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Platelet-to-Lymphocyte Ratio (PLR) Is Associated with Immune Thrombocytopenia (ITP) Recurrence: A Retrospective Cohort Study

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Current guidelines are inadequate for use in predicting ITP recurrence. Therefore, our primary goal in this study was to investigate the association of platelet-to-lymphocyte ratio (PLR) at diagnosis with ITP recurrence in Chinese patients.





Material/Methods: We performed a historical cohort study and non-selectively enrolled 233 patients with newly-identified ITP from March 2013 to June 2017. The independent variable was PLR recorded at diagnosis and the dependent variable was recurrence-free survival (RFS) at 6 months. Data on the following variables were also collected for establishing a multivariate Cox regression model: demographic details, general details, and variables found to be closely related to PLR in previous studies, as well as risk factors for ITP recurrence.

Results: During follow-up, 85 patients had an event within 6 months. At the range of 0.86–9.7 of PLR, a 1-unit increase in PLR was associated with a 13% decrease in ITP recurrence (hazard ratio: 0.87; 95% confidence interval: 0.78–0.97), whereas no association was detected at the range of 9.7–33.75 of PLR (hazard ratio: 0.99; 95% confidence interval: 0.95–1.04). An interaction test indicated that patients with HP infection (0.91 (0.86–1.97)) or diabetes history (0.86 (0.78–0.96)) showed a stronger association compared with patients without HP infection (1.01 (0.95–1.04) and those without diabetes (1.01 (0.97–1.04)).

Conclusions: Our findings suggest that PLR is a useful parameter to consider when hematologists attempt to assess the risk of recurrence in ITP patients receiving first-line therapy, and the nonlinearity of PLR and ITP recurrence risk must be fully considered when constructing predictive models.

MeSH Keywords: **Blood Platelets • Purpura, Thrombocytopenic, Idiopathic • Recurrence**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/917531>

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Background

Immune thrombocytopenia (ITP) is an immune-mediated acquired disease. Its clinical manifestations include transient or persistent decrease of the platelet count, thrombocytopenia, and bleeding. The traditional concept holds that the core pathogenesis of ITP is the presence of antibodies against platelet glycoproteins [1]. More recently, inflammation has also been shown to be closely related to the pathogenesis and prognosis of ITP [1]. According to the current Chinese Consensus for Immune Thrombocytopenia (ITP) Diagnosis and Treatment (2016 version) [2], between 75 000 and 150 000 (5–10/100 000) adult cases would be newly diagnosed with immune thrombocytopenia (ITP) and roughly half of these cases would relapse within 6 months after first-line treatment in China in 2016. Although there has been important progress in the diagnosis and treatment of ITP in recent years, there are no well-established Chinese guidelines to predict recurrent risk at diagnosis [3]. Due to the high recurrence rate of newly-diagnosed ITP, sensitive markers are needed to improve risk-stratification algorithms.

Platelet-to-lymphocyte ratio (PLR) is an inflammatory biomarker that might play an important role in predicting the prognosis of patients with gastrointestinal and female reproductive system tumors [4–7]. PLR is also used to predict the prognosis of other diseases [8–10]. However, there appear to be have been no previous studies investigating the link between PLR and the risk of relapse in newly-diagnosed ITP in adults. A recent series of observational studies have reported that absolute lymphocyte count and platelet count at baseline are associated with ITP clinical characteristics and outcomes [11–13]. Growing evidence also suggests that ITP is closely correlated with inflammation, and inflammation can trigger ITP. In summary, we speculate that the baseline PLR, which is an indicator derived from platelets, lymphocytes, and inflammatory response factor, may be associated with the risk of recurrence in adult patients with newly-identified ITP who have received first-line treatment.

We used a historical cohort study to investigate whether PLR obtained at baseline is independently associated with ITP relapse after adjusting for other covariates.

Material and Methods

Study design

This was a historical cohort study.

Study setting

The Guizhou provincial People's Hospital, Guiyang city, China.

Data source

We non-selectively and consecutively retrieved data for all participants with newly-diagnosed ITP from electronic medical records. In our center, each patient has a unique hospitalization number. When we extracted patients' clinical records to build a database, we used the hospital number information instead of their names. In addition to our final data analysis, we removed the hospitalization number and generated a unique sequence based on each unique hospitalization number. Therefore, the requirement for patient informed consent was waived and the data was anonymous and the privacy of patients was protected. The Hospital Institutional Review Board approved this study.

