88540_Auto_Edited.docx

WORD COUNT 2350
TIME SUBMITTED 15-DEC-2023 04:59PM
PAPER ID 105515561

Name of Journal: *World Journal of Critical Care Medicine*

Manuscript NO: 88540

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

The predictive value of thrombocytopenia for bloodstream infection in patients with sepsis and septic shock

Xia Li, Sheng Wang, Jun Ma, Su Ge Bai, Su Zhen Fu

Abstract

BACKGROUND

Thrombocytopenia is common in patients with sepsis and septic shock.

AIM

The aim of this study was to analyse a decrease in the number of platelets for predicting blood stream infection in patients with sepsis and septic shock in the intensive care unit (ICU)

METHODS

A retrospective analysis of patients admitted with sepsis and septic shock in Xingtai People Hospital was revisited. Patient population characteristics and laboratory data were collected for analysis

RESULTS

The study group consisted of 85 (39%) inpatients with blood stream infection, and the control group consisted of 133 (61%) with negative or contamination. The percentage decline in platelet counts (PPC%) in patients positive for pathogens (57.1 (41.3-74.6)) was distinctly higher than that in the control group (18.2 (5.1–43.1)) ($p<0.001$), whereas

the PPC was insignificantly different among gram-positive bacteraemia, gram-negative bacteraemia, and fungi. Using receiver operating characteristic (ROC) curves, the AUC of the platelet drop rate was 0.839 (95%CI: 0.783-0.895).

CONCLUSION

The percentage decline in platelet counts is sensitive in predicting blood stream infection in patients with sepsis and septic shock. However, it cannot identify gram-positive bacteraemia, gram-negative bacteraemia, and fungi.

INTRODUCTION

Blood stream infection (BSI) is a life-threatening condition caused by the presence of microorganisms, generally bacteria or fungi, in blood. The ability to diagnose BSI early can have a significant impact on patient outcomes. Platelets constantly roam the vascular system and play an active role in pathogen capture. Platelets can kill bacterial pathogens directly *via* microbicidal proteins, known as thrombocidins [1]. Platelets are able to release cytokines, recruit leukocytes, interact with bacteria and the endothelium, and promote microthrombi formation [2,3]. Either a relative or an absolute decrease in the platelet number is often seen in patients who most likely develop sepsis and septic shock. However, few reports have documented the relationship between a drop in platelet counts and BSI. The aims of this study were to determine the diagnostic ability of the percentage decline of platelet counts (PPC) for predicting the presence of BSI and evaluating the cut-off point for detecting BSI.

MATERIALS AND METHODS

We conducted a retrospective cohort study at Xingtai People's Hospital, Hebei Province, China, which has 2200 beds serving the local residents. Adult patients (age ≥ 18 years) who were admitted to the ICU with a diagnosis of sepsis and septic shock and stayed at least 3 days in the ICU were included in the study. The exclusion criteria

included haematologic disease, acute bleeding, history of platelet disorders, cirrhosis, and use of chemotherapy (in the last 30 days prior to admission). The following variables were collected from the electronic medical records: patient population characteristics (age, sex); underlying disease (hypertension, diabetes mellitus, COPD, cardiovascular disease, cerebrovascular disease); laboratory data (aetiology, daily platelet counts, white blood cell count, neutrophil count, haemoglobin, C-reactive protein, procalcitonin, blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, serum bilirubin, serum albumin, fibrinogen, D-dimer, PT, APTT); source of infection; primary diagnosis, mechanical ventilation, requirement for renal replacement therapy; and Acute Physiology and Chronic Health Evaluation II score (APACHE-II score). This study was a retrospective clinical data analysis and no invasive procedure were made on patients.

According to the sepsis 3 guidelines [4], sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The clinical criteria for sepsis include suspected or documented infection and an acute increase in two or more Sequential Organ Failure Assessment (SOFA) points as a proxy for organ dysfunction. Septic shock was defined by the clinical criteria of sepsis and vasopressor therapy needed to elevate mean arterial pressure ≥65 mmHg and lactate>2 mmol/L (18 mg/dL) despite adequate fluid resuscitation. Blood cultures were drawn from the patients within 1 h after ascertaining the patient had sepsis or septic shock. BSI was defined as one or more bacterial species in blood samples. Blood stream infection caused by coagulase-negative staphylococci was made after careful evaluation by the doctor according to the clinical manifestations and treatment effect. Negative specimen culture was defined as negative culture for 5 days. Daily platelet counts began to be recorded on the day when the blood cultures were taken. If the platelet counts were performed twice or more within 24 h, we recorded the lowest count for analysis. The rate of the drop of Platelets was calculated by the formula $(\text{Platelet}_1 - \text{Platelet}_{low})/\text{Platelet}_1$, where Platelet_1 is the Platelet value at the time of drawing blood cultures, and Platelet_{low} is obtained as the lowest platelet value within the following 3 days.

RESULTS

Patients' characteristics

During the study period, a total of 218 patients with sepsis and septic shock were enrolled. Of these, 85 had positive blood cultures, and 133 had negative cultures or contamination. Demographic, clinical and laboratory characteristics are presented in Table 1 and Table 2. The median age was 63 years, and 122 (56%) patients were male. There was no difference in age, sex, underlying comorbidities (hypertension, diabetes, cardiovascular disease, COPD), APACHE II score, mechanical ventilation, renal replacement therapy, or 28-day mortality between patients with positive blood cultures and those with negative blood cultures or contamination. However, patients with cerebrovascular disease had fewer positive blood cultures (P = 0.044). Regarding the primary source of infection, respiratory tract infections were the most common infections in patients in the ICU, which were detected in 101 patients (46.3%). Patients with positive blood cultures were more often admitted with hepatobiliary and urinary infections and less often with respiratory tract infections.

Laboratory findings

At admission, patients with positive blood cultures had higher levels of procalcitonin, neutrophils, and C-reactive protein but not white blood cell counts than those with negative cultures or contamination (Table 2). Remarkable differences were also found in the levels of PT, APTT, D-dimer, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and creatinine. These indicators were significantly higher in patients with positive blood cultures than in those with negative cultures or contamination. No significant differences were found for fibrinogen, urea nitrogen, serum albumin, haemoglobin, or glycosylated haemoglobin (P> 0.05).

Among the 85 bacteraemia episodes, 24 were caused by gram-positive bacteria, 59 by gram-negative bacteria and 2 by fungi. The most commonly isolated bacterial species were *Escherichia coli* (n = 36) and *Klebsiella pneumoniae* (n = 15), which accounted for 60% of blood infections (Table 3).

Daily platelet count

The daily platelet count over time was recorded as the median (25th, 75th percentile) (Figure 1). The median platelet count dropped to a nadir of 60 (range, 30-128)×109/L in the group positive for pathogens and 148 (range, 73-200)×109/L in the group negative for pathogens or contamination on the fourth day after admission to the ICU and subsequently increased. The platelet count did not differ between the two groups on the first day. From Day 2 to Day 7, the platelet count in the pathogen-positive group was significantly lower than that in the control group (p<0.05).

The percentage decline of platelet counts (PPC) in different groups (Fig2).

In the present study, the percentage decline in platelet counts (PPC%) in patients who were positive for pathogens (57.1 (41.3-74.6)) was distinctly higher than that in patients who were negative or had contamination (18.2 (5.1–43.1)) (p <0.001) (Figure A). There were also significant differences in the lowest platelet count between the patients who were positive for pathogens (54 (27-119)) and those who were negative or contaminated (140 (77-182)) (p <0.001) (Figure B). However, in the subgroup of positive with pathogens, the PPCs were not significantly different among gram-positive the bacteraemia, gram-negative bacteraemia, and fungi groups (p > 0.05).

ROC curves of serum biomarkers

The ROC curves were made for PPC predicting blood stream infection (Figure 3). The areas under the ROC curves (AUCs) were calculated to evaluate the biomarkers (PPC, PCT, lowest platelet count, CRP, and neutrophil percentage) for determining the presence of bacteraemia. PPC presents a high diagnostic utility for predicting BSI. Its predictive ability is greater than that of PCT; the AUC of PPC was 0.839 (95%CI: 0.783-0.895). Additionally, that of PCT was 0.718 (95%CI: 0.644-0.791), whereas CRP and neutrophil percentage did not detect BSI (p > 0.05). Using the lowest platelet count, the area under the ROC curve was 0.274 (95%CI: 0.201-0.347), showing a low, not significant accuracy for BSI diagnosis. At a cut-off point of 35%, the sensitivity and specificity of PPC were 0.84 and 0.73, respectively, and the Youden index was 0.57. At

cut-off points of 50% and 60%, the sensitivity was reduced to 0.63 and 0.44, respectively, but yielded high specificities of 0.82 and 0.90.

DISCUSSION

Early recognition of blood stream infection and establishing early treatment are important for patients with infection. In this retrospective cohort, we demonstrated that the ratio of platelet drop was independently associated with bloodstream infection. This is the first study to investigate the association between them. The study encompassed 218 sepsis and sepsis shock patients, in whom demographic variables and clinical and laboratory characteristics are described. Patients with blood stream infection were associated with the severity of sepsis and sepsis shock, as indicated by higher inflammatory biomarkers (PCT, CRP, neutrophil), higher percentage decline of platelet counts, liver and kidney function injury, and coagulation disorder (PT, APTT, D-dimer), compared to the patients who did not have a blood stream infection. It has been reported that bacteraemia is an independent risk factor for nosocomial infection-related mortality[5]; however, in our study, 28-day mortality was not significantly different between bacteraemia and nonbacteraemic patients. This could be due to respiratory failure caused by a respiratory infection, which was detected in 46.3% of patients in the ICU in our study, it was the main cause of death and these patients had a low incidence of blood flow infection. We recorded the daily platelet count and found that the median (IQR) duration of thrombocytopenia occurred on Day 4 after admission to the ICU (Figure 1), which is in accordance with the results of previous research [6,7].

In our study, the most common organism isolated was *Escherichia coli*, with *Klebsiella pneumoniae* being the second most common pathogen in blood infections. This is consistent with a previous finding showing that *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae* and *Streptococcus pneumoniae* were the most commonly isolated organisms in community-acquired bloodstream infections [8]. In recent years, it has been reported that respiratory tract, urinary tract, and intra-abdominal infections are the main sources of sepsis and sepsis shock [9,10,] and gram-negative bacteraemia has a higher

frequency in the ICU [11]. Similarly, our study also showed that respiratory tract infection was the main reason for admission to the ICU but had a lower blood flow infection rate. However, the urogenital and hepatobiliary tract have a higher incidence of bloodstream infection for patients in the ICU.

Our results confirm that the rate of platelet drop but not the lowest platelet count has a high predictive ability for bloodstream infection. It has been reported that PCT levels are a good biomarker for bacterial infections, and PCT has been introduced into clinical use [12,13]. Similarly, our study supports this option. Comparing other inflammatory markers, the diagnostic utility of PPC (AUC of 0.839) was significantly higher than that of PCT (AUC of 0.718), CRP (AUC of 0.583) and neutrophils (AUC of 0.564). A cut-off point of 35% for PPC achieved a sensitivity of 84% and a specificity of 73%, whereas a cut-off point of 50% was correlated with a sensitivity of 62.7% and a specificity of 82%. A cut-off point of 60% reduced the sensitivity to 44%, but the specificity reached 90.1%. Therefore, clinicians should consider bloodstream infections in sepsis and sepsis shock patients with a rapid drop in platelet count.

Thrombocytopenia is very common in patients with sepsis and sepsis shock, and there are several putative mechanisms, as stated below. First, the interactions between bacteria and platelets cause the consumption of platelets. Bacteria can bind to platelets *via* receptors either directly or indirectly, suggesting that they may induce aggregation, which has been described for *Streptococcus sanguinis*, *S. epidermidis*, or S. pneumoniae infections [14]. Preclinical findings from murine models suggested that platelets bind to adherent neutrophils through Toll-like receptor 4 and form neutrophil extracellular traps (NETs). NETs have the greatest capacity for bacterial trapping and ensnared bacteria within the vasculature [15]. In addition to containing pathogens, human and murine platelets can exert direct microbicidal activity, such as releasing platelet microbicidal proteins (PMPs) to kill pathogens [16,17]. Second, bacterial infections cause damage to the vascular endothelial lining and the release of inflammatory factors, accelerating adhesion, removal and immune-mediated destruction of platelets. Third, bacterial infections cause marrow depression, decreasing the production of platelets.

Our study has some limitations. 1) We only recorded platelet changes within 7 days after admission to the ICU in sepsis and sepsis shock patients and did not consider changes in platelets in patients with secondary infection during ICU hospitalization, which may affect mortality. 2) In our study, the median time of the platelet count dropping to a nadir was on Day 4. However, the platelet counts were very low in some patients when they came to the hospital, and their platelets dropped to the lowest value on Day 2 after admission, which affected the ratio of platelet decline. 3) We used culture-based methods as the gold standard for the diagnosis of bloodstream infection, and the initiation of empirical antimicrobial therapy in some patients significantly reduced the sensitivity of blood cultures. Future studies can be used to determine if there is a drop in platelet count in animal experiments of animals with bloodstream infection.

CONCLUSION

In conclusion, the percentage decline in platelet counts is sensitive in predicting BSI in patients with sepsis and sepsis shock. However, it cannot identify gram-positive bacteraemia, gram-negative bacteraemia, and fungi. Dynamic detection of platelet counts appears to have an early alert for the clinician identifying the site of infection and evaluating serious infection. This will guide the performance of blood cultures and the use of empirical antibiotics.

88540_Auto_Edited.docx

ORIGINALITY REPORT

8%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	95 words — 4%
2	wprim.whocc.org.cn Internet	18 words — 1%
3	f6publishing.blob.core.windows.net Internet	17 words — 1%
4	journals.viamedica.pl Internet	17 words — 1%
5	hdl.handle.net Internet	16 words — 1%
6	Jiaying Li, Xiuqin Ma, Xuetao Zeng, Chen Zhou, Taofeng Zhu. "Risk Factors of Readmission Within 90 Days for Chronic Obstructive Pulmonary Disease Patients with Frailty and Construction of an Early Warning Model", International Journal of Chronic Obstructive Pulmonary Disease, 2023 Crossref	12 words — < 1%
7	Lauren Allen, Rachel Bartash, Grace Y. Minamoto, Kelsie Cowman et al. "Impact of Narrowing Perioperative Antibiotic Prophylaxis for Left Ventricular Assist Device Implantation", Transplant Infectious Disease, 2022 Crossref	12 words — < 1%

8 www.my.onexamination.com
Internet

12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS