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ABOUT COVER

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Retrospective Study

Correlation between thrombopoietin and inflammatory factors, platelet indices, and thrombosis in patients with sepsis: A retrospective study

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Abstract

BACKGROUND

Thrombopoietin (TPO) is a primary regulator of thrombopoiesis in physiological conditions. TPO, in combination with its specific cytokine receptor c-Mpl, drives platelet production by inducing the proliferation and differentiation of megakaryocytes. However, the role of TPO in sepsis is not well determined. The elevated levels of TPO are often accompanied by a decrease of platelet count (PLT) in systemic infected conditions, which is contrary to the view that TPO promotes platelet production under physiological conditions. In addition, whether TPO mediates organ damage in sepsis remains controversial.

AIM

To explore the relationships between TPO and inflammatory factors, platelet indices, and thrombotic indicators in sepsis.

METHODS

A total of 90 patients with sepsis diagnosed and treated at the emergency medicine department of The First People's Hospital of Foshan between January 2020 and March 2021 were enrolled in this study. In addition, 110 patients without sepsis who came to the emergency medicine department were included as controls. Clinical and laboratory parameters including age, gender, TPO, blood cell count in peripheral blood, platelet indices, inflammatory factors such as high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-21, and IL-6, organ damage indicators, and thrombotic indicators were collected and analyzed by using various statistical approaches.

RESULTS

The results showed that the TPO levels were higher in the sepsis group than in controls [86.45 (30.55, 193.1) *vs* 12.45 (0.64, 46.09) pg/mL, $P < 0.001$], but PLT was lower ($P < 0.001$). Multivariable analysis showed that white blood cell count (WBC) [odds ratio (OR) = 1.32; 95% confidence interval (CI): 1.01-1.722; $P = 0.044$], TPO (OR = 1.02; 95%CI: 1.01-1.04; $P = 0.009$), IL-21 (OR = 1.02; 95%CI: 1.00-1.03; $P = 0.019$), troponin I (OR = 55.20; 95%CI: 5.69-535.90; $P = 0.001$), and prothrombin time (PT) (OR = 2.24; 95%CI: 1.10-4.55; $P = 0.027$) were independent risk factors associated with sepsis. TPO levels were positively correlated with IL-21, IL-6, hs-CRP, creatinine, D-dimer, PT, activated prothrombin time, international normalized ratio, fibrinogen, WBC count, and neutrophil count, and negatively correlated with PLT, thrombin time, red blood cell count, and hemoglobin concentration ($P < 0.05$). Receiver operating characteristic analysis showed that TPO had fair predictive value in distinguishing septic patients and non-septic patients (the area under the curve: 0.788; 95%CI: 0.723-0.852; $P < 0.001$). With an optimized cutoff value (28.51 pg/mL), TPO had the highest sensitivity (79%) and specificity (65%).

CONCLUSION

TPO levels are independently associated with sepsis. High TPO levels and low PLT suggest that TPO might be an acute-phase response protein in patients with infection.

Key Words: Sepsis; Thrombopoietin; Interleukin-21; Platelets; Thrombosis

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Core Tip: This retrospective study was focused on the correlation between thrombopoietin (TPO) levels and platelet indices and inflammatory factors in sepsis patients. The potential role played by TPO in sepsis was investigated. The results demonstrated that TPO was significantly elevated in the sepsis group compared to the non-infected control group, with a negative correlation with platelet count (PLT) and a positive correlation with inflammatory factors. TPO may be an acute response protein in sepsis and may be negatively regulated by decreased PLT.

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INTRODUCTION

According to the Third International Consensus Definition for Sepsis and Septic Shock, sepsis is a life-threatening organ dysfunction caused by the dysregulated host response to infection[1]. Sepsis occurs when the host response to an infectious pathogen causes life-threatening organ dysfunction, as manifested by an increase in sequential (sepsis-related) organ failure assessment (SOFA) score of ≥ 2 [1]. Approximately 750000 cases of sepsis occur annually in the United States, representing 2% of hospitalizations in developed countries and 6%-30% of patients in intensive care units[2,3]. Without timely treatment, sepsis may advance to septic shock, which is defined as vasodilatory hypotension with a mean arterial pressure (MAP) < 65 mmHg and lactate level > 2 mmol/L and is associated with high

mortality (> 40%)[1,4-6].

Thrombopoietin (TPO) is the primary regulator of megakaryocytic lineage and stimulates platelet production[7]. The liver is the main source of TPO (endocrine fashion), followed by marrow stromal cells (paracrine fashion)[7,8]. Inflammatory conditions can increase the secretion of TPO, and the blood levels of TPO are determined by its production and sponging by the orphan cytokine receptor (c-Mpl) and senescent platelets[7,9-11]. Studies reported that TPO is upregulated in sepsis[12,13].

In addition to promoting platelet production, *in vitro* experiments have confirmed that TPO has a protective effect on organs (such as the myocardium and brain)[14-18]. On the other hand, preclinical mouse experiments showed that TPO reduction could alleviate organ damage[19]. In addition, TPO correlated with *ex vivo* platelet activation and might contribute to triggering thrombosis and multi-organ dysfunction in sepsis[13,20]. TPO also decreases cardiac contractility and could mediate pancreatitis[21,22]. Therefore, the results about the involvement of TPO in sepsis are conflicting.

Various risk factors have been associated with the prognosis of sepsis. The predisposition, insult/infection, response, and organ dysfunction model is based on age, chronic liver disease, congestive cardiomyopathy, type of infection, tachypnea, and organ dysfunction[23,24]. The mortality in emergency department sepsis score recognizes terminal illness, tachypnea/hypoxemia, septic shock, low platelets, high white blood cell count, age, pneumonia, nursing home residence, and altered mental status as prognostic factors in sepsis[25]. The risk, injury, failure, loss, and end-stage kidney disease system includes kidney dysfunction, kidney injury, and kidney failure to predict sepsis mortality[26]. Still, the relationship between TPO and these various prognostic factors is poorly known.

Therefore, this study aimed to explore the relationships between TPO and inflammatory factors such as interleukin (IL)-21 and IL-6, platelet indices, and thrombotic indicators in patients with sepsis. The results could help determine the clinical significance of TPO levels in sepsis, and it might be a potential predictive indicator for sepsis.

MATERIALS AND METHODS

Study design and patients

This retrospective study included patients with sepsis diagnosed and treated at the Emergency Medicine Department of The First People's Hospital of Foshan between January 2020 and March 2021. This study was approved by the Medical Ethics Committee of The First People's Hospital of Foshan, Approval No: L[2021]No.8. The requirement for informed consent was waived due to the retrospective nature of this study.

The inclusion criteria of the sepsis group were: (1) Diagnosed with sepsis caused by infection; and (2) ≥ 18 years of age. The exclusion criteria were: (1) History of malignant tumors; (2) severe cardiovascular and cerebrovascular diseases (not including mild strokes); (3) patients using glucocorticoids and immunosuppressants; (4) use of anticoagulants (warfarin or heparin) within 1 mo (but antiplatelet drugs such as aspirin and clopidogrel were allowed); (5) pregnancy status; and (6) incomplete data.

The control group included patients aged 18 years or older without sepsis or infection who came to the Emergency Medicine Department due to acute onset of hypertension or mild ischemic or hemorrhagic stroke. The exclusion criteria for the control group were the same as those for the sepsis group.

Data collection

After diagnosis, demographic data and clinical indicators were collected: TPO (ELISA Kit, R&D Systems, MN, United States), IL-21 (ELISA Kit, MEIMIAN, China), IL-6, high-sensitivity C-reactive protein (hs-CRP), procalcitonin (PCT), WBC, neutrophil count (N#), red blood cell count (RBC), hemoglobin concentration (Hb), platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), platelet large cell ratio (P-LCR), total bilirubin (TBIL), creatinine (Cre), oxygenation index, MAP, D-dimer (DD), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR), and fibrinogen (FIB).

For patients with infection or suspected infection, sepsis was diagnosed when the SOFA score increased by ≥ 2 points from baseline. Septic shock was based on sepsis with persistently low blood pressure and blood lactic acid concentration > 2 mmol/L; under complete volume resuscitation, vasoactive drugs are still needed to maintain MAP ≥ 65 mmHg[1].

Statistical analysis

The statistical methods were reviewed by Xu WH, Mo LC, Shi MH, and Rao H from Nanfang Hospital, Southern Medical University, and The First People's Hospital of Foshan.

SPSS 22.0 (IBM, Armonk, NY, United States) was used for the statistical analyses. The Shapiro-Wilk method was used to test the normality of the continuous data. The continuous data conforming to a normal distribution are expressed as the mean \pm SD and were analyzed using Student's *t*-test. The continuous data with a non-normal distribution are presented as the median (25th percentile, 75th percentile) and were analyzed using the Mann-Whitney *U* test. Categorical data are expressed as *n* (%)

and analyzed using the chi-square test or Fisher's exact probability method. Pearson's correlation analysis was used for bivariable analyses of data with a normal distribution, while Spearman's correlation analysis was used for bivariable analyses of data with a non-normal distribution. Logistic regression models were used for univariable and multivariable regression analyses with sepsis as the outcome. Receiver operator characteristic (ROC) curve analysis was used to explore the abilities of TPO, MPV, and other inflammatory factors (IL-6, IL-21, and hs-CRP) to predict sepsis. ROC curves are presented, and the area under the curve (AUC) was calculated. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the patients