Study cohort

The cohort included 437 patients aged 14–89 years with newly-diagnosed ITP. Cohort entry was the date of the first PLR any time from March 2013 to June 2017. We diagnosed patients according to the published guidelines [14]. Patients were included if they: (1) were newly identified with ITP (ITP diagnosis time was under 3 months); (2) were non-secondary ITP (e.g., other thrombocytopenic diseases or myelofibrosis); or (3) had no spleen enlargement. Exclusion criteria were: (a) hepatitis B, hepatitis C, or AIDS patients; (b) pregnant; (c) had concurrent severe dysfunction in a vital organ (e.g., heart, kidneys, liver, or lungs); (d) history of immunosuppressive use in the last 3 months; or (e) had no response to first-line treatment.

Variables

We specified the value of PLR at diagnosis as an untransformed continuous variable. For each enrolled patient, 2 ml of venous blood was put in an anticoagulant tube containing EDTA, and then tested using a blood cell classification automatic analyzer (BM830, Bao Ling Man Sunshine Technology Co., China) at the central laboratory of our institution. The reference ranges at our institute for platelet and absolute lymphocyte counts are $100\text{--}300\times 10^9/\text{L}$ and $1.1\text{--}3.2\times 10^9/\text{L}$, respectively.

The selection of covariates included in this study was based on our previous work and other relevant published studies. Therefore, we collected data on the following variables for data analysis: sex, age, height, weight, smoking status, drinking alcohol, HP burden status [15], comorbidity (type 2 diabetes [16], CVD [17–19], hyperuricemia [20]), bleeding-related symptoms (in skin, in mucosa, or in organs), first-line treatment (including oral prednisone or intravenous drip high-dose dexamethasone, intravenous immunoglobulin), mean platelet volume (MPV) [21], and mean platelet distribution width (MPD) at diagnosis.

We used recurrence-free survival (RFS) within 6 months as the outcome in this study. On the basis of the published guideline [14], the definition of ITP relapse was loss of complete remission (or response) during the follow-up period (6 months). To ensure accuracy, we used the 2 lowest platelet counts recorded at least 1 day apart. If patients were lost to follow-up, their data were excluded from the event records. The criteria for determining complete remission were mainly determined by platelet calculation (above $100 \times 10^9/L$) with bleeding symptoms (absence) after a cycle of first-line treatment. The criteria for determining response (R) were based on platelet calculation (beyond $30 \times 10^9/L$) and platelet trend (at least a 2-fold elevation of platelet count at diagnosis) and bleeding symptom (absence). We defined no response (NR) as platelet calculation under $30 \times 10^9/L$, a 2-fold increase in platelet count at baseline, or bleeding.

First-line treatment strategies

The first-line treatment was glucocorticoid administration, including oral prednisone or intravenous drip high-dose dexamethasone with or without intravenous immunoglobulin. The selection of first-line treatment alternatives for enrolled patients was determined by their pre-treatment platelet count and severity of bleeding symptoms [14].

- 1) High-dose dexamethasone: 40 mg/day, orally, days 1–4 and days 15–18, monitoring blood pressure and blood glucose during treatment, and simultaneously receiving proton pump inhibitors to protect gastric mucosa.
- 2) Oral prednisone: Starting dose at 1 mg/kg/day, orally, quickly reduced to the maintenance dose (15 mg/day) after remission, until drug withdrawal.
- 3) Intravenous immunoglobulin (IVIg) regimen: 400 mg/kg/day, days 1–5, mainly used for emergency treatment of ITP (continuous and severe bleeding symptoms, platelets below $20 \times 10^9/L$).

Statistical analysis

According to the data distribution, we expressed continuous variables as mean±standard deviation (normal distribution) or median (quartile) (skewed distribution). We expressed categorical variables as percentages. To observe the distribution of baseline characteristics among different PLR groups (quartile, Q1 to Q4), we used the chi-square test (categorical variables), one-way ANOVA (normal distribution), or Kruskal-Wallis H test (skewed distribution).

