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ORIGINAL ARTICLE

Efficacy of Immature Platelet Fraction in Predicting Septic Acute Kidney Injury

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SUMMARY

Background: **Immature platelet fraction (IPF) is a new hematological parameter. Although its value in predicting the severity and mortality of sepsis patients has been shown, no study has assessed whether IPF can predict sepsis-associated acute kidney injury (S-AKI). Thus, this study aimed to analyze the predictive value of IPF in the occurrence and mortality of S-AKI.**
Methods: **Sepsis patients from the intensive care unit were screened and divided into S-AKI (n = 53) and non-S-AKI (n = 71) groups. IPF values were calculated by using the CDR mode of the BC-6800Plus hematology analyzer (Mindary, Shenzhen, China). Relevant data, such as serum creatinine (Scr) and uric acid (UA) levels, of the patients were obtained through the hospital information-management system.**
Results: **The sepsis patients with S-AKI had lower high-density lipoprotein (HDL) levels, higher IPF values, higher Scr, UA, C-reactive protein (CRP), and procalcitonin (PCT) levels, and higher SOFA and APACHE II scores than the non-S-AKI patients ($p < 0.05$). IPF value was found correlated with Scr, HDL, CRP, and PCT levels and APACHE II score but not with age, UA level, urine output in 24 hours, or SOFA score. Multivariate logistic regression analysis suggested that IPF, UA, and HDL are independent risk factors for S-AKI. The area under the curve (AUC) of IPF in the identification of S-AKI incidence was found superior to the AUC of UA and 1/HDL with a cutoff value of 12.15. However, IPF was not found associated with mortality in S-AKI.**
Conclusions: **IPF can serve as a biomarker to predict S-AKI in sepsis patients.**
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KEYWORDS

sepsis, acute kidney injury, immature platelet fraction, biomarker

INTRODUCTION

Sepsis is a systemic inflammatory response caused by infection [1], with higher morbidity and mortality in intensive care unit (ICU) patients than in other patients [2]. The kidney is among the earliest injured organs during sepsis. About two-thirds of patients with septic shock develop acute kidney injury (AKI) [3,4], and half of these patients develop AKI prior to presentation to the emergency department [5]. Patients with septic AKI have a higher risk of death and are hospitalized longer than non-septic AKI patients [6]. Early diagnosis and

risk stratification of AKI would be beneficial for favorable prognosis and implementation of timely and effective interventions in sepsis patients.

Diagnosis of sepsis-associated AKI (S-AKI) is based on serum creatinine (Scr) level and urine output (UO) in 24 hours. Although Scr level can accurately reflect renal parenchymal damage, it is not sensitive because Scr level significantly rises only when the glomerular filtration rate drops substantially. Furthermore, UO in 24 hours is also influenced by non-renal factors, such as water intake, diarrhea, and urinary-tract infection. Therefore, Scr level and UO in 24 hours are not suitable or reliable to predict S-AKI. Dhainaut et al. have found that coagulation abnormalities result in organ failure and mortality in sepsis patients by activating platelets [7]. Immature platelet fraction (IPF) is the percentage of circulating platelets with high RNA levels and a new hematological factor routinely analyzed. A systematic review involving 10 studies has indicated that IPF can predict the onset of sepsis, and IPF value is correlated with high mortality in sepsis patients [8]. Moreover, platelet indices (platelet distribution width and plateletcrit) have been demonstrated to be able to predict sepsis and S-AKI [9]. However, no study has investigated whether IPF can be used to predict S-AKI and associated mortality.

This study aimed to evaluate whether elevated IPF values are associated with increased S-AKI risk and 30-day mortality after ICU admission and whether IPF is superior to traditional biomarkers in predicting S-AKI and mortality.

MATERIALS AND METHODS

Participants

In total, 124 sepsis patients were recruited from the Zhongda Hospital, Southeast University (Nanjing, Jiangsu Province, China) between June 2021 and March 2022. Sepsis was defined by Sepsis-3 diagnostic criteria as a sequential [sepsis-related] organ failure assessment (SOFA) score ≥ 2 on ICU admission with a suspicion of infection [10]. Septic shock was defined as the need for vasopressor therapy to maintain a median arterial pressure of 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L persisting after fluid resuscitation [10]. The diagnostic criteria for S-AKI [11] specify that in S-AKI, renal function suddenly decreases within 48 hours, and Scr level rises to ≥ 26.5 μmol/L or 1.5 times the baseline value within 7 d, or UO drops to < 0.5 mL/kg/hour in 6 hours.

