The Predictive Role of Platelet-to-Lymphocyte Ratio and Systemic Immune-Inflammation Index in Young and Middle-Aged Patients with Tibial Plateau Fractures

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Research article

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Abstract

Background

There is suggestive evidence that the platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) are related to the severity of fracture. The purpose of this study was to investigate the role of PLR and SII in predicting fracture severity in young and middle-aged patients with tibial plateau fractures (TPFs).

Methods

The retrospective cohort study involving 229 isolated TPFs was performed between January 2015 and December 2019. Medical records of hospitalized patients were extracted from the electronic case system. Three experienced orthopedic surgeons classified the imaging data according to the Schatzker classification. All the patients were divided into two groups: group1 consisted of fractures of mild to moderate severity (Schatzker types I-IV), and group2 consisted of fractures of severe severity (Schatzker types V-VI). Platelet, neutrophil, and lymphocyte values at admission were obtained. The $PLR = \text{platelet} / \text{lymphocyte}$ counts and the $SII = \text{platelet} \times \text{neutrophil} / \text{lymphocyte}$ counts were noted. Patients in groups 1 and 2 were statistically compared in terms of PLR and SII value on hospital admission.

Results

There were significant differences in the blood PLR, SII, Na^+ and K^+ levels, and neutrophil count between the two groups. According to the receiver operating characteristic (ROC) curve, the cut-off of PLR and SII were 157.9 and 923.9, respectively. Our results showed that high PLR and SII were remarkably associated with the severity of TPFs. The sensitivity was 60% and the specificity was 86.9% when using the $PLR \geq 157.9$ to predict the severity of the TPFs whereas the sensitivity was 63.3% and the specificity was 74.4% to predict the severity of TPFs at $SII \geq 923.9$. In the multivariate analyses, the high preoperative PLR and SII were identified as independent predictors of severe TPFs.

Conclusions

The PLR and SII are simple and economical biomarkers that can be calculated from routine blood tests and can be used to predict the severity of tibial plateau fractures.

Background

The tibial plateau is one of the main load-bearing parts of the human body which bears 5 times the human body weight [1]. The tibial plateau is easily damaged by external forces, resulting in soft-tissue damage which can impair the range of motion and stability of the knee joint [2–4]. Tibial plateau fracture

is a complex intraarticular fracture usually caused by high energy injury. It presents a great challenge to trauma surgeons due to its complexity and the risk of various complications such as nerve and vascular injury, delayed or non-union of fractures [5]. The young and middle-aged people are the common population affected by TPFs [6, 7].

Radiological classification systems of fractures, designed to group fractures according to injury mechanisms and fracture patterns, have been utilized to assess the severity of fracture injury [8]. The Schatzker classification, based on a two-dimensional representation of the fracture, is the most commonly used type of tibial plateau fracture which can classify TPFs into I-VI types [2]. The tibial plateau experiences more violent injuries, more knee instability, and a poorer prognosis with the increase in digital classification [9].

Recent studies have shown that some blood indicators can serve as potential biomarkers to predict the severity of tissue damage. The platelet-to-lymphocyte ratio, calculated as the absolute platelet count divided by the absolute lymphocyte count, is a predictor of diagnosis and prognosis of a variety of diseases such as hip fracture, inflammatory diseases, cancer, systemic lupus erythematosus, and cardiovascular disease [10–13]. Moreover, there is a critical balance between the pro-inflammatory and anti-inflammatory systems in a traumatic immune response [14]. Severe trauma can lead to an imbalance in the immune system, resulting in an increase in neutrophils and a decrease in lymphocytes in the circulatory system. Therefore, it is reasonable to use SII to predict the severity of trauma severity.

However, the relationship between the PLR, SII levels and the severity of TPFs has not been carefully clarified. Therefore, this study aimed to explore the predictive role of PLR and SII in young and middle-aged patients with TPFs and further elaborate their important practical role in guiding clinical work.

Methods

Study design and patients

This retrospective study was conducted in the level I electronic case system, spanning five years (between January 2015 and December 2019). The enrolled participants were young and middle-aged adults between 18 and 60 years, the diagnosis was unilateral isolated closed TPF, and blood test and imaging records were complete. The exclusion criteria were: (a) participants with cardiovascular disease, malignancies, autoimmune disease, multiple traumas, open wounds, postoperative infections, severe neurovascular injury, and systemic inflammatory or infectious diseases, (b) participants whose time from injury to admission were > 48 hours. A total of 229 patients with isolated TPFs were included in the study.