Following the suggestions in the STROBE statement [21], the whole statistical analysis can be summarized as follows: (1) We assessed the linear relationship between the exposure variable (PLR) and ITP recurrence (i.e., the multivariable Cox model) after adjusting for other potential confounders;

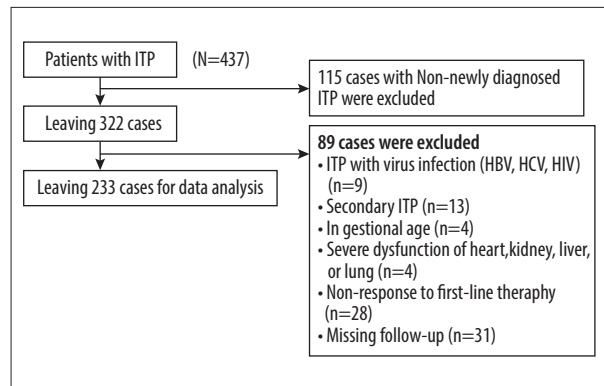


Figure 1. Flow chart of participant selection. The figure shows the full process of subject selection. We initially collected a total of 437 patients who were diagnosed as having ITP. Then, we restricted our analyses to patients with newly-diagnosed ITP (n=322, 115 cases were excluded). Then, we have further excluded 85 patients with virus infection (n=9), secondary ITP (n=13), pregnancy (n=4), severe organ dysfunction (n=4), and non-response to first-line therapy (n=28). During follow-up, 31 cases were excluded due to loss to follow-up, leaving 233 patients for final data analyses.

(2) Since PLR is a continuous variable, we also discussed its nonlinear correlation (in the generalized additive model); once we found the existence of a nonlinear relationship, we then calculated the inflection point [22] and clarified the correlation on the left and right sides of the inflection point (using the two-piecewise model); (3) We assessed the difference in the association between PLR and ITP recurrence in different populations (using the stratified proportional hazard model).

For data analysis, we used the R package (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Boston, MA) statistical software. P values less than 0.05 (two-sided) were considered statistically significant.

Results

Screening and baseline characteristics of patients

There were 437 adult participants between the ages of 14 and 89 years with newly-diagnosed ITP. After screening, 233 patients remained for data analysis (Figure 1). Among these 233 patients, 85 patients (85/233, 36.48%) had an event within 6 months. The mean and standard deviations of age of selected patients was 41.1 ± 19.0 years, and 33.9% (79/233) were male. According to quartile of PLR, no statistically significant differences were detected in age, sex, weight, height, smoking status, alcohol consumption, HP infection, diabetes

Table 1. The description of baseline clinical characteristics of patients with newly-identified ITP.

PLR, quartile	Q1	Q2	Q3	Q4	P value
N	57	59	58	59	
Age (year, median (min, max))	44.00 (15.00–81.00)	40.00 (15.00–79.00)	37.50 (14.00–88.00)	31.00 (14.00–89.00)	0.359
Height (cm, mean±sd)	161.84 (9.52)	161.17 (7.96)	163.78 (8.96)	162.54 (8.06)	0.408
Weight (kg, mean±sd)	59.23 (10.70)	59.49 (10.01)	57.38 (9.79)	57.41 (7.98)	0.487
MPD (fL, mean±sd)	16.38 (4.33)	15.87 (4.34)	16.15 (4.56)	16.96 (4.24)	0.58
Relapse time (day, mean±sd)	128.35 (57.71)	146.51 (49.66)	140.55 (53.73)	145.02 (52.25)	0.252
Sex (n, %)					0.621
Male	23 (40.35%)	20 (33.90%)	19 (32.76%)	17 (28.81%)	
Female	34 (59.65%)	39 (66.10%)	39 (67.24%)	42 (71.19%)	
Smoking (n, %)					0.956
No	38 (66.67%)	40 (67.80%)	38 (65.52%)	44 (74.58%)	
Current smoker	14 (24.56%)	15 (25.42%)	15 (25.86%)	11 (18.64%)	
Ex-smoker	5 (8.77%)	4 (6.78%)	5 (8.62%)	4 (6.78%)	
Alcohol consumption (n, %)					0.376
No	45 (78.95%)	45 (76.27%)	48 (82.76%)	52 (88.14%)	
Yes	12 (21.05%)	14 (23.73%)	10 (17.24%)	7 (11.86%)	
HP infection (n, %)					0.616
Negative	43 (75.44%)	49 (83.05%)	49 (84.48%)	47 (79.66%)	
Positive	14 (24.56%)	10 (16.95%)	9 (15.52%)	12 (20.34%)	
Diabetes history (n, %)					0.99
No	49 (85.96%)	51 (86.44%)	51 (87.93%)	50 (86.21%)	
Yes	8 (14.04%)	8 (13.56%)	7 (12.07%)	8 (13.79%)	
Hyperuricemia (n, %)					0.851
No	48 (84.21%)	51 (86.44%)	48 (82.76%)	52 (88.14%)	
Yes	9 (15.79%)	8 (13.56%)	10 (17.24%)	7 (11.86%)	
Cardiovascular diseases (n, %)					0.59
No	52 (91.23%)	50 (84.75%)	49 (84.48%)	53 (89.83%)	
Yes	5 (8.77%)	9 (15.25%)	9 (15.52%)	6 (10.17%)	
Bleeding in skin (n, %)					0.541
No	42 (73.68%)	47 (79.66%)	43 (74.14%)	40 (67.80%)	
Yes	15 (26.32%)	12 (20.34%)	15 (25.86%)	19 (32.20%)	
Bleeding in mucosa (n, %)					0.35
No	47 (82.46%)	45 (76.27%)	40 (68.97%)	42 (71.19%)	
Yes	10 (17.54%)	14 (23.73%)	18 (31.03%)	17 (28.81%)	

Table 1 continued. The description of baseline clinical characteristics of patients with newly-identified ITP.

PLR, quartile	Q1	Q2	Q3	Q4	P value
Bleeding in organ (n, %)					0.857
No	53 (92.98%)	53 (89.83%)	54 (93.10%)	53 (89.83%)	
Yes	4 (7.02%)	6 (10.17%)	4 (6.90%)	6 (10.17%)	
High-dose dexamethasone (n, %)					0.578
No	45 (78.95%)	41 (69.49%)	40 (68.97%)	41 (69.49%)	
Yes	12 (21.05%)	18 (30.51%)	18 (31.03%)	18 (30.51%)	
Oral prednisone (n, %)					0.578
No	12 (21.05%)	18 (30.51%)	18 (31.03%)	18 (30.51%)	
Yes	45 (78.95%)	41 (69.49%)	40 (68.97%)	41 (69.49%)	
IVIG (n, %)					<0.001
No	12 (21.05%)	21 (35.59%)	46 (79.31%)	45 (76.27%)	
Yes	45 (78.95%)	38 (64.41%)	12 (20.69%)	14 (23.73%)	
Outcome (n, %)					0.394
No relapse	31 (54.39%)	40 (67.80%)	37 (63.79%)	40 (67.80%)	
Relapse	26 (45.61%)	19 (32.20%)	21 (36.21%)	19 (32.20%)	
Duration of prednisone (Day)	34.05 (5.56)	34.47 (5.90)	33.02 (5.05)	33.69 (5.35)	0.528
MPV	14.23 (6.57)	12.04 (5.99)	13.41 (6.10) 12.20	12.98 (6.14)	0.289
Peripheral blood lymphocyte count	1.14 (0.43)	1.06 (0.28)	1.13 (0.25)	1.04 (0.22)	0.200
Platelet count at baseline	3.78 (1.87)	8.67 (2.31)	15.31 (4.19)	22.40 (4.48)	<0.001

MPV – indicates mean platelet volume; MPD – indicates mean platelet distribution width; HP – indicates infection of helicobacter pylori; IVIG – indicated intravenous immunoglobulin; PLR – indicated platelet-to-lymphocyte ratio.

history, hyperuricemia, cardiovascular diseases, MPV, bleeding in skin, bleeding in mucosa, bleeding in organ, high-dose dexamethasone, oral prednisone, MPD, or duration of prednisone use among different PLR groups. Compared with group Q1, there were significantly fewer patients using IVIG in group Q2–Q4 (Table 1).

Univariate analysis

Univariate Cox regression analysis (Table 2) showed that age (1.03, 1.02–1.04), HP infection (hazard ratio (HR): 3.17; 95% confidence interval (CI): 2.03–4.94), bleeding in mucosa (HR: 2.07; 95% CI: 1.33–3.23), bleeding in organ (HR: 1.88; 95% CI: 1.04–3.39), MPV (HR: 1.20; 95% CI: 1.15–1.24), MPD (HR: 1.06; 95% CI: 1.01–1.11), and duration of prednisone use (HR: 1.06; 95% CI: 1.02–1.10) were risk factors for ITP relapse. Conversely, the use of IVIG (HR: 0.60; 95% CI: 0.39–0.94) was a protective factor for ITP recurrence.