Table 1 presents the characteristics of the patients. The median age of the patients (*n* = 200) was 66 (54, 75) years, and 54.5% were male. Compared with the control group (*n* = 110), the patients in the sepsis group (*n* = 90) were older (*P* = 0.002), had higher WBC (*P* < 0.001), N# (*P* < 0.001), IL-21 (*P* < 0.001), IL-6 (*P* < 0.001), hs-CRP (*P* < 0.001), MPV (*P* = 0.035), TBIL (*P* < 0.001), Cre (*P* < 0.001), DD (*P* < 0.001), PT (*P* < 0.001), APTT (*P* < 0.001), INR (*P* < 0.001), and FIB (*P* < 0.001), and lower levels of RBC (*P* < 0.001), Hb (*P* < 0.001), PLT (*P* < 0.001), oxygenation index (*P* < 0.001), MAP (*P* < 0.001), and TT (*P* < 0.001). The TPO level was higher in the sepsis group than in controls [86.45 (30.55, 193.1) *vs* 12.45 (0.64, 46.09) pg/mL, *P* < 0.001].

Multivariable analysis

The multivariable analysis showed that WBC [odds ratio (OR) = 1.32; 95% confidence interval (CI): 1.01-1.722; *P* = 0.044], TPO (OR = 1.02; 95%CI: 1.01-1.04; *P* = 0.009), IL-21 (OR = 1.02; 95%CI: 1.00-1.03; *P* = 0.019), troponin I (TnI) (OR = 55.20; 95%CI: 5.69-535.90; *P* = 0.001), and PT (OR = 2.24; 95%CI: 1.10-4.55; *P* = 0.027) were independent risk factors for patients with sepsis (**Table 2**).

Correlations of TPO levels with other factors

Figure 1 and **Table 3** show that TPO levels were positively correlated with IL-21 (*r* = 0.362, *P* < 0.001) (**Figure 1A**), IL-6 (*r* = 0.385, *P* < 0.001) (**Figure 1B**), hs-CRP (*r* = 0.531, *P* < 0.001) (**Figure 1C**), Cre (*r* = 0.219, *P* = 0.002) (**Figure 1E**), DD (*r* = 0.453, *P* < 0.001) (**Figure 1F**), PT (*r* = 0.311, *P* < 0.001) (**Figure 1G**), APTT (*r* = 0.203, *P* = 0.004), INR (*r* = 0.310, *P* < 0.001), FIB (*r* = 0.438, *P* < 0.001) (**Figure 1H**), WBC (*r* = 0.176, *P* = 0.013) (**Figure 1I**), and N# (*r* = 0.235, *P* = 0.001), and negatively correlated with PLT (*r* = -0.177, *P* = 0.012) (**Figure 1D**), TT (*r* = -0.307, *P* < 0.001), RBC (*r* = -0.246, *P* < 0.001), and Hb (*r* = -0.209, *P* = 0.003) (**Figure 1J**).

ROC curve analysis for sepsis

TPO, MPV, and the inflammatory factors (IL-6, IL-21, and hs-CRP) showed significant AUCs for distinguishing septic patients from non-septic patients. The AUC of TPO (0.788; 95%CI: 0.723-0.852; *P* < 0.001) was larger than that of MPV (0.589; 95%CI: 0.506-0.671; *P* = 0.036) but smaller than that of the inflammatory factors (**Figure 2**). According to the maximum value of Youden's index, the cut-off level for TPO to distinguish sepsis and non-sepsis was 28.51 pg/mL.

DISCUSSION

The role of TPO in sepsis is not well determined, and conflicting results were obtained from different studies[13,14,17,19]. This study aimed to investigate the role of TPO in sepsis and explore the relationships between TPO and inflammatory factors such as IL-21 and IL-6, platelet indices, and thrombotic indicators in patients with sepsis. Our results showed that the TPO levels were independently associated with sepsis. High TPO levels and low PLT in the sepsis patients implied that TPO might be an acute-phase response protein in patients with infection.

Neutralizing TPO in sepsis appears to alleviate organ damage[19], while TPO administration in thrombocytopenic patients improves their prognosis[27,28]. The primary role of TPO is to induce platelet production, either in an endocrine (TPO produced by the liver) or a paracrine manner (TPO produced by marrow stromal cells)[7,8]. In normal conditions, blood TPO is removed by the receptor c-Mpl on platelets[29]. Under inflammatory conditions, the liver production of TPO is increased, and the high TPO levels are more due to increased production than reduced removal[29]. In the present study, sepsis was independently associated with high TPO levels (6.9-fold that of controls), as supported by previous studies that reported elevated TPO levels in sepsis[12,13]. Still, in the present study, these high TPO levels did not result in increased platelet production since the platelet level was 28% lower in the sepsis group compared with the controls, which is also supported by studies reporting low platelet levels in the acute care setting[30,31]. It could be explained, at least in part, by the fact that platelets play