Imaging Data And Patient Grouping

All images of the patients were taken from the hospital's Picture Archiving and Communication Systems (PACS). Patients who met the inclusion criteria had their images read independently by three experienced

orthopedic surgeons. The surgeons worked independently and did not communicate with each other. The imaging data of all patients with tibial plateau fractures were classified according to the Schatzker classification system. Types I to III are fractures of the lateral tibial plateau, whereas Type IV is the isolated fracture of the medial column of the tibial plateau. Types I-IV are simple fractures that are often associated with minor injuries, whereas Type V-VI are complex fractures and are often associated with more violent injuries and a significant compromise of the soft tissue envelope [2]. Therefore, the patients were divided into two groups: Group 1 was mild to moderate TPFs, representing patients of Schatzker type I–IV fractures, whereas group 2 was severe TPFs, representing patients of Schatzker type V-VI fractures.

Data Collection

Patient characteristics obtained from the electronic medical records included: Demographic characteristics, lifestyle risk factors, comorbid diseases, laboratory data such as white blood cell count ($\times 10^9/\text{L}$, reference range 3.5–9.5), platelet counts ($\times 10^9/\text{L}$, reference range 100–300), lymphocyte counts ($\times 10^9/\text{L}$, reference range 1.1–3.2), albumin (g/L, reference range 35.0–55.0), creatinine ($\mu\text{mol/L}$, reference range 53.0–106.0) and C-reaction protein (mg/L, reference range 0.5–8) (Table 1). The patient's venous blood was drawn by a trained nurse on admission. The PLR = platelet/lymphocyte counts, SII = platelet $\times$ neutrophil/lymphocyte counts, and the Schatzker classification was used to assess the severity of TPFs.

Table 1
Clinicopathological characteristics of patients with TPFs

Variable	Group1 (n = 180)	Group2 (n = 49)	P-value
Gender (male)	105 (58.3%)	29 (59.2%)	0.915
Age (years) mean $\pm$ SD	39.65 $\pm$ 11.54	45.55 $\pm$ 9.46	
18–45	99 (55%)	23 (47%)	
46–60	81 (45%)	26 (53%)	
Smoking	31 (17.2%)	7 (14.3%)	0.624
Alcoholism	25 (13.9%)	9 (18.3%)	0.434
Hypertension	31 (17.2%)	11 (22.4%)	0.402
Diabetes	16 (8.9%)	1 (2%)	0.105
Time from injury to admission (h)			0.626
0–24	157 (87.2%)	44 (89.8%)	
25–48	23 (12.8%)	5 (10.2%)	
Neutrophil count ($> 6.30 \times 10^9/L$)	76 (42.2%)	27 (55.1%)	0.108
Lymphocyte count ($< 1.10 \times 10^9/L$)	21 (11.7%)	7 (14.3%)	0.620
PLT ($10^9/L$)			0.936
125–350 reference	168 (93.3%)	45 (91.8%)	
< 125	9 (5%)	3 (6.1%)	
> 350	3 (1.7%)	1 (2.1%)	
ALT ($> 50 U/L$)	11 (6.1%)	1 (2.1%)	0.257
AST ($> 40 U/L$)	4 (2.2%)	0 (0%)	0.292
WBC ($> 10 \times 10^9/L$)	21 (11.7%)	5 (10.2%)	0.775
PLR mean $\pm$ SD	134.14 $\pm$ 54.45	204.93 $\pm$ 53.79	< 0.001
< 157.9	140 (77.8%)	9 (18.4%)	
≥ 157.9	40 (22.2%)	40 (81.6%)	< 0.001
SII mean $\pm$ SD	836.06 $\pm$ 500.96	1011.72 $\pm$ 495.16	0.01
< 923.9	124 (68.9%)	24 (49.0%)	
≥ 923.9	56 (31.1%)	25 (51.0%)	
ASA			0.332