The results of multivariate Cox regression models

In the crude model, the hazard ratio (HR) was 0.98 and the range of 95% confidence interval (CI) was 0.95–1.01 (Table 3), showing that the 1-unit increase in PLR was associated with a 5% decreased risk of ITP relapse. The same trend also was observed in another model in which we only adjusted for age, sex, height, and weight). In the completed adjusted model (adjusted for all covariates presented in Table 1), a 1-unit increase in PLR was associated with a 4% decrease in ITP recurrence, and the 95% CI was 0.93–1.00.

Addressing nonlinearity

We used GAM and two-piecewise Cox equation to elucidate this nonlinear link and observe the potential saturation or threshold effect (Figure 2, Table 4). In this research, we observed that the relationship between PLR and risk of relapse was nonlinear (after adjusting for all covariates presented in Table 1).

Table 2. Univariate analysis for the link among variables.

	HR 95% CI (lower, upper)	P values		HR 95% CI (lower, upper)	P values
Sex			Bleeding in mucosa		
Male	Reference		No	Reference	
Female	0.95 (0.60, 1.48)	0.81	Yes	2.07 (1.33, 3.23)	0.01
Smoking			Bleeding in organ		
No smoking	Reference		No	Reference	
Current smoking	0.99 (0.60, 1.65)	0.97	Yes	1.88 (1.04, 3.39)	0.04
Ex-smoking	1.33 (0.64, 2.79)	0.45	High-dose dexamethasone		
Alcohol consumption			No	Reference	
No	Reference		Yes	1.30 (0.82, 2.05)	0.26
Yes	1.31 (0.78, 2.21)	0.31	Oral prednisone		
HP infection			No	Reference	1.0
Negative	Reference		Yes	0.77 (0.49, 1.21)	0.25
Positive	3.17 (2.03, 4.94)	<0.0001	IVIg		
Diabetes history			No	Reference	
No	Reference		Yes	0.60 (0.39, 0.94)	0.02
Yes	1.46 (0.84, 2.56)	0.18	MPV	1.20 (1.15, 1.24)	<0.0001
Hyperuricemia			MPD	1.06 (1.01, 1.11)	0.02
No	Reference		PLR	0.98 (0.95, 1.01)	0.25
Yes	1.07 (0.59, 1.93)	0.82	Duration of prednisone use	1.06 (1.02-1.10)	0.003
Cardiovascular diseases			Age	1.03 (1.02, 1.04)	<0.0001
No	Reference		Height	1.01 (0.97, 1.02)	0.91
Yes	1.42 (0.80, 2.52)	0.23	Weight	1.02 (1.00, 1.04)	0.12
Baseline platelets	0.99 (0.96, 1.02)	0.54			
Bleeding in skin					
No	Reference				
Yes	0.61 (0.36, 1.06)	0.07			

HR – indicates hazard ratio; CI – indicates confidence interval; Ref – indicates reference.

Table 3. Multivariate analysis and presentation using non-adjusted and adjusted models.

Exposure	Crude model (HR, 95% CI, P)	Adjusted model 1(HR, 95% CI, P)	Adjusted model 2(HR, 95% CI, P)
PLR	0.98 (0.95, 1.01) 0.364	0.99 (0.96, 1.02) 0.595	0.97 (0.93, 1.00) 0.074
Lymphocyte count	4.83 (2.58, 9.03) <0.0001	3.60 (1.89, 6.87) 0.0001	2.08 (1.12, 3.87) 0.0203
Platelet count	0.99 (0.97, 1.02) 0.5561	0.99 (0.97, 1.02) 0.6338	0.97 (0.94, 1.00) 0.0521

Crude model: not adjusted for other covariates. Adjusted model 1: adjusted for age and sex. Adjusted model 2: adjusted for age, sex, HP infection, MPV, bleeding in mucosa, bleeding in organ, IVIG, MPD, duration of prednisone. HR – hazard ratio; CI – confidence interval.