Table 1 Characteristics of the patients

Clinical information	Total (n = 200)	Control group (n = 110)	Sepsis group (n = 90)	P value
Age, yr	66 (54, 75)	64 (51, 71)	71 (57, 80)	0.002
Sex, male, n (%)	109.0 (54.5)	55.0 (50.0)	54.0 (60.0)	0.158
Hypertension, n (%)		40.0 (36.4)		
Infection site				
Lungs, n (%)			22.0 (24.4)	
Abdomen, n (%)			54 (60)	
Skin and soft tissue infections, n (%)			4.0 (4.4)	
Central nervous system infection, n (%)			1.0 (1.1)	
Others, n (%)			9 (10)	
SOFA, n (%)			5 (3, 7)	
WBC, $\times 10^9/L$	9.20 (7.15, 13.58)	8.03 (6.55, 10.29)	13.12 (8.80, 18.39)	< 0.001
N#, $\times 10^9/L$	7.02 (4.88, 11.47)	5.75 (4.11, 7.28)	10.69 (7.24, 16.58)	< 0.001
RBC, $\times 10^{12}/L$	4.30 (3.67, 4.77)	4.44 (4.13, 4.88)	3.83 (3.24, 4.53)	< 0.001
Hb, g/L	129.5 (107.0, 145.0)	134.5 (126.0, 148.0)	110.5 (98.0, 136.0)	< 0.001
PLT, $\times 10^9/L$	221.0 (159.5, 276.0)	241 (198, 283)	174.5 (118, 251)	< 0.001
PDW, fL	11.9 (10.6, 13.5)	11.80 (10.55, 12.95)	11.90 (10.60, 14.15)	0.343
P-LCR	0.28 (0.23, 0.34)	0.280 (0.230, 0.325)	0.30 (0.23, 0.37)	0.059
MPV, fL	10.4 (9.8, 11.2)	10.3 (9.8, 11.0)	10.5 (9.9, 11.6)	0.035
TPO, pg/mL	37.91 (6.10, 107.91)	12.45 (0.64, 46.09)	86.45 (30.55, 193.1)	< 0.001
IL-21, pg/mL	506 (418, 566)	436 (366, 493)	565 (524, 610)	< 0.001
IL-6, pg/mL	16.7 (4.6, 219.0)	5.0 (2.0, 12.0)	310.4 (41.9, 1582.4)	< 0.001
hs-CRP, mg/L	10.8 (1.6, 114.4)	2.1 (0.8, 6.1)	130.7 (58.4, 196.5)	< 0.001
PCT, ng/mL			10.26 (0.97, 31.70)	
TBIL, $\mu\text{mol/L}$	11.05 (8.5, 16.9)	10.10 (7.75, 14.00)	14.25 (9.60, 23.00)	< 0.001
Cre, $\mu\text{mol/L}$	78 (60, 133)	69 (55, 87)	120.5 (73.0, 187.0)	< 0.001
TnI, ng/mL				< 0.001
≥ 0.01 , n (%)	61.0 (30.7)	3.0 (2.7)	58.0 (65.2)	
< 0.01, n (%)	138.0 (69.3)	107.0 (97.3)	31.0 (34.8)	
Oxygenation index				< 0.001
≥ 400 , n (%)	124.0 (64.9)	110 (100)	14.0 (17.3)	
< 400, n (%)	67.0 (35.1)	0 (0)	67.0 (82.7)	
MAP, mmHg				< 0.001
≥ 70 , n (%)	161.0 (80.9)	110.0 (100.0)	51.0 (57.3)	
< 70, n (%)	38.0 (19.1)	0 (0)	38.0 (42.7)	
DD, $\mu\text{g/mL}$	0.960 (0.340, 2.795)	0.38 (0.22, 0.82)	3.120 (1.395, 6.440)	< 0.001
PT, s	12.50 (11.60, 14.05)	11.8 (11.2, 12.5)	14.0 (13.1, 15.4)	< 0.001
APTT, s	27.15 (24.95, 30.60)	26.4 (24.7, 27.8)	30.1 (26.5, 34.6)	< 0.001
TT, s	16.2 (15.3, 17.2)	16.60 (15.75, 17.40)	15.7 (14.8, 16.7)	< 0.001
INR	1.090 (1.010, 1.225)	1.03 (0.97, 1.09)	1.22 (1.14, 1.34)	< 0.001
FIB, g/L	3.450 (2.750, 4.655)	2.91 (2.58, 3.48)	4.58 (3.65, 5.95)	< 0.001

All data are shown as the median (P25, P75) or *n* (%). SOFA: Sequential organ failure assessment; N#: Neutrophile; WBC: White blood cell count; RBC: Red blood cell count; Hb: Hemoglobin concentration; PLT: Platelet count; PDW: Platelet distribution width; P-LCR: Platelet large-cell ratio; MPV: Mean platelet volume; TPO: Thrombopoietin; IL: Interleukin; hs-CRP: High-sensitivity C-reactive protein; PCT: Procalcitonin; TBIL: Total bilirubin; Cre: Creatinine; TnI: Troponin I; MAP: Mean arterial pressure; DD: D-dimer; PT: Prothrombin time; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; FIB: Fibrinogen.

Table 2 Univariable/multivariable analyses of sepsis

	Univariable			Multivariable		
	OR	95%CI	P	OR	95%CI	P value
Age, yr	1.025	1.005-1.045	0.013	1.022	0.967-1.081	0.436
Gender						
Male	Reference					
Female	0.667	0.379-1.171	0.158			
WBC	1.230	1.140-1.328	< 0.001	1.317	1.007-1.722	0.044
N#	1.315	1.202-1.439	< 0.001			
RBC	0.404	0.272-0.600	< 0.001	1.398	0.376-5.197	0.617
Hb	0.972	0.960-0.985	< 0.001			
TPO	1.016	1.010-1.022	< 0.001	1.021	1.005-1.037	0.009
IL-21	1.020	1.015-1.026	< 0.001	1.016	1.003-1.029	0.019
IL-6	1.066	1.039-1.093	< 0.001			
hs-CRP	1.054	1.036-1.073	< 0.001			
PLT	0.993	0.990-0.997	< 0.001	0.996	0.984-1.008	0.523
PDW	1.116	0.995-1.251	0.06			
MPV	1.439	1.082-1.915	0.012	1.876	0.784-4.49	0.158
TBIL	1.084	1.04-1.13	< 0.001	1.023	0.925-1.131	0.658
Cre	1.005	1.001-1.008	0.004	0.993	0.981-1.005	0.26
TnI						
≥ 0.01	66.731	19.556-227.712	< 0.001	55.199	5.686-535.903	0.001
< 0.01	Reference					
DD	1.608	1.326-1.951	< 0.001	1.089	0.941-1.259	0.253
PT	2.677	2.004-3.576	< 0.001	2.235	1.097-4.554	0.027
APTT	1.310	1.190-1.443	< 0.001	1.057	0.809-1.381	0.684
TT	0.943	0.822-1.082	0.404			
FIB	2.594	1.917-3.509	< 0.001	0.85	0.407-1.774	0.665

Variables with $P < 0.05$ in univariate analysis were entered in multivariate analysis, while variables with strong collinearity or correlation were excluded: IL-6, hs-CRP, PDW, N#, and Hb. OR: Odds ratio; CI: Confidence interval; WBC: White blood cell count; N#: Neutrophils; RBC: Red blood cell count; Hb: Hemoglobin concentration; TPO: Thrombopoietin; IL: Interleukin; hs-CRP: High-sensitivity C-reactive protein; PLT: Platelet count; PDW: Platelet distribution width; MPV: Mean platelet volume; TBIL: Total bilirubin; Cre: Creatinine; TnI: Troponin I; MAP: Mean arterial pressure; DD: D-dimer; PT: Prothrombin time; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; FIB: Fibrinogen.

roles in inflammation, tissue repair, and pathogen killing[32], which are processes that consume platelets. Therefore, platelet depletion in sepsis could be due to the host response to the infection, and the much-increased TPO levels could be a compensatory mechanism to activate platelet production[32]. There may be a negative feedback mechanism in this process, which must be further confirmed *in vitro*. Future studies must elucidate the cause-to-effect relationships between TPO and clinical events.

Inflammatory factors can increase TPO production by the liver[7,9-11], as suggested in the present study by the correlations between TPO, hs-CRP, and inflammatory factors (IL-21 and IL-6). Furthermore, we found that TPO had superior diagnostic efficiency in sepsis prediction by using the

Table 3 Correlation analyses between indicators and thrombopoietin

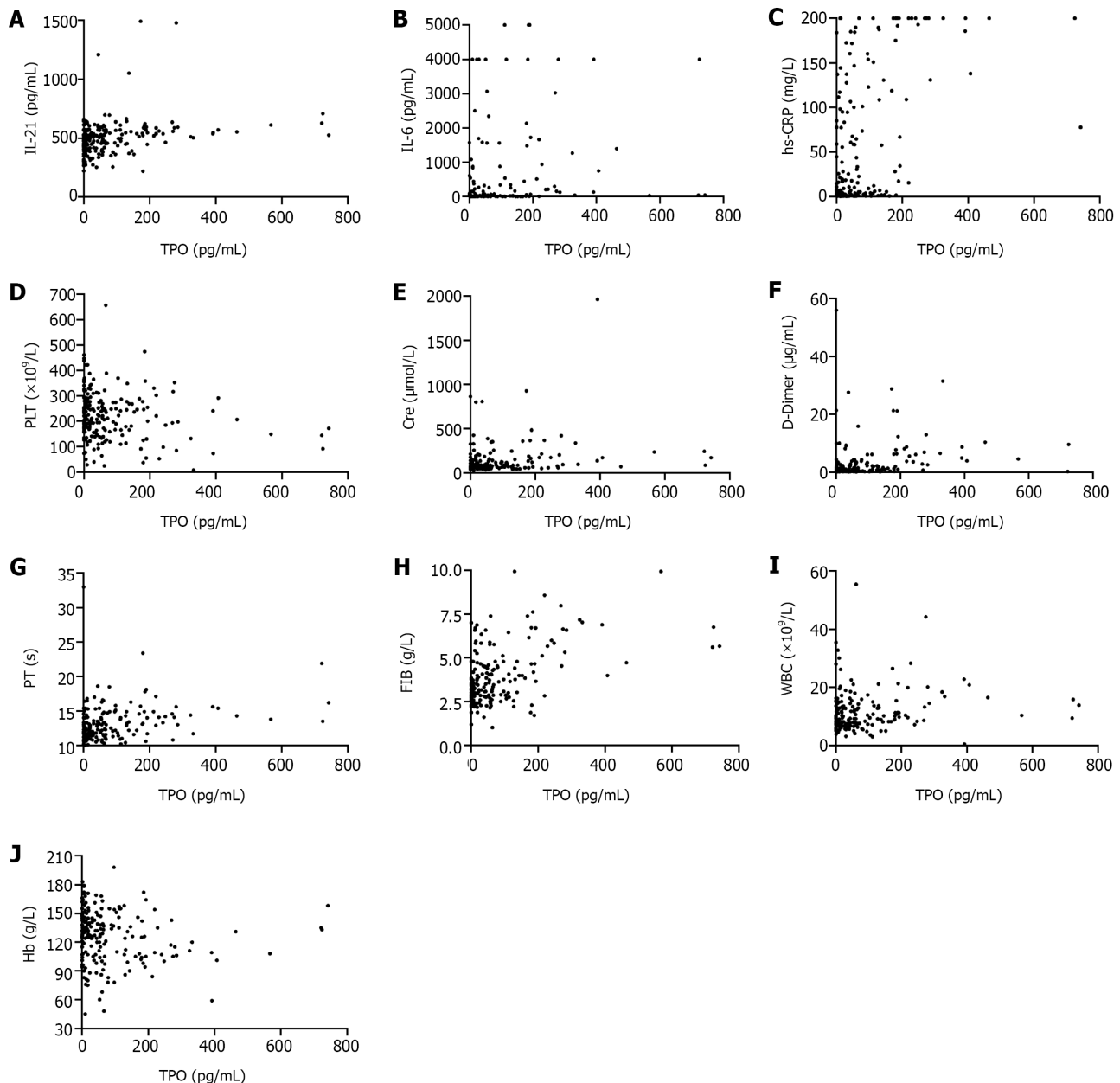
Factor	Spearman correlation coefficient	P value
Age, yr	0.138	0.052
TPO	1	
IL-21	0.362	< 0.001
IL-6	0.385	< 0.001
hsCRP	0.531	< 0.001
PLT	-0.177	0.012
PDW	-0.043	0.556
MPV	0.034	0.641
P-LCR	0.017	0.819
TBIL	0.118	0.098
Cre	0.219	0.002
DD	0.453	< 0.001
PT	0.311	< 0.001
APTT	0.203	0.004
TT	-0.307	< 0.001
INR	0.310	< 0.001
FIB	0.438	< 0.001
WBC	0.176	0.013
N#	0.235	0.001
RBC	-0.246	< 0.001
Hb	-0.209	0.003

TPO: Thrombopoietin; IL-21: Interleukin-21; IL-6: Interleukin-6; hs-CRP: High-sensitivity C-reactive protein; PLT: Platelet count; PDW: Platelet distribution width; MPV: Mean platelet volume; P-LCR: Platelet large cell ratio; DD: D-dimer; TBIL: Total bilirubin; Cre: Creatinine; PT: Prothrombin time; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; FIB: Fibrinogen; WBC: White blood cell count; N#: Neutrophils; RBC: Red blood cell count; Hb: Hemoglobin concentration.

ROC curve analysis. Therefore, TPO in the context of sepsis could be an acute-phase protein. Segre *et al* [33] reported that TPO levels could be used as an early biomarker for sepsis and used to assess sepsis severity in patients with systemic inflammatory response syndrome (SIRS). The reason why TPO might be considered an acute phase marker is that inflammatory thrombocytosis is related to acute phase reactants that act through TPO to increase the PLT[34] and that TPO levels are increased through the action of IL-6 on the liver[34,35]. TPO has been suggested by Ceresa *et al*[36] to be an acute-phase protein correlated with IL-6 levels in various inflammatory conditions. Acute-phase proteins all share the characteristic of being increased together in the acute phase of inflammation. Accordingly, the present study showed significant correlations between the levels of IL-6, IL-21, and hsCRP, which are acute-phase markers[37].

The present study also showed that WBC, IL-21, TnI, and PT were independently associated with sepsis. Elevated WBC is already included in the SIRS model[1]. IL-21 plays a central role in the proliferation, survival, differentiation, and function of lymphoid, myeloid, and epithelial cells in the differentiation of B cells into plasma cells and various T cells and in autoimmune diseases[38]. Still, data about IL-21 in sepsis are scarce. One study reported that IL-21 could be a biomarker of neonatal sepsis[39]. TnI is a marker of cardiac injury and could be a marker of hypoperfusion in sepsis[40]. Sepsis is also associated with coagulopathy, as shown by abnormal PT[41,42]. Hence, besides TPO, the other independent biomarkers of sepsis identified by the present study are supported by the literature. Indeed, TPO has a protective effect on the myocardium and brain[14-18]. Still, future studies could aim to develop predictive models that could include TPO levels and other factors. That will be undertaken in future studies.

Of note, the correlation analyses indicated various metabolic variables to be associated with sepsis, such as Cre, DD, APTT, TT, INR, FIB, RBC, and Hb. The exact prognostic significance of TPO in relation to those metabolic markers remains to be determined. Still, TPO levels are elevated in renal injury[43],



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Figure 1 Correlation analyses between thrombopoietin levels and indicators. A: Interleukin (IL)-21 ($r = 0.362$, $P < 0.001$); B: IL-6 ($r = 0.385$, $P < 0.001$); C: High-sensitivity C-reactive protein ($r = 0.531$, $P < 0.001$); D: Platelet count ($r = -0.177$, $P = 0.012$); E: Creatinine ($r = 0.219$, $P = 0.002$); F: D-dimer ($r = 0.453$, $P < 0.001$); G: Prothrombin time ($r = 0.311$, $P < 0.001$); H: Fibrinogen ($r = 0.438$, $P < 0.001$); I: white blood cells (WBC) ($r = 0.176$, $P = 0.013$); J: Hemoglobin concentration ($r = -0.209$, $P = 0.003$). TPO: Thrombopoietin; IL-6: Interleukin-6; IL-21: Interleukin-21; hs-CRP: High-sensitivity C-reactive protein; PLT: Platelet count; Cre: Creatinine; DD: D-dimer; PT: Prothrombin time; FIB: Fibrinogen; Hb: Hemoglobin concentration.

and renal injury usually carries a poor prognosis in sepsis[44]. Anemia[45] and coagulopathy[46] are also associated with a poor prognosis in sepsis. Microvascular thrombosis, as one of the major complications after sepsis, is caused by the activation of coagulation[46]. The strength of this study is that we presented result that TPO is significantly correlated with thrombotic index (D-Dimer) and coagulation indicators (APTT, TT, INR, and FIB); however, the direct relationship between TPO and prothrombotic process of sepsis is doubted. Despite the fact that a previous study[20] argued that TPO could promote platelet aggregation in sepsis, more studies *in vitro* are needed to confirm it. TPO levels are high in patients with an acute respiratory syndrome, in whom it could participate in the development of thrombocytosis[47]. Still, given the cross-sectional nature of the study, the causal relationships between TPO and these markers remain to be examined.

This study has limitations. The retrospective study design limited the data that could be analyzed to the data available in the charts. All patients were from a single center, resulting in a small sample size, and the bias cannot be avoided from this study. Although the eligibility criteria were relatively broad, using such criteria will inevitably introduce some selection bias. The results of this study can only

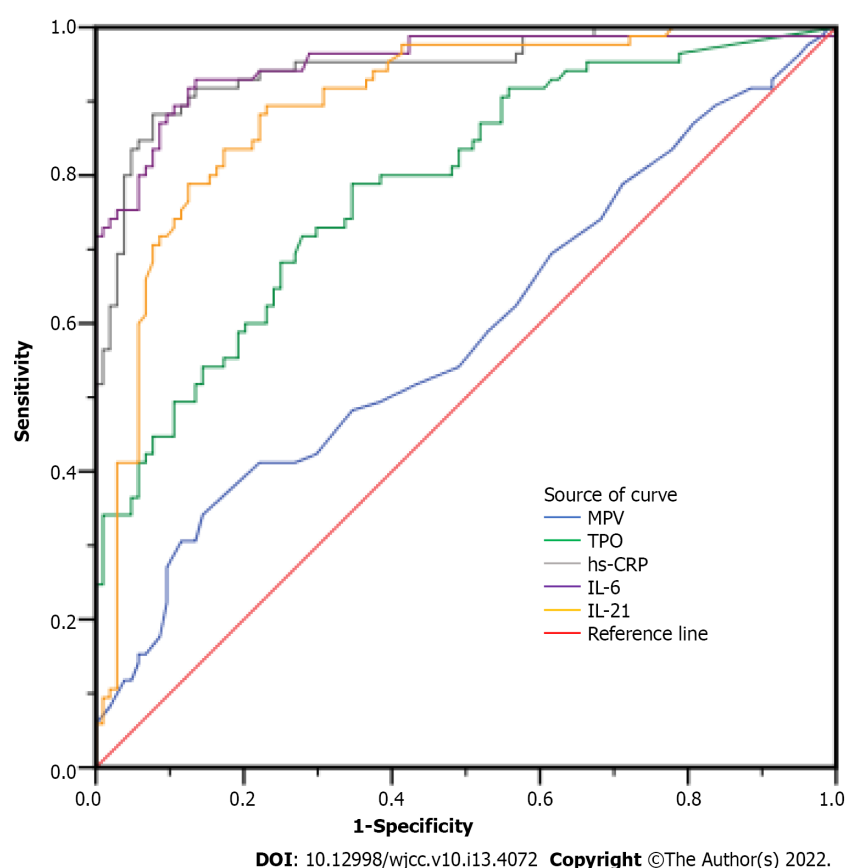


Figure 2 Receiver operator characteristic curve analysis for sepsis. Thrombopoietin (TPO) [area under the curve (AUC) = 0.788; 95%CI: 0.723-0.852; $P < 0.001$]; mean platelet volume (AUC = 0.589; 95%CI: 0.506-0.671; $P = 0.036$); high-sensitivity C-reactive protein (AUC = 0.947; 95%CI: 0.915-0.979; $P < 0.001$); interleukin (IL)-6 (AUC = 0.953; 95%CI: 0.922-0.984; $P < 0.001$); IL-21 (AUC = 0.895; 95%CI: 0.848-0.941; $P < 0.001$). At a TPO cut-off level of 28.51 pg/mL, the sensitivity was 79%, and specificity was 65%. MPV: Mean platelet volume; TPO: Thrombopoietin; hs-CRP: High-sensitivity C-reactive protein; IL-6: Interleukin-6; IL-21: Interleukin-21.

explain correlations among various biomarkers associated with sepsis, but it cannot explain their potential causality or the prognosis of sepsis. The patients could not be subgrouped according to mild sepsis and septic shock based on the available data. It also needs prospective, multicenter trials with a large sample size to provide high-level evidence of the role of TPO in sepsis.

CONCLUSION

In summary, TPO levels are independently associated with sepsis. The results suggest that TPO might be an acute phase response protein in patients with infection. Increased TPO levels in sepsis may result from the involvement of platelets in the inflammation or a negative feedback effect caused by decreased platelets.

ARTICLE HIGHLIGHTS

Research background

Elevated levels of thrombopoietin (TPO) are often accompanied by a decrease in platelet count (PLT) in systemic infectious conditions, contrary to the view that TPO promotes platelet production under physiological conditions. In addition, whether TPO mediates organ damage in sepsis remains controversial.

Research motivation

The role of TPO in sepsis is not well determined. It is necessary to understand the role of TPO in the pathophysiological process of sepsis and the relationship between TPO and other inflammatory factors, platelet indices, and thrombotic indicators.

Research objectives

To explore the relationships between TPO and inflammatory factors, platelet indices, and thrombotic indicators in sepsis.

Research methods

Patients with sepsis diagnosed and treated at the Emergency Medicine Department were enrolled in this study. Patients without sepsis were included as controls. Clinical and laboratory parameters were collected. Pearson's and Spearman's correlation analyses were used for bivariable analyses of data with a normal- and non-normal distribution, respectively. Logistic regression models were used for univariable and multivariable regression to analyze the risk factors of sepsis. Receiver operator characteristic analysis was executed to evaluate the discriminative ability of the monograph.

Research results

TPO levels were higher in the sepsis group than in controls, but platelets were lower. TPO was an independent risk factor associated with sepsis. TPO levels were positively correlated with inflammatory factors and some thrombotic indicators, and negatively correlated with PLT. TPO had fair predictive value in distinguishing septic patients and non-septic patients.

Research conclusions

TPO levels are independently associated with sepsis. TPO might be an acute-phase response protein in patients with infection.

Research perspectives

Future studies will further investigate whether TPO has prognostic value in sepsis.

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FOOTNOTES

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Informed consent statement: Informed consent to the study is not required due to the retrospective nature of this study.

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