The inclusion criteria for the patients were as follows: (1) 20 - 75 years of age; (2) stable vital signs and normal cognitive function; and (3) no history of kidney injury. Individuals with a severe liver, brain, or kidney disease, mental disorder, or inflammatory arthritic condition were excluded from the study. The associated 30-day mortality data were obtained from the Lis system and relatives of the patients.

This study obtained the approval of the Ethics committee of the Zhongda Hospital, Southeast University (ID: 2020ZDSYLL287-P01) in 2020 and followed the Declaration of Helsinki. All the participants signed an informed consent form before inclusion.

Assessment of the laboratory parameters and clinical symptoms

The demographic data and clinical characteristics of all the participants were obtained from the hospital information-management system. We obtained the following data of the sepsis patients: age; IPF value; SOFA and acute physiology and chronic health evaluation (APACHE II) scores; levels of C-reactive protein (CRP), procalcitonin (PCT), Scr, uric acid (UA), and high-density lipoprotein (HDL); UO in 24 hours; and survival status within 30 days. IPF value was calculated by using the CDR mode of the BC-6800 Plus hematology analyzer (Mindary, Shenzhen, China).

Statistical analysis

The SPSS 22.0 software (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) was used for the statistical analyses. The categorical data (n, %) were analyzed using the chi-squared test. Continuous data that satisfied a normal distribution were analyzed using Student's *t*-test or one-way ANOVA and are presented as mean ± SD. The non-parametric test was used for continuous data that did not show a normal distribution (median [Q1, Q3]). The correlation between IPF value and any other laboratory parameter was assessed using Spearman's correlation test. Uni- and multi-variate logistic regression analyses were used to identify the independent risk factors for S-AKI. We used the receiver operating characteristic (ROC) curve to analyze the efficacy of IPF value in predicting the occurrence and mortality of S-AKI. $p < 0.05$ was considered to indicate statistical significance.

RESULTS

The characteristics of the participants

In total, 124 sepsis patients were enrolled in this study, and their baseline characteristics are shown in Table 1. The proportion of men, and the median age were 65.3% and 66.0, respectively. These patients were grouped into S-AKI (12, 13, and 28 patients in stages 1, 2, and 3, respectively) and non-S-AKI (71 patients without AKI) groups. Among 53 AKI patients, 10 patients with AKI stage 3 needed renal replacement therapy. The values/levels of laboratory parameters (IPF, Scr, UA, HDL, CRP, and PCT) and severity scores (SOFA and APACHE II) were remarkably higher in the S-AKI group than in the non-S-AKI group ($p < 0.05$). However, no significant differences were found between the two groups in terms of UO in 24 hours or the proportion of septic shock ($p > 0.05$).

Table 1. Baseline characteristics of the study population.

Variables	Total patients (n = 124)	Patients with S-AKI (n = 53)	Patients without AKI (n = 71)	p-value
Male (%)	81 (65.3%)	37 (69.8%)	44 (62.0%)	0.537
Age (years)	66.0 (53.0, 75.0)	68.00 (57.00, 74.50)	65.00 (53.00, 75.00)	0.393
Laboratory parameters				
IPF	10.00 (7.63, 16.37)	15.70 (9.90, 21.00)	8.60 (6.10, 10.40)	< 0.001
UO in 24 hours (mL)	2,146.00 (1,432.50, 3,077.50)	1,920.00 (1,115.0, 2,850.00)	2,314.00 (1,660.0, 3,200.0)	0.053
Scr (µmo/L)	100.50 (73.25, 162.00)	119.00 (97.00, 184.00)	81.00 (65.00, 120.00)	< 0.001
UA (µmo/L)	235.0 (161.3, 368.3)	297.0 (167.5, 431.0)	215.0 (139.0, 306.0)	0.017
HDL (mmol/L)	0.60 ± 0.30	0.49 ± 0.26	0.68 ± 0.30	< 0.001
CRP (mg/L)	113.8 (66.5, 194.5)	148.56 (96.09, 217.89)	91.13 (35.65, 173.27)	< 0.001
PCT (ng/mL)	2.25 (0.36, 2.25)	3.87 (1.33, 8.81)	0.95 (0.09, 4.11)	< 0.001
Severity scoring				
APACHE II	21.10 ± 8.29	23.38 ± 9.29	19.39 ± 7.06	0.008
SOFA	8.00 (5.00, 10.00)	9.00 (6.00, 11.00)	6.00 (5.00, 9.00)	0.009
Septic shock (%)	70 (56.5%)	35 (66.0%)	35 (49.3%)	0.063
Mortality (%)	36 (29.0%)	18 (34.0%)	18 (25.4%)	0.296

