[29,30] by promoting the release of inflammatory cytokines that initiate the inflammatory process.[31,32] In addition, evidence has also indicated that lymphocytes are also an important inflammatory factor in different diseases, such as cardiovascular diseases[33] and type 2 diabetes.[34] Therefore, the PLR was proposed as a new marker for inflammation in various disorders. For example, an elevated PLR was associated with adverse survival probabilities in patients with colon,[31] breast,[15] and small cell lung cancer,[32] which may be caused by an intensified systemic inflammatory reaction. Kurtul et al[13] examined 1,016 patients with acute coronary syndrome and reported that an increased PLR (>150) was significantly associated with severity and complexity of coronary atherosclerosis. Similarly, a possible explanation for this may be an increased inflammatory response. In another study, the PLR was found to be lower in the early stages of diabetes, but significantly higher in the later stages.[33] Our results showed that a high PLR value (>100) was an independent risk factor for delirium, even after adjusting for potential confounders. As it is easily calculated, the PLR could be a useful predictor of delirium in critically ill patients, thereby enabling early interventions to be implemented.

4.1. Limitations

First, this was a pilot observational study; therefore, selection bias could have occurred. In clinical practice it is difficult to evaluate for delirium during invasive mechanical ventilation in critically ill patients, so a proportion of patients with delirium may not have been diagnosed, and so these results should be interpreted with caution. Second, the number of patients with delirium in this study was small and we were not able to perform stratified analyses for subtypes of delirium. Finally, the study population was heterogeneous, including medical and surgical patients, and among the latter, patients who had undergone different types of surgery. However, our results can be generalized to all critically ill patients.

5. Conclusion

Delirium is a neurobehavioral syndrome; it is unlikely that a single cascade will explain the phenomena of delirium. Our study found that a high PLR value on ICU admission was associated with a higher incidence of delirium. The PLR is simple to calculate, inexpensive, and could be used to predict delirium in critically ill patients.

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Author contributions

Conceptualization: Xuandong Jiang, Yanfei Shen, Qiang Fang, Xuping Cheng.
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