Variable	Group1 (n = 180)	Group2 (n = 49)	P-value
1	148 (82.2%)	40 (81.6%)	
2	28 (15.6%)	6 (12.2%)	
3	4 (2.2%)	3 (6.2%)	
TP (< 60 g/L)	108 (60%)	34 (69.4%)	0.230
ALB (< 35 g/L)	97(53.9%)	27 (55.1%)	0.880
A/G			0.619
1.2–2.4 reference	167 (92.8%)	44 (89.8%)	
< 1.2	1 (0.56%)	0 (0%)	
> 2.4	12 (6.64%)	5 (10.2%)	
HCRP (> 8 mg/L)	141 (78.3%)	39 (79.6%)	0.849
UA (> 428 µmol/L)	34 (18.9%)	6 (12.2%)	0.277
CREA (> 73 µmol/L)	35 (19.4%)	9 (18.4%)	0.865
Na ⁺ (mmol/L)			0.018
137–147 reference	162 (90%)	37 (75.5%)	
< 137	17(9.4%)	12 (24.5%)	
> 147	1 (0.6%)	0 (0%)	
K ⁺ (mmol/L)			0.008
3.5–5.3 reference	149 (82.8%)	49 (100%)	
< 3.5	30(16.7%)	0 (0%)	
> 5.3	1 (0.5%)	0 (0%)	
Cl ⁻ (mmol/L)			0.376
99–110 reference	166 (92.2%)	42 (85.7%)	
< 99	6 (3.3%)	3 (6.1%)	
> 110	8 (4.5%)	4 (8.2%)	

Numbers are significant at P < 0.05;

The continuous data of normal distribution are expressed as mean ±SD;

The continuous data of skewed distribution is categorized by reference, and categorical variables are summarized as frequency (percent)

Statistical analysis

All statistical analyses and graphics in this study were analyzed using SPSS21.0 (IBM Corp, Armonk, NY, USA). Continuous data were expressed as mean $\pm$ standard deviation (SD) and categorical variables were expressed as absolute values and percentages. Student's t-test was used for continuous variables conforming to the normal distribution, and the chi-square test was used for categorical variables to compare the differences between the two groups. Univariate analysis was used to screen the risk factors of TPFs. Factors with $P \leq 0.05$ in univariate analysis were further analyzed using multivariate logistic analysis. Odds ratio (OR) and 95% confidence interval (CI) were used to measure the strength of association between risk factors and TPFs. Moreover, the ROC curve was used to calculate the cutoff points of blood PLR and SII. In the multiple logistic regression analysis, $P \leq 0.05$ was considered to be significantly associated with TPFs and was included in the model. For all statistical tests, $P \leq 0.05$ was considered statistically significant (Fig. 1).

Results

Over the five years (January 2015 to December 2019), 229 patients were identified with TPFs eligible for inclusion criteria comprising 134 (58.5%) men and 95 (41.5%) women. The average age of the patients was 43.20 (SD 10.46). The patients were divided into two groups according to the Schatzker classification: Group 1 consisted of 180 patients with mild to moderate TPFs (Schatzker types I-IV), Group 2 consisted of 49 patients with severe injuries (Schatzker types V-VI). Other items of patients are shown in Table 1.

The ROC curve was used to determine the cutoff value of PLR, SII to predict the relationship between PLR, SII level and the severity of TPFs. For PLR of group 2, the area under the curve was 0.738 (95%CI 0.654–0.821) (Fig. 2-A), whereas for SII, the area under the curve was 0.705 (95%CI 0.624–0.785) (Fig. 2-B). In the univariate analysis, patients with severe TPFs were significantly different from those with mild to moderate TPFs in the following aspects: PLR ($P < 0.001$), $\text{PLR} \geq 157.9$ ($P < 0.001$), SII ($P = 0.01$), $\text{SII} \geq 923.9$ ($P = 0.01$), $\text{Na}^+ < 137$ mmol/L ($P = 0.018$) and $\text{K}^+ < 3.5$ mmol/L ($P = 0.008$) level. It is worth noting that the proportion of patients with blood $\text{PLR} \geq 157.9$ and $\text{SII} \geq 923.9$ in group 2 was 81.6% and 51% respectively, both of which were significantly higher than that of $\text{PLR} \geq 157.9$ (22.2%) and $\text{SII} \geq 923.9$ (31.1%) in group 1 (Fig. 3).

Tibial plateau fracture is a very common fracture, often occurring in young people or men, and is often the result of a violent injury, such as bicycle falls or car crashes, which can lead to serious knee movement problems, therefore, age and gender were included in the multiple regression analysis. In

multiple logistic regression analyses, $PLR \geq 157.9$ and $SII \geq 923.9$ were significantly associated with the severity of tibial plateau fractures (Table 2).

Table 2
Multivariate analyses for TPFs

Variable	Multivariate analysis		P-value
	OR	95% CI	
$PLR \geq 157.9$	2.205	1.014–4.795	0.046
$SII \geq 923.9$	2.307	1.213–4.387	0.011
PLT ($10^9/L$)			
125–350 reference			
<125	0.502	0.110–2.281	0.372
> 350	0.438	0.025–7.762	0.573
Time from injury to admission (h)			
0–24	1.187	0.510–2.762	0.690
25–48			
TP (< 60 g/L)	0.714	0.335–1.521	0.383
Na + (> 147 mmol/L)	0.340	0.134–0.866	0.024
Gender (Male)	1.061	0.490–2.297	0.881
Age (years)			
18–45	1.581	0.738–3.385	0.239
46–60			
Diabetes	0.084	0.01–0.712	0.023
Neutrophil count ($> 6.30 \times 10^9/L$)	1.147	0.525–2.505	0.731
K^+ (< 3.5mmol/L)	1.916	0.646–5.681	0.241

Numbers are significant at $P < 0.05$;

OR odds ratio, CI confidence interval

(PLR platelet-to-lymphocyte ratio, SII systemic immune-inflammation index, TP total protein)

Discussion

To the best of our knowledge, this is the first study to examine the relationship between PLR, SII levels and the severity of TPFs. Our study found that patients with severe TPFs were found to have higher PLR and SII compared with patients with mild to moderate TPFs. These results demonstrate that PLR and SII, as economical, simple, and easily measured laboratory parameters, can reflect the radiographic severity of TPFs in young and middle-aged adults, and simultaneously can also be used as effective predictors of the severity of TPFs.

The tibial plateau fracture is a common intraarticular fracture in which the fracture lines usually involving the proximal end of the tibia. These fractures account for 1%-2% of all fractures and often result in knee joint mobility disorders and instability. The commonly used Schatzker classification, which is based on two-dimensional imaging can effectively reflect the severity of TPFs and reveal more details of TPFs. The six basic types of TPFs have been proven and generally accepted as a practical classification criterion. However, the more details the classification presents, the higher the likelihood of disagreement in an inter- and intra-observer basis [2], therefore, the Schatzker classification is easily influenced by doctors' experience and familiarity with the Schatzker classification.

The PLR and SII indicators have been widely studied in recent years as immunoinflammatory indicators as they are easy to obtain and cost-effective in clinical application. The PLR has great value in predicting the severity and mortality in many diseases such as hip fracture, inflammatory diseases, malignancy, systemic lupus erythematosus, and cardiovascular disease [10–12, 15]. Moreover, the SII has been associated with the prognosis of malignancies, post-traumatic thrombosis, and fractures following osteoporosis [16–18]. Platelets contain a large amount of soluble and cell-related immunomodulatory molecules that enhance the immune response when the body is damaged [19]. Therefore, platelets not only serve as important hemostatic cells but also bind to leukocytes and vascular cells to regulate cellular responses which play an important role in immune defense and inflammatory responses and lead to the activation of inflammation or apoptosis of cells [20, 21]. Multiple studies have shown that various stress events such as tissue damage, severe trauma, and major surgery can stimulate an increase in circulating white blood cells, which are characterized by an increase in neutrophils [6]. For example, Morell *et al.* found a positive correlation between white blood cell count and the injury severity score [22]. Moreover, Neutrophils can promote tissue repair after injury by removing tissue debris at the site of injury and secreting growth factors or pro-angiogenic factors. Therefore, neutrophils play a similar role in immune defense as platelets and can be triggered by trauma or tissue inflammation [23, 24]. In addition, Numerous stressful events can lead to lymphocyte depletion and further reflect the body's immune system's resistance and adaptability [25]. Therefore, the induction of immune defense and inflammatory responses in the body after a violent injury, such as TPFs, can lead to an increase in platelets and neutrophils and a decrease in lymphocytes, which supports the use of PLR and SII to predict the severity of TPFs.

There are a variety of factors can affect PLR and SII levels. This study tried to exclude the influence of confounding factors. The PLR is an effective predictor of cardiovascular and rheumatic diseases as has been demonstrated in many studies [13, 15]. In addition, PLR has been reported to be associated with the

prognosis of many severe injuries, dementia, and malignancies in recent years [10, 16, 26]. For example, Wang *et al.* found that patients with a high PLR (≥ 189) had a higher one-year mortality rate than patients with low PLR (< 189) [10]. Mao *et al.* found that PLR > 193.55 in patients indicates malnutrition and more advanced cancer stage [12]. Many studies have reported SII to be closely related to fracture after osteoporosis. For example, Fang *et al.* found that SII ≥ 834.89 was identified as a significant risk factor for postmenopausal osteoporotic fracture [17]. Therefore, in the screening stage of TPFs cases, we tried to exclude the interference of the above confounding disease factors.

Tibial plateau fractures are usually caused by high-energy injuries and usually involve the lateral plateau, which is prone to serious knee ligament disorders and neurovascular injuries. More importantly, Bicondylar tibial plateau fractures (Schatzker types V-VI) [2] are often accompanied by severe intramedullary fractures, comminuted fractures, and extensive intramedullary hemorrhage, and may lead to greater latent blood loss [6]. However, Schatzker classification based on two-dimensional imaging system is still not satisfactory in displaying the above TPFs-related injuries, so PLR and SII have unique advantages in reflecting the severity of local TPFs. Moreover, there is often a concentration of body fluids, loss of hemoglobin, and redistribution of red blood cells in patients with severe TPFs, which can lead to changes in HGB, and electrolyte concentration. Therefore, these indicators cannot be used to represent the severity of TPFs[27, 28].

This study also has some limitations. First, the PLR and SII values were only collected at admission; their dynamic changes were not monitored over time after admission. Second, it was a single-center retrospective study with a relatively small sample size and a multi-center large sample retrospective study is needed to confirm our findings. Third, this study failed to elaborate the detailed physiological mechanism of the elevation of PLR and SII in patients with severe TPFs, and there was a lack of clinical evidence to guide surgical treatment. Finally, some elderly patients with low-energy impairments were excluded from the study which may result in selection bias.

Conclusions

In summary, TPF is a highly prevalent intra-articular fracture that can result in extensive soft tissue injury and knee mobility impairment. Our results innovatively identified PLR and SII as novel serological markers of inflammation which combine the inflammatory and immune systems play an important role in predicting the severity of TPFs. Close monitoring of the changes in PLR and SII at the early stage of admission and combined with imaging examinations can help clinicians to make a more scientific and effective judgment on the severity of TPFs. PLR and SII are likely to be a focus of future research.

Abbreviations

TPFs	Tibial plateau fractures
PLR	Platelet-to-lymphocyte ratio
SII	Systemic immune-inflammation index
TP	Total protein
ROC curve	Receiver operating characteristic curve
OR	Odds ratio
CI	Confidence interval
PACS	Picture Archiving and Communication Systems
HGB	Hemoglobin
PLT	Platelet
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
WBC	White blood cell
ASA	American Society of Anesthesiologists classification
TP	Total protein
ALB	Albumin
A/G	Albumin/globulin ratio
HCRP	Hypersensitive C-reactive protein
UA	Uric Acid
CREA	Creatinine

Declarations

Ethics approval and consent to participate

This study was approved by the clinical research ethics committee of the Third Affiliated Hospital of Hebei Medical University.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the electronic case system and hospital's Picture Archiving and Communication Systems

Competing interests

The authors declare that they have no competing interests in this section.

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Authors' contributions

YZZ designed the study. QCS, HZH and XTD searched the relevant studies. QCS and HZH collected and analyzed the data. QCS wrote the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow diagram of patients included in this study

Figure 2

The figure was produced by SPSS21.0 (IBM Corp, Armonk, NY, USA) (A) ROC curve analysis when the PLR cut-off point was 157.9, the sensitivity and specificity of PLR for predicting severe TPFs on admission were 60% and 86.9%, respectively, the area under curve was 0.738. (B) When the SII cutoff point was 923.9, the sensitivity and specificity of SII to predict severe TPFs at admission were 63.3% and 74.4%, respectively, the area under curve was 0.705

Figure 3

The image was produced by GraphPad Prism 5.0 (A) The number and percent of patients with PLR ≥ 157.9 were 40 (22.2%) in group 1 and 40 (81.6%) in group 2. (B) The number and percent of patients with SII ≥ 923.9 were 56 (31.1%) in group 1 and 25 (51%) in group 2