By use of a recurrence method algorithm, we found the inflection point was 9.7. Using the two-piecewise Cox regression model, we observed different trends of HR on left and

right sides of the inflection point. On the left of the inflection point (PLR <9.7), a 1-unit increase in PLR at diagnosis was correlated with a 13% decrease in ITP relapse risk (HR=0.87, 95%

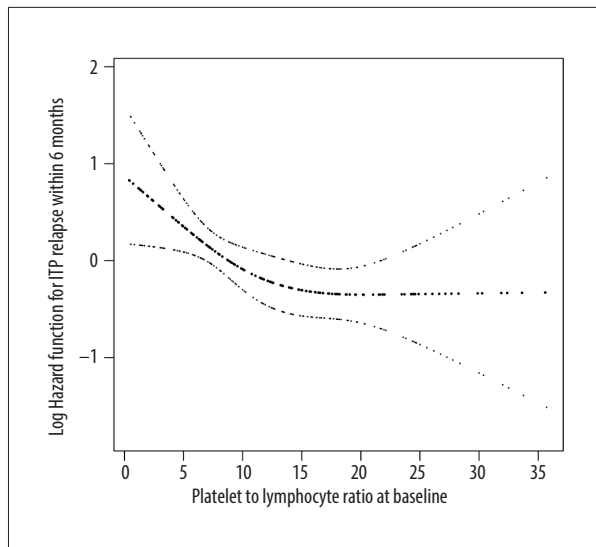


Figure 2. The icon for nonlinearity of PLR and risk of ITP recurrence. The saturate effect can be observed from Figure 2, as we did not observe a corresponding decrease for the risk of relapse after PLR exceeded 9.7.

CI was 0.78–0.97). On the right of the inflection point, however, the link between PLR and ITP relapse was not detected (HR=0.99, 95% CI: 0.95–1.04), meaning that this decrease in risk is saturated after PLR exceeds 9.7, as the concomitant risk of ITP relapse is not apparent with PLR above 9.7. We also showed the non-adjusted results of the two-piece model. Although the HR values and 95% CI showed slight changes compared with adjusted results, a PLR less than 9.7 was still significantly associated with ITP recurrence during follow-up.

The results of subgroup analyses

We found a significant interaction between PLR and diabetes history (P for interaction was 0.037). Subgroup analyses (Table 5) revealed that patients complicated with diabetes had a higher estimated protective effect (HR: 0.86; 95% CI: 0.78–0.96) of newly-diagnosed ITP relapse in association with PLR than in patients who had no diabetes history (HR: 1.01; 95% CI: 0.97–1.04). The protective effect of PLR associated with ITP

relapse was significantly below 1 in the diabetes subgroups, but this protective effect was not observed in non-diabetic populations. We also detected a significant interaction between PLR and Hp infection (P for interaction=0.029). In terms of HP infection, the direction of effect size HR of ITP relapse on PLR is reversed in patients with or without a HP infection (as assessed by log likelihood ratio test). The negative correlation between PLR and newly-identified ITP recurrence was only detected in patients with HP infection (HR: 0.91; 95% CI: 0.86–0.97) and was not detected in those without HP infection (HR: 1.01; 95% CI: 0.97–1.03).

Discussion

This retrospective cohort study investigated the association of PLR at baseline with ITP recurrence at 6-month follow-up and found that PLR at the range of 0.86–9.7 was associated with a significantly decreased risk of ITP relapse. However, when the PLR was greater than 9.7, a continued increase did not further reduce the risk of ITP recurrence. In subgroup analyses, a lower recurrence risk was observed in patients with HP infection and diabetes (with a 9% and 14% decreased risk, respectively). In summary, our analysis suggests that PLR at baseline is associated with decreased ITP recurrence risk and has potential use as a marker for prediction of ITP recurrence.

Although the treatment of ITP has made great progress, the risk of recurrence of ITP is still high. Unfortunately, the causes and risk factors for recurrence in ITP patients have not yet been elucidated. Epidemiological data indicated that ITP recurrence events occur in about half of newly-diagnosed ITP patients who received first-line treatment. We found that 85 patients (85/233, 36.48%) relapsed after 6 months. Although there is a paucity of published data from observational and experimental studies on the correlation between PLR and ITP recurrence, the prognostic values of initial platelet and lymphocyte counts have been reported. In a small (n=64) observational study, platelet counts $>6.950/\text{mm}^3$ and absolute lymphocyte counts (ALC) $\leq 2.050/\text{mm}^3$ were associated with a significant risk for developing chronic ITP [23]. In a larger (n=188) observational

Table 4. Nonlinearity addressing using two-piecewise model.

Inflection point of PLR	Effect size (HR)	95% CI	P value
<9.7	0.87	0.78–0.97	0.01*
≥9.7	0.99	0.95–1.04	0.77*
<9.7	0.90	0.74–0.95	0.03#
≥9.7	1.03	0.74–1.24	0.83#

Independent variable: PLR Dependent variable: ITP recurrence after treating with first-line treatment (no relapse, relapse).

* The strategy of adjustment was the same as Table 3; # no covariates were adjusted.

Table 5. Results of subgroup analysis and interaction analysis.

Characteristic	HR (95% CI)	P for interaction
Sex		0.310
Male	0.96 (0.91–1.01)	
Female	1.00 (0.96–1.04)	
Alcohol consumption		0.968
No	0.98 (0.95–1.01)	
Yes	0.97 (0.89–1.06)	
HP infection		0.029
Negative	1.01 (0.95–1.04)	
Positive	0.91 (0.86–1.97)	
Diabetes history		0.037
No	1.01 (0.97–1.04)	
Yes	0.86 (0.78–0.96)	
Hyperuricemia		0.981
No	1.01 (0.97–1.03)	
Yes	0.93 (0.85–1.03)	
CVD		0.628
No	0.98 (0.95–1.01)	
Yes	0.97 (0.89–1.07)	
Bleeding in skin		0.616
No	0.98 (0.95–1.01)	
Yes	1.00 (0.94–1.08)	
Bleeding in mucosa		0.594
No	0.98 (0.94–1.01)	
Yes	1.00 (0.94–1.06)	0.94

Characteristic	HR (95% CI)	P for interaction
Bleeding in organ		0.248
No	1.01 (0.97–1.94)	
Yes	0.95 (0.87–1.05)	
High-dose dexamethasone		0.058
No	1.01 (0.95–1.08)	
Yes	0.92 (0.87–0.98))	
Oral prednisone		0.058
No	0.92 (0.87–0.98))	
Yes	1.01 (0.95–1.08)	
IVIg		0.445
No	0.97 (0.94–1.01)	
Yes	0.95 (0.89–1.01)	
Smoking status		0.116
No	0.99 (0.95, 1.03)	
Current smoker	0.95 (0.87, 1.03)	
Ex-smoker	0.79 (0.66, inf)	
Age (quintile)		0.640
Q1 (14–22 year)	1.02 (0.94, 1.11)	
Q2 (23–31year)	0.94 (0.86, 1.03)	
Q3 (32–44 year)	0.99 (0.92, 1.07)	
Q4(45–61 year)	0.94 (0.86, 1.04)	
Q5 (62–88 year)	0.98 (0.91, 1.05)	

Above model adjusted for covariates presented in Table 1. For each interaction term, we did not adjust for the stratification variable.

study of newly-diagnosed ITP, ALC <3050/mL was associated with a significant risk for development of persistent ITP beyond 6 months [24]. Akbayram et al. reached a similar conclusion [25]. However, the target populations for the above studies were children, and no corresponding data have been reported in adult ITP patients. A French multicenter prospective cohort study published in *Haematologica* (2016) reported that higher platelet counts at diagnosis are negatively correlated with the risk of chronicity [26], which is consistent with our finding.

Following the suggestions of the STROBE statement, subgroup analysis is helpful to explore information in data analysis. Our present of interaction test results are shown in Table 5. A different trend of hazard ratio was observed in HP infection and

diabetes history. Compared with patients without HP infection, the protective effect of PLR on ITP recurrence was weak in patients with HP infection. The same trend also was observed with diabetes. Therefore, the results obtained by subgroup analysis have the following clinical utility. (1) The effect of PLR on the recurrence of ITP (protection effect) is population-specific. Hematologists can develop more individual treatment protocol based on PLR value at diagnosis and precisely assess prognosis in different subgroups. (2) Both HP infection and diabetes are correlated with ITP clinical characteristics and outcomes, and this relationship has been confirmed by previous clinical studies [15,27,28]. In this study, our findings at least demonstrated that PLR can weaken the adverse effect on ITP relapse caused by HP infection and diabetes. However, it must

be noted that this result was observed only in this study and further studies are needed to validate our results, and the underlying mechanisms need to be clarified.

The present systematic study aimed to construct a model used to assess the risk of recurrence in ITP patients. Therefore, the applicability of PLR as a marker for relapse risk stratification assessment should be considered. For linear relationship discovery of PLR on ITP relapse, only the completely adjusted model was statistically significant, meaning that use of PLR to assess the risk of ITP recurrence will be affected by other factors, which is not conducive to its clinical application. In contrast, the nonlinear exploration of PLR on ITP showed better clinical utility. In our study, although the adjusted and unadjusted results were slightly different between the HR values and the 95% confidence intervals, both results suggested that higher PLR was statistically associated with a decrease in risk of ITP relapse, indicating that clinicians can directly assess the risk of recurrence of ITP patients based on PLR due to less influence of other covariates. In summary, the elaboration of the association between PLR and ITP recurrence in this study will help to construct a predictive model for ITP recurrence assessments in the future, and will help hematologists to initially assess the risk of recurrence for newly-diagnosed ITP patients who receive first-line treatment.

Our study has some strengths. Firstly, we treated PLR as a continuous variable as well as a categorical variable (quartiles), and tested the P for trend, which is useful in evaluating the robustness of data analysis. Secondly, we built a Cox model to evaluate the linearity and used the generalized additive model (GAM) to explain the nonlinearity. The use of GAM is powerful to detect the real link between PLR and recurrence of newly-identified ITP [29]. Thirdly, this was a historical cohort study, and was thus susceptible to potential confounding. However, we used strict statistical adjustment to minimize the effect of residual confounders. Fourthly, the subgroup and interaction tests improved the use of data and yielded interesting findings. Fifthly, more stringent cohort inclusion and exclusion criteria are useful to eliminate potential confounders at the patient screening stage. Finally, we used 6 months as the follow-up time period and also analyzed ITP recurrence within 12 months. Since only 6 patients relapsed after 180 days,

we did not report in the results, but rather added them to supplemental materials (Supplementary Table 1). Sensitivity analysis showed at these 2 timepoints, the HR showed no significant change in magnitude or direction.

There are several limitations to be considered in this study. To best avoid the bias caused by confounders, we included only those patients who had no history of hepatitis B, which limits the generalizability of our results to individuals with hepatitis B infection. We also restricted our study population to pregnant woman, which means that our findings are not necessarily applicable to patients who are not pregnant. Additionally, the non-newly identified ITP was not involved in our cohort; therefore, the effect attributed to undergoing second-line treatment was unknown. Finally, because platelet and lymphocyte counts alone may have predictive value, the comparison of performance among PLR, platelet count, and lymphocyte counts should be performed. However, the main purpose of this study was to investigate the association between PLR and risk of recurrence of ITP. Therefore, a comparison of the predictive value of these 3 ways to predict ITP recurrence risk was not reported in this study, but was shown in a subsequent model-driven study.

Conclusions

The present work non-selectively enrolled 233 patients with newly-identified ITP who received steroid treatment with or without IVIG, showing there is a saturation effect in this correlation between PLR and risk of relapse, as we did not observe a corresponding decrease for the risk of relapse after PLR exceeded 9.7. Our findings suggest that PLR has the potential to be used as a predictive marker for ITP recurrence.

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Conflict of interest

None.

Supplementary Data

Supplementary Table 1. The results of HR using 6 months and 12 months as endpoints.

Exposure	Fully adjusted model (HR, 95% CI) 6 month	Fully adjusted model (HR, 95% CI, P) 12 month
PLR	0.96 (0.93, 0.99)	0.93 (0.90, 0.99)
PLR (quartile)		
Q1	Reference	Reference
Q2	0.51 (0.25, 1.02)	0.44 (0.23, 0.85)
Q3	0.39 (0.19, 0.82)	0.35 (0.17, 0.71)
Q4	0.39 (0.18, 0.85)	0.35 (0.17, 0.72)
P for trend	0.02	0.006

Fully adjusted model: we adjusted for age, sex, weight, height, smoking status, alcoholic consumption, HP infection, diabetes history, hyperuricemia, cardiovascular diseases, mean platelet volume, bleeding in skin, bleeding in mucosa, bleeding in organ, treatment protocol (high-dose dexamethasone, oral prednisone, IVIG), MPD, and duration of prednisone use. HR – hazard ratio; CI – confidence interval.

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