*** - Underlined values indicate significant difference.**
Abbreviation: AKI - acute kidney injury, IPF - immature platelet fraction, Scr - serum creatinine, UO - urine output, UA - uric acid, HDL - high density lipoprotein, CRP - C reactive protein, PCT - procalcitonin, APACHE II - acute physiology and chronic health evaluation scoring system, SOFA - sequential [sepsis-related] organ failure assessment.

Table 2. The association of baseline IPF with other parameters.

Variables	R	p-value
Age	-0.070	0.439
Scr	0.499	< 0.001
UA	0.090	0.322
HDL	-0.194	0.031
UO in 24 hours	-0.031	0.731
CRP	0.268	0.003
PCT	0.180	0.045
APACHE II score	0.240	0.007
SOFA score	0.157	0.081

*** - Underlined values indicate significant difference.**
Abbreviation: IPF - immature platelet fraction, Scr - serum creatinine, UO - urine output, UA - uric acid, HDL - high density lipoprotein, CRP - C reactive protein, PCT - procalcitonin, APACHE II - acute physiology and chronic health evaluation scoring system, SOFA score - sequential [sepsis-related] organ failure assessment score.

Correlation between IPF and other clinical characteristics in sepsis patients

Baseline IPF value was positively correlated with Scr, HDL, CRP, and PCT levels and APACHE II score in the sepsis patients ($p < 0.05$, Table 2). However, no significant association was observed between IPF and age, UA level, UO in 24 hours, and SOFA score ($p > 0.05$).

Assessment of the predictive values of biomarkers in S-AKI

IPF value was higher in the S-AKI group than in the non-S-AKI group (Figure 1). The patients with stage 2 or 3 AKI had significantly higher IPF values than that in patients without AKI (Figure 1).

Multivariate logistic regression analysis was used to as-

Table 3. The values of included parameters for AKI by multivariate logistic regression analysis.

Variables	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
IPF	1.324 (1.158, 1.512)	< 0.001	1.338 (1.165, 1.536)	< 0.001
Scr (μmoI/L)	0.992 (0.983, 1.000)	0.057	0.991 (0.983, 1.000)	0.052
UA (μmol/L)	1.008 (1.003, 1.012)	0.001	1.008 (1.003, 1.012)	0.001
HDL (mmol/L)	0.041 (0.004, 0.383)	0.005	0.046 (0.005, 0.440)	0.007
CRP (mg/L)	1.006 (1.000, 1.012)	0.049	1.006 (0.999, 1.012)	0.076
PCT (ng/mL)	1.015 (0.930, 1.108)	0.741	1.005 (0.916, 1.102)	0.920
SOFA score	1.065 (0.895, 1.267)	0.480	1.069 (0.892, 1.281)	0.468
APACHE II score	1.034 (0.962, 1.112)	0.368	1.026 (0.951, 1.106)	0.510

*** - Underlined values indicate significant difference.**
 # - Adjusted for age, gender, and septic shock.
Abbreviation: AKI - acute kidney injury, IPF - immature platelet fraction, Scr - serum creatinine, UA - uric acid, HDL - high density lipoprotein, CRP - C reactive protein, PCT - procalcitonin, APACHE II - acute physiology and chronic health evaluation scoring system, SOFA score - sequential [sepsis-related] organ failure assessment score.

Table 4. The values of included parameters in predicting 30-day mortality by multivariate logistic regression analysis.

Variables	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
IPF	1.027 (0.913, 1.155)	0.659	1.030 (0.914, 1.162)	0.623
Scr (μmoI/L)	0.998 (0.988, 1.008)	0.738	0.998 (0.988, 1.008)	0.731
UA (μmol/L)	1.000 (0.996, 1.004)	0.906	1.000 (0.996, 1.004)	0.948
HDL (mmol/L)	1.508 (0.225, 10.086)	0.672	1.559 (0.232, 10.498)	0.648
CRP (mg/L)	0.998 (0.991, 1.004)	0.489	0.997 (0.990, 1.004)	0.449
PCT (ng/mL)	0.980 (0.911, 1.053)	0.574	0.976 (0.904, 1.055)	0.546
SOFA score	2.043 (1.539, 2.712)	< 0.001	2.048 (1.541, 2.721)	< 0.001
APACHE II score	1.057 (0.979, 1.142)	0.156	1.055 (0.976, 1.140)	0.179

*** - Underlined values indicate significant difference.**
 # - Adjusted for age, gender and septic shock.
Abbreviation: IPF - immature platelet fraction, Scr - serum creatinine, UA - uric acid, HDL - high density lipoprotein, CRP - C reactive protein, PCT - procalcitonin, APACHE II - acute physiology and chronic health evaluation scoring syste, SOFA score - sequential [sepsis-related] organ failure assessment score.

sess the association between laboratory or clinical parameters and AKI (Table 3). Our results showed that IPF and UA are independent risk factors for AKI (IPF: OR [95% CI], 1.338 [1.165 - 1.536], $p < 0.001$; UA: OR [95% CI], 1.008 (1.003 - 1.012], $p = 0.001$), but HDL was a protective factor (OR [95% CI], 0.046 [0.005 - 0.440], $p < 0.001$) before/after adjusting for age, gender, and septic shock. CRP was found to be a significant risk factor for AKI before, but not after, adjustment.

ROC analysis was applied to examine the values of IPF, UA, and HDL in predicting AKI. The area under the curve (AUC) of IPF was 0.806 (0.724 - 0.888), which was superior to the AUC of UA (0.625) or HDL reciprocal (0.688) (Figure 2). The sensitivity, specificity, and Youden indices were 69.8%, 91.3%, and 0.614, respectively, when the optimal cutoff value was 12.15.

The relationship between IPF and 30-day mortality

The OR (95% CI) and p-value of the SOFA score for 30-day mortality were 2.043 (1.539 - 2.712) and < 0.001, respectively. The positive results remained strong after adjusting for age, gender, and septic shock. However, IPF, UA, and HDL exhibited unclear associations with 30-day mortality before/after adjustment (Table 4).

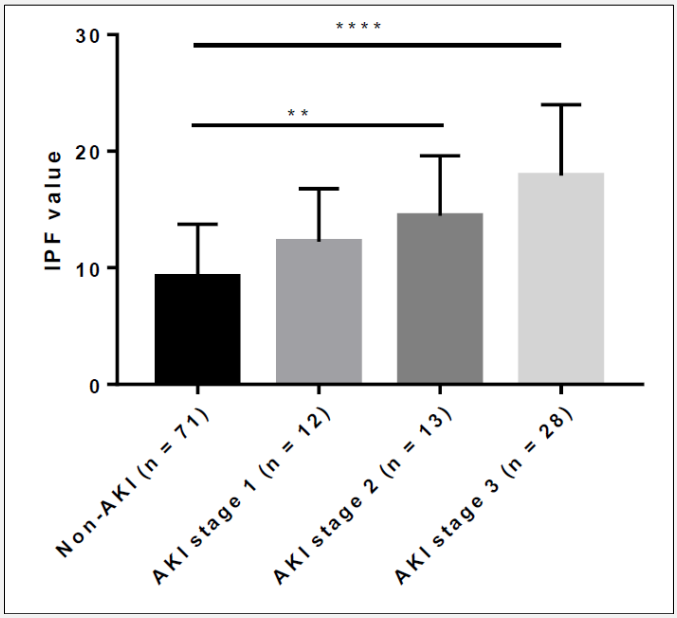

Figure 1. IPF value in various AKI stages.

**** - p < 0.01, **** - p < 0.0001.**

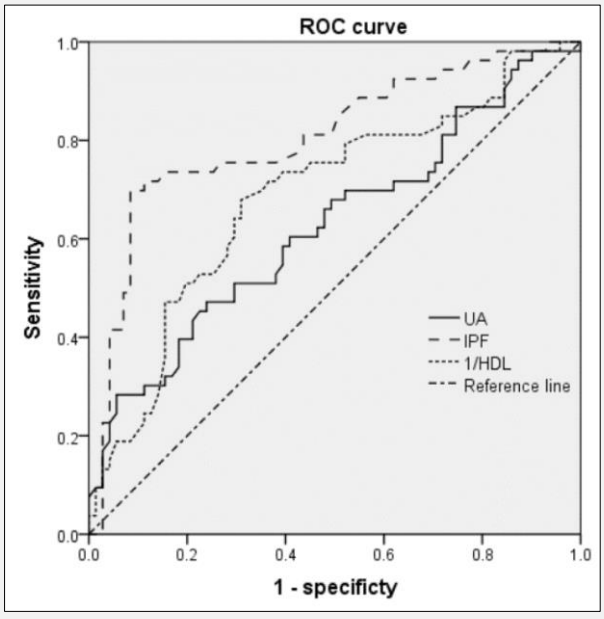

Figure 2. Receiver operating characteristic curve of clinical indicators for diagnostic prediction of sepsis-associated AKI.

UA - uric aci, IPF - immature platelet fraction, 1/HDL - the reciprocal of high-density lipoprotein.

DISCUSSION

Through various methods, this study revealed that IPF value is an independent risk factor for S-AKI. Furthermore, IPF value was higher in the patients who died than in the survivors. However, elevated IPF value was not found to be associated with prognosis in S-AKI. AKI develops within the first 24 hours of sepsis in 64% of patients [12]. However, animal experiments have shown no tubular-cell necrosis or apoptosis within the first 48 hours of sepsis [13]. A meta-analysis has revealed that patients who die within one month of sepsis have higher levels of platelet/lymphocyte ratio (PLR) than survivors [14]. Moreover, elevated PLR has been proposed to predict a poor prognosis in S-AKI [15]. In patients with aplastic anemia, leukemia, or solid tumors, the total number of platelets is reduced due to bone-marrow suppression, but IPF remains unaffected [16]. Therefore, this case-control study was performed to examine the value of IPF in predicting S-AKI and associated mortality. To the best of our knowledge, this is the first study on the correlation of IPF with S-AKI and associated 30-day mortality. Our results revealed that increased IPF value is associated with S-AKI.

AKI is characterized by the activation of intra-renal hemostatic and inflammatory processes, and platelets are the first cells to arrive at the sites of the acute injury [17]. We observed that platelet count was lower in the sepsis patients and negatively correlated with IPF value. Laine et al. have observed increased consumption of platelets and active thrombopoiesis (higher mean platelet volume and IPF value) in patients with severe AKI compared with mild AKI [18]. Additionally, the incidence of postoperative AKI has been shown to be 54% when the median platelet count is 121 x 10^9/L [19]. For every 30 x 10^9/L reduction in platelet count, the risk for postoperative AKI increases by 14% [19]. Generally, S-AKI is associated with high morbidity and mortality [20]. PLR is correlated with poor prognosis in S-AKI (high mortality) [15]. However, no significant association between IPF and 30-day mortality was observed in this study. The following reasons may account for this disparity. First, we could not rule out the possibility of false-negative or false-positive results due to the limited sample size. Second, different sites of sepsis infection and different treatment methods lead to different prognoses. Third, although IPF value is elevated in AKI, it is not significantly associated with AKI stage. Therefore, IPF may not be a suitable biomarker for predicting 30-day mortality.

This study had several limitations. First, the study may be underpowered due to the limited sample size and selection bias that may have resulted from its single-center nature. Second, we did not consider any susceptible factors, such as patient history of chronic kidney disease or diabetes. Finally, our study did not examine the kinetics of IPF value during the pathogenesis of S-AKI due to limited conditions.

In conclusion, an initial elevated IPF value may contribute to the occurrence of S-AKI, and thus assessment of this parameter is beneficial in the early diagnosis and intervention of S-AKI.

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None.

Declaration of Interest:
The authors declare that they have no competing interests.

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