Hematological parameters in patients with bloodstream infection: A retrospective observational study

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Abstract

Introduction: To date, the relationship between the causative pathogens and the changes of hematological parameters was rarely referred and deserves further investigation.

Methodology: A total of 825 adult patients, including 134 negative blood cultures patients and 691 bloodstream infection (BSI) patients, were screened for eligibility in this study. Receiver operating characteristic curves and binary logistic regression models were used to assess the power of hematological parameters to distinguish patients with BSI caused by different pathogens.

Results: Except for platelet-to-lymphocyte ratio (PLR) and platelet larger cell count (P-LCC), the other hematological parameters investigated in the study were significantly different in patients with BSI caused by different pathogens, including Candida. The specific combinations of lymphocyte count (LYM), platelet count (PLT), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), MPV-to-PLT ratio (MPV/PLT), platelet larger cell ratio (P-LCR), and C-reactive protein (CRP) can improve the ability to distinguish various BSI from negative blood cultures. The highest area under the curve was 0.753 (95% CI 0.709-0.797) for positive blood cultures, 0.715 (95% CI 0.658-0.771) for Gram-positive pathogens BSI, 0.777 (95% CI 0.730-0.824) for Gram-negative pathogens BSI, 0.797 (95% CI 0.747-0.846) for Escherichia coli BSI, 0.943 (95% CI 0.899-0.987) for Enterobacter aerogenes BSI, 0.830 (95% CI 0.740-0.921) for Pseudomonas aeruginosa BSI, and 0.767 (95% CI 0.695-0.839) for Staphylococcus aureus BSI.

Conclusions: The specific combinations of hematological parameters can improve the power to distinguish patients with BSI caused by different pathogens. Attention to these parameters can be easily integrated into daily medical activities, without extra costs.

Key words: bloodstream infection; blood cultures; hematological parameters; differential ability.

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cells and monocytes, enhancing adaptive immune responses [15]. Moreover, during BSI, platelets detect pathogens via their Toll-like receptors [16], glomming onto neutrophils. In response, the neutrophils release neutrophil extracellular traps (NETs), webs of DNA, ensnaring pathogens [17,18]. Platelets are needed for the recruitment of neutrophils to tissues of inflammation and infection [19]. Additionally, pathogens that enter the bloodstream will produce diverse extracellular proteins and toxins, resulting in platelet activation or inhibition of platelet activation [20]. Taken together, it is apparent that the interaction between platelets and pathogens not only has important consequences for the pathophysiological response to pathogenic infection but also affect PLT and other platelet-related parameters.

To date, the relationship between the causative pathogens and the changes of hematological parameters was rarely referred and deserves further investigation. Given the protective role of neutrophils, lymphocytes, and platelets in immunity against pathogens, in this retrospective observational study, we sought to systematically investigate the changes of hematological parameters and their differential ability in patients with BSI caused by different pathogens.

Methodology
Study design and data collection
This retrospective observational study was conducted using laboratory and clinical data collected from the microbial information system, laboratory information system, and laboratory electronic medical record system of the Second Hospital of Anhui Medical University, a 2,200-bed tertiary teaching hospital in Hefei (8.0 million inhabitants), Anhui province, China. Since the vast majority of our daily blood cultures were negative, to balance the sample size between groups, we collected data between February 2011 and June 2019 for positive blood cultures and May 2019 to June 2019 (randomly selected) for negative blood cultures.

The inclusion criteria were as follows: (1) age of at least 18 years; (2) clinical suspicion of BSI; and (3) C-reactive protein (CRP), hematological tests, and blood culture ordered, simultaneously. The exclusion criteria were as follows: (1) concomitant hematological diseases; (2) cancer; (3) preexisting immunodeficiency; (4) receiving chemotherapy such as glucocorticoids; (5) chronic liver disease; (6) splenomegaly; and (7) massive hemorrhage.

Instrument and reagent
Serum CRP concentration was detected by Dimension EXL with LM automatic biochemistry analyzer (Siemens Healthcare Diagnostics, Newark, DE). Hematological parameters, such as NEU, lymphocyte count (LYM), PLT, mean platelet volume (MPV), platelet distribution width (PDW), and platelet larger cell ratio (P-LCR), were determined on Sysmex XE2100 hematology analyzer (Sysmex Corporation, Kobe). Subsequently, plateletcrit (PCT), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume-to-platelet count ratio (MPV/PLT), and platelet larger cell count (P-LCC) were calculated. Blood cultures were incubated in BACTEC FX automatic blood culture system (Becton Dickinson, Sparks, MD). The suspected positive bottles were removed and subjected to culturing tests by using Colombian blood agar plate, chocolate agar plate, and anaerobe 5% sheep blood agar plate [10]. Identification of microorganisms was performed with VITEKII Compact system (BioMérieux, Marcy L’Etoile) and matrix-assisted laser desorption/ionization time-of-flight Microflex LT mass spectrometer (Bruker Daltonics, Hamburg). When no bacterial growth was detected for five days, the result was considered negative.

Statistical analysis
Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL). Firstly, all variables were tested for normal distribution by the Kolmogorov-Smirnov test. In accordance with the result of this test, the statistical significance of differences was tested using the Student's t-test or Mann-Whitney U test (two groups’ comparison). In the case of multigroup comparison, One-Way ANOVA (LSD) or nonparametric (Kruskal-Wallis) test was applied. Through the above steps, we examined the relationship between all independent variables and dependent variable, consequently, some independent variables that may be meaningless were filtered out. Then, binary logistic regression analysis was conducted. Odds ratios (OR) and 95% CI were calculated to determine the strength of the association between hematological parameters and BSI pathogens. Besides, receiver operating characteristic (ROC) curves were constructed to investigate area under the curve (AUC), 95% confidence intervals (CI), sensitivity, specificity, and cut-off value of hematological parameters [21]. Continuous variables were reported as mean values ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables
were expressed as count and percentage. Two-sided p < 0.05 was considered to represent a statistically significant difference.

Ethics statement

Ethical approval was not required as all data used in this study were acquired retrospectively from the microbial information system, laboratory information system, and laboratory electronic medical record system.

Results

Demographic and laboratory characteristics of study subjects

A total of 825 patients were included in the study. Blood cultures were positive in 691 patients. The demographic characteristics of all patients are summarized in Table 1. As for gender distribution, there was no significant difference between positive and negative blood cultures. Nevertheless, patients with positive blood cultures were older than those with negative blood cultures (p = 0.001). Furthermore,
patients with isolated Gram-negative pathogens were older than that with Gram-positive pathogens (p < 0.001) and negative blood culture (p < 0.001) (Table 2). Moreover, patients with E. coli BSI were older than those with S. aureus BSI (p < 0.001) and negative blood culture (p < 0.001) (Table 3).

Changes of hematological parameters in negative and positive blood cultures

Other than PLR (p = 0.881) and P-LCC (p = 0.122), the other hematological parameters were significantly different between the two groups. NEU, MPV, PDW, PCT, MPV/PLT, P-LCR, and P-LCR were higher in patients with positive blood cultures, while PCT, LYMPH, and PLT were lower (Table 1).

Table 3. Demographic and laboratory characteristics of patients with negative blood cultures and different pathogens positive blood cultures.

| Characteristics | Negative | S. epidermidis | S. haemolyticus | S. aureus | E. faecalis | E. faecium | Candida | P value |
|-----------------|----------|---------------|----------------|----------|-------------|------------|---------|---------|
| Number of patients | 134 | 106 | 28 | 92 | 27 | 25 | 20 | — |
| Males, number (%) | 67 (50.0%) | 61 (57.5%) | 22 (78.6%) | 59 (64.1%) | 17 (63.0%) | 12 (48.0%) | 8 (40.0%) | — |
| Age (years) | 6.95 (4.48-10.14) | 7.58 (5.42-11.62) | 8.47 ± 5.11 | 9.16 ± 5.32 | 8.63 ± 4.34 | 11.17 ± 6.82 | 11.04 ± 10.26 | <0.001 |
| NEU (10^3/L) | 1.06 (0.72-1.35) | 0.93 (0.58-1.53) | 1.06 ± 0.49 | 0.90 ± 0.57 | 0.89 ± 0.70 | 0.92 ± 0.46 | 0.73 ± 0.52 | <0.001 |
| PDW (%) | 15.90 (13.00-16.30) | 15.75 (13.02-16.58) | 14.50 ± 3.52 | 16.10 (13.92-16.98) | 15.61 ± 3.25 | 15.26 ± 2.31 | 14.28 ± 2.96 | 0.01 |
| NLR | 0.20 (0.08-0.72) | 0.22 (0.01-0.11) | 0.16 ± 0.06 | 0.15 (0.11-0.22) | 0.17 ± 0.10 | 0.23 ± 0.16 | 0.20 ± 0.11 | <0.001 |
| CRP (g/L) | 7.58 (4.12-11.69) | 8.38 (4.46-15.16) | 10.29 ± 8.55 | 10.48 (8.61-16.21) | 14.24 ± 11.77 | 15.11 ± 13.52 | 14.39 (8.13-27.10) | <0.001 |
| PLR | 50.70 (24.40-114.65) | 81.39 ± 55.13 | 119.88 ± 75.13 | 146.45 ± 106.06 | 103.41 ± 78.87 | 110.14 ± 85.46 | 138.45 ± 77.37 | <0.001 |
| P-LCR (%) | 27.02 ± 11.77 | 29.91 ± 9.76 | 31.33 ± 9.14 | 29.09 ± 9.61 | 32.71 ± 11.95 | 31.10 ± 8.61 | 27.76 ± 8.06 | <0.001 |

Table 3 (continued). Demographic and laboratory characteristics of patients with negative blood cultures and different pathogens positive blood cultures.

| Characteristics | E. coli | K. pneumoniae | E. aerogenes | E. cloacae | P. aeruginosa | A. baumannii | P value |
|-----------------|---------|---------------|-------------|-----------|--------------|-------------|---------|
| Number of patients | 235 | 80 | 11 | 20 | 30 | 17 | — |
| Males, number (%) | 82 (34.9%) | 48 (60.0%) | 11 (54.5%) | 12 (60.0%) | 19 (63.3%) | 15 (88.2%) | — |
| Age (years) | 63.00 (50.00-74.00) | 60.46 ± 14.55 | 54.09 ± 13.49 | 65.90 ± 11.90 | 63.77 ± 16.34 | 52.88 ± 18.48 | <0.001 |
| NEU (10^3/L) | 10.06 (7.09-14.09) | 11.06 ± 6.16 | 12.17 ± 12.21 | 9.59 ± 4.37 | 11.38 ± 9.00 | 9.70 ± 6.47 | <0.001 |
| MPV (FL) | 0.66 (0.46-0.94) | 0.80 ± 0.53 | 0.50 ± 0.19 | 0.78 ± 0.40 | 0.90 ± 0.56 | 1.07 ± 0.67 | <0.001 |
| PLT (10^3/L) | 145.82 ± 78.64 | 143.40 ± 83.54 | 127.54 ± 45.86 | 134.15 ± 61.58 | 161.43 ± 105.41 | 182.76 ± 118.23 | <0.001 |
| MPV (%) | 10.92 ± 1.52 | 11.08 ± 1.49 | 10.80 ± 1.22 | 10.88 ± 1.64 | 10.82 ± 1.27 | 10.59 ± 1.54 | <0.001 |
| PDW (%) | 16.10 (14.50-16.70) | 16.40 (13.90-17.00) | 16.41 ± 1.41 | 15.84 ± 2.39 | 15.01 ± 2.88 | 14.69 ± 3.46 | 0.01 |
| NLR | 0.16 (0.12-0.20) | 0.16 ± 0.08 | 0.14 ± 0.04 | 0.16 ± 0.04 | 0.18 ± 0.10 | 0.19 ± 0.11 | <0.001 |
| CRP (g/L) | 14.70 (9.47-24.78) | 14.26 (8.37-25.19) | 23.57 ± 19.44 | 16.31 ± 11.55 | 9.43 (5.27-18.28) | 10.45 ± 7.22 | <0.001 |
| P-LCR (%) | 7.50 (5.30-10.90) | 8.10 (5.50-12.75) | 9.35 ± 3.59 | 8.28 ± 3.20 | 9.81 ± 7.32 | 9.21 ± 7.66 | <0.001 |

Data are shown as number (%) or mean ± standard deviation, if not otherwise specified. BSI: bloodstream infection; CRP: C-reactive protein; LYMPH: lymphocyte count; MPV: mean platelet volume; MPV/PLT: mean platelet volume-to-platelet count ratio; NEU: neutrophil count; NLR: neutrophil-to-lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; PLT: platelet count; PLR: platelet-to-lymphocyte ratio; P-LCC: platelet larger cell count; P-LCR: platelet larger cell ratio.
Changes of hematological parameters in negative, Gram-positive, Gram-negative, and Candida blood cultures

Similarly, other than PLR ($p = 0.158$) and P-LCC ($p = 0.075$), the other hematological parameters were significantly different among the four groups (Table 2). Compare to negative blood cultures, Gram-negative pathogens BSI have higher values of CRP, NEU, PDW, MPV, MPV/PLT, NLR, and P-LCR, but lower values of PLT, LYM, and PCT (Supplementary Figure 1); Gram-positive pathogens BSI have higher values of CRP, MPV, MPV/PLT, NLR, and P-LCR, but the lower value of PLT (Supplementary Figure 1a, 1c, 1d, 1e); Candida BSI have higher value of NLR, whereas a lower value of LYM (Supplementary Figure 1b, 1e). Furthermore, compared to Gram-positive pathogens BSI, Gram-negative pathogens BSI have higher values of CRP, NEU, MPV/PLT, NLR, and P-LCR, while lower values of PLT, LYM, and PCT (Supplementary Figure 1a, 1b, 1d, 1e). See Table 4 for more details.

Changes of hematological parameters in negative blood cultures and different pathogens BSI

Likewise, other than PLR ($p = 0.178$) and P-LCC ($p = 0.254$), the other hematological parameters were significantly different among negative blood cultures and different pathogens BSI (Table 3). Compare to negative blood cultures, E. coli BSI has higher values of CRP, NEU, MPV/PLT, NLR, and P-LCR, while lower values of PLT, LYM, and PCT (Supplementary Table 4.

### Table 4. Changes of hematological parameters in patients with negative, Gram-positive, Gram-negative, and Candida blood cultures.

| Comparison                    | Hematological parameters |
|-------------------------------|---------------------------|
| Negative vs. Gram-positive     | PLT, CRP, MPV, MPV/PLT, NLR, P-LCR |
| Gram-negative vs. Gram-negative| PLT, LYM, PCT, CRP, NEU, PDW, MPV, MPV/PLT, NLR, P-LCR |
| Candida vs. Gram-negative      | PLT, LYM, PCT, CRP, NEU, MPV/PLT, NLR, P-LCR |

CRP: C-reactive protein; LYM: lymphocyte count; MPV: mean platelet volume; MPV/PLT: mean platelet volume-to-platelet count ratio; NEU: neutrophil count; NLR: neutrophil-to-lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; PLT: platelet count; PLR: platelet-to-lymphocyte ratio; P-LCC: platelet larger cell count; P-LCR: platelet larger cell ratio; ↑: the value of hematological parameters increase; ↓: the value of hematological parameters decrease.

### Table 5. Changes of hematological parameters in patients with negative blood cultures and different pathogens positive blood cultures.

| Comparison                    | Hematological parameters |
|-------------------------------|---------------------------|
| Negative vs. S. epidermidis    | PLT, P-LCR               |
| S. haemolyticus vs. E. coli    | P-LCR                    |
| S. aureus vs. E. faecalis      | P-LCR                    |
| E. faecium vs. K. pneumoniae   | P-LCR                    |
| E. coli vs. P. aeruginosa      | P-LCR                    |
| Candida vs. S. epidermidis     | MPV/PLT                  |
| E. aerogenes vs. E. coli       | MPV/PLT                  |
| K. pneumoniae vs. E. aerogenes | MPV/PLT                  |
| S. haemolyticus vs. E. coli    | NLR                      |
| E. aerogenes vs. K. pneumoniae | NLR                      |
| S. aureus vs. K. pneumoniae    | P-LCR                    |
| Candida vs. E. coli            | MPV                      |

CRP: C-reactive protein; LYM: lymphocyte count; MPV: mean platelet volume; MPV/PLT: mean platelet volume-to-platelet count ratio; NEU: neutrophil count; NLR: neutrophil-to-lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; PLT: platelet count; PLR: platelet-to-lymphocyte ratio; P-LCC: platelet larger cell count; P-LCR: platelet larger cell ratio; ↑: the value of hematological parameters increase; ↓: the value of hematological parameters decrease.
Figures 2, 3, 4, 5, 6); *K. pneumoniae* BSI has higher values of CRP, NEU, PDW, MPV, MPV/PLT, NLR, and P-LCR, while lower values of PLT, LYM, and PCT (Supplementary Figures 2, 3, 4, 5, 6); *E. aerogenes* BSI has higher values of NLR, and P-LCR, whereas lower value of LYM (Supplementary Figures 3, 6); *E. cloacae* BSI has higher values of MPV, and P-LCR (Supplementary Figures 4, 6); *P. aeruginosa* BSI has higher values of CRP, MPV, and P-LCR (Supplementary Figures 2, 4, 6); *S. epidermidis* BSI has higher value of P-LCR (Supplementary Figure 6); *S. haemolyticus* BSI has higher value of MPV (Supplementary Figure 4); *S. aureus* BSI has higher values of CRP, MPV (*p* = 0.002), and MPV/PLT, while lower value of PLT (Supplementary Figures 2, 4, 5); *E. faecalis* BSI has higher values of MPV, and P-LCR.

**Figure 1.** ROC curves of hematological parameters for differentiating negative blood cultures from positive blood cultures (a), Gram-positive pathogens bloodstream infection (BSI) (b), Gram-negative pathogens BSI (c), *Candida* BSI (d), *S. epidermidis* BSI (e), *S. haemolyticus* BSI (f), *S. aureus* BSI (g), *E. faecalis* BSI (h), *E. faecium* BSI (i), *K. pneumoniae* BSI (k), *E. aerogenes* BSI (l), *E. cloacae* BSI (m), and *P. aeruginosa* BSI (n).
(Supplementary Figures 4, 6); *E. faecium* BSI has higher value of MPV (Supplementary Figure 4); *Candida* BSI only has higher value of NLR (Supplementary Figure 6).

More importantly, compared to *S. epidermidis* BSI, *E. coli* BSI has higher values of CRP, MPV, MPV/PLT, and NLR, but lower values of PLT, LYM, and PCT (Supplementary Figures 2-6); *K. pneumoniae* BSI has higher values of MPV, MPV/PLT, NLR, and P-LCR, whereas lower values of PLT, and PCT (Supplementary Figures 2, 4, 5, 6); *E. aerogenes* BSI only has a lower value of LYM (Supplementary Figure 3); *S. aureus* BSI has a higher value of MPV/PLT, while lower values of PLT, and PCT (Supplementary Figures 2, 5).

Besides, compared to *S. haemolyticus* BSI, *E. coli* BSI has a higher value of NLR (Supplementary Figure 6); *E. aerogenes* BSI has a lower value of LYM (Supplementary Figure 3). Moreover, compared to *S. aureus* BSI, both *E. coli* BSI and *K. pneumoniae* BSI have a higher value of P-LCR (Supplementary Figure 6). Similarly, compare to *Candida* BSI, both *E. coli* BSI and *K. pneumoniae* BSI have a higher value of P-LCR as well (Supplementary Figure 6). See Table 5 for more details.

**Differential ability of hematological parameters**

ROC curves were constructed to evaluate the power of hematological parameters to distinguish patients with BSI caused by different pathogens. The AUC, optimal cutoff value, sensitivity, and specificity of each hematological parameter are presented in Supplementary Table 1. The related ROC curves are presented in Figures 1 and Figure 2.

![Figure 2](image-url)

**Figure 2.** ROC curves of hematological parameters for Gram-positive pathogens bloodstream infection (BSI) vs. Gram-negative pathogens BSI (a), *S. epidermidis* BSI vs. *S. aureus* BSI (b), *S. epidermidis* BSI vs. *E. coli* BSI (c), *S. epidermidis* BSI vs. *K. pneumoniae* BSI (d), *S. epidermidis* BSI vs. *E. aerogenes* BSI (e), *S. haemolyticus* BSI vs. *E. coli* BSI (f), *S. haemolyticus* BSI vs. *E. aerogenes* BSI (g), *S. aureus* BSI vs. *E. coli* BSI (h), *S. aureus* BSI vs. *K. pneumoniae* BSI (i), *Candida* BSI vs. *E. coli* BSI (j), *Candida* BSI vs. *K. pneumoniae* BSI (k).
Furthermore, we performed univariate logistic regression analysis to examine the associations of each hematological parameter with different pathogens BSI, and calculated the standardized regression coefficient ($\beta$) and the odds ratio (OR) for each blood cell parameter. See Supplementary Table 2 for more details. The combined ROC curves of relevant hematological parameters were shown in Figure 3. The combinations of relevant hematological parameters can increase the differential ability to different pathogens BSI.

Discussion

Blood culture is the most definitive way to confirm BSI. Nonetheless, this gold standard needs at least one day to get the result and may be influenced by many factors [22]. Besides, partly due to differences in both pathogen and host, individual clinical responses to BSI vary greatly [23]. To date, early recognition, rapid microbiological diagnosis, as well as prompt initiation of appropriate antibiotics are always the goals of clinicians who confront probable BSI [24]. Therefore, there is an urgent need for efficient and rapid detection of BSI. For this purpose, it is important to explore BSI comprehensively and deeply, especially the relationship between the causative pathogens and the changes of hematological parameters.

Previous studies have shown that, during BSI, secreted immunomodulatory proteins of pathogen activate platelets and the coagulation system [25-27]. Consequently, the platelet-leukocyte aggregates formed [28] and adhere to endothelium [29,30]. Eventually, the platelets are activated, aggregated, and consumed [31]. Additionally, it has been demonstrated that platelets with higher MPV values have a larger surface area and more granules, which is associated with their activation [32]. Furthermore, MPV, MPV/PLT, and PLR were considered as diagnostic adjunct tests for BSI [33-36]. Nevertheless, Johansson et al. have reported that there was no association between bacterial species and the occurrence of thrombocytopenia [37]. However, each species of bacterium, and even individual strains, have different mechanisms for interacting with platelets [18]. Actually, the immune responses of the host to Gram-positive pathogens are fundamentally different from Gram-negative pathogens [38,39]. Therefore, the kinds of causative pathogens should be taken into account. Opposite to our results, Djordjevic and coauthors reported [9] that patients with Gram-positive BSI have significantly lower values of MPV/PLT and PLR than those with negative blood cultures. Comparing to Gram-positive BSI and negative blood cultures, patients with Gram-negative BSI have the highest values of PLR. It should be noted that the population.

Figure 3. ROC curves of the specific combination of hematological parameters for differentiating negative blood cultures from positive blood cultures (a), Gram-positive pathogens bloodstream infection (BSI) (b), Gram-negative pathogens BSI (c), E. coli BSI (d), E. aerogenes BSI (e), P. aeruginosa BSI (f), S. aureus BSI (g).
included in that research were patients with critically ill BSI and severe trauma. Altogether, to some extent, platelet-related parameters may reflect the distinction of platelet activation in BSI caused by different pathogens. Although in a study by Wu et al., no significant differences were found in WBC, PLT, and CRP between BSI and negative blood cultures [11], while most of the previous studies have shown that the immune responses to BSI have obvious characteristics, such as the increase of NEU, NLR, PDW, and CRP [40], as well as the decrease of LYM [41]. These are consistent with our results. Furthermore, NLR and MPV were found to reflect the severity of BSI, as well as an independent predictor of death [9,42]. Currently, we provided the first retrospective observational study to systematically investigate the changes of more kinds of hematological parameters and their differential ability in patients with BSI caused by different pathogens, including Candida spp. Notably, our results provided some fundamental data, most of which were reported for the first time.

It is undeniable that our present study has some limitations. Firstly, the study was conducted at a single center, and the findings may not be readily suitable to patients with different demographic characteristics. Secondly, we excluded patients suffering from the severe underlying disease. Thirdly, patients with positive blood cultures were significantly older than those with negative blood cultures. Although this may be because older patients are more prone to BSI than younger patients, age-matched groups can better reflect the effects of different pathogens on hematological parameters. Fourthly, except for retrospective observational design, implementation of strict inclusion and exclusion criteria led to a lower number of patients with BSI caused by S. haemolyticus, E. faecalis, E. faecium, E. aerogenes, E. cloacae, P. aeruginosa, A. baumannii, and Candida. To explore the changes of hematological parameters and their differential ability in patients with BSI caused by more kinds of pathogens, further larger prospective studies are warranted.

**Conclusions**

Taken together, the specific combinations of hematological parameters can improve the power to distinguish patients with BSI caused by different pathogens. Attention to these parameters can be easily integrated into daily medical activities, without extra costs.

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**Annex – Supplementary Items**

**Supplementary Figure 1.** Hematological parameters among and between negative, Gram-positive, Gram-negative, and *Candida* blood cultures. (a) platelet count (PLT) and C-reactive protein (CRP); (b) neutrophil count (NEU) and lymphocyte count (LYM); (c) platelet distribution width (PDW) and mean platelet volume (MPV); (d) plateletcrit (PCT) and mean platelet volume-to-platelet count ratio (MPV/PLT); (e) neutrophil-to-lymphocyte ratio (NLR) and platelet larger cell ratio (P-LCR). Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining blood cultures and the row-defining blood cultures. Significant results are bolded and underscored. Green means that, in comparison, the former is lower than the latter. Red means that, in comparison, the former is higher than the latter.

|   | Negative | Z = -4.454 | Z = -7.946 | Z = -2.476 |
|---|----------|------------|------------|------------|
|   | Gram-positive | Z = -3.031 | Z = -3.737 | Z = -0.889 |
|   | P = 0.015 | P < 0.001 | P < 0.001 | P = 0.880 |
|   | Gram-negative | Z = -6.912 | Z = -4.756 | Z = -1.78 |
|   | P < 0.001 | P < 0.001 | P = 1.000 |
|   | Z = -1.001 | Z = -0.340 | Z = -1.969 | P = 0.293 |
|   | P = 1.000 | P = 1.000 | C. spp |

|   | Negative | Z = -2.477 | Z = -5.973 | Z = -3.354 |
|---|----------|------------|------------|------------|
|   | Gram-positive | Z = -2.139 | Z = -4.301 | Z = -2.348 |
|   | P = 0.195 | P < 0.001 | P = 0.113 |
|   | Gram-negative | Z = -5.00 | Z = -4.150 | Z = -0.901 |
|   | P < 0.001 | P < 0.001 | P = 1.000 |
|   | Z = -1.500 | Z = -0.582 | Z = -0.831 |
|   | P = 0.801 | P = 1.000 | C. spp |

|   | Negative | Z = -3.780 | Z = -5.834 | Z = -0.502 |
|---|----------|------------|------------|------------|
|   | Gram-positive | Z = -2.131 | Z = -2.376 | Z = -1.168 |
|   | P = 0.199 | P < 0.001 | P = 1.000 |
|   | Gram-negative | Z = -3.835 | Z = -2.028 | Z = -1.989 |
|   | P < 0.001 | P = 0.255 | P = 0.280 |
|   | Z = -0.116 | Z = 1.071 | Z = -1.773 |
|   | P = 1.000 | P = 1.000 | C. spp |

|   | Negative | Z = -3.369 | Z = -6.708 | Z = -0.456 |
|---|----------|------------|------------|------------|
|   | Gram-positive | Z = -2.029 | Z = -4.018 | Z = -1.069 |
|   | P = 0.255 | P < 0.001 | P = 1.000 |
|   | Gram-negative | Z = -4.918 | Z = -3.528 | Z = -2.484 |
|   | P < 0.001 | P < 0.001 | P = 0.078 |
|   | Z = -0.548 | Z = -0.339 | Z = -1.547 |
|   | P = 1.000 | P = 1.000 | C. spp |

|   | Negative | P = 0.004 | P < 0.001 | P = 0.805 |
|---|----------|------------|------------|------------|
|   | Gram-positive | P = 0.012 | P = 0.003 | P = 0.403 |
|   | P = 0.001 | P = 0.001 | P = 0.075 |
|   | C. spp | Z = -3.473 | Z = -2.196 | Z = -0.195 |
|   | P = 0.003 | P = 0.168 | P = 1.000 |
**Supplementary Figure 2.** Platelet count (PLT) and C-reactive protein (CRP) values among and between negative blood cultures and bloodstream infection (BSI) caused by different pathogens. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining blood cultures and the row-defining blood cultures. Significant results are bolded and underscored. Green means that, in comparison, the former is lower than the latter. Red means that, in comparison, the former is higher than the latter.

| Negative | S. epidermidis | S. haemolyticus | S. aureus | E. faecalis | E. faecium | E. coli | E. aerogenes | E. cloacae |
|----------|----------------|-----------------|----------|------------|------------|---------|-------------|----------|
| Z = 0.126 | 0.804 | 0.026 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 |
| P = 0.391 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 |

**Supplementary Figure 3.** Neutrophil count (NEU) and lymphocyte count (LYM) values among and between negative blood cultures and bloodstream infection (BSI) caused by different pathogens. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining blood cultures and the row-defining blood cultures. Significant results are bolded and underscored. Green means that, in comparison, the former is lower than the latter. Red means that, in comparison, the former is higher than the latter.

| Negative | S. epidermidis | S. haemolyticus | S. aureus | E. faecalis | E. faecium | E. coli | E. aerogenes | E. cloacae |
|----------|----------------|-----------------|----------|------------|------------|---------|-------------|----------|
| Z = 0.932 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| P = 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 |

| Negative | S. epidermidis | S. haemolyticus | S. aureus | E. faecalis | E. faecium | E. coli | E. aerogenes | E. cloacae |
|----------|----------------|-----------------|----------|------------|------------|---------|-------------|----------|
| Z = 2.506 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| P = 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 |
Supplementary Figure 4. Platelet distribution width (PDW) and mean platelet volume (MPV) values among and between negative blood cultures and bloodstream infection (BSI) caused by different pathogens. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining blood cultures and the row-defining blood cultures. Significant results are bolded and underscored. Green means that, in comparison, the former is lower than the latter. Red means that, in comparison, the former is higher than the latter.

| Negative | PDW | MPV |
|----------|-----|-----|
| S. epidermidis | 0.059 | 0.068 |
| S. haemolyticus | 0.059 | 0.068 |
| S. aureus | 0.059 | 0.068 |
| E. faecalis | 0.059 | 0.068 |
| E. coli | 0.059 | 0.068 |
| K. pneumoniae | 0.059 | 0.068 |
| E. cloacae | 0.059 | 0.068 |
| S. haemolyticus | 0.059 | 0.068 |
| S. enteritidis | 0.059 | 0.068 |
| C. difficile | 0.059 | 0.068 |

Supplementary Figure 5. Plateletcrit (PCT) and mean platelet volume-to-platelet count ratio (MPV/PLT) values among and between negative blood cultures and bloodstream infection (BSI) caused by different pathogens. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining blood cultures and the row-defining blood cultures. Significant results are bolded and underscored. Green means that, in comparison, the former is lower than the latter. Red means that, in comparison, the former is higher than the latter.

| Negative | PCT | MPV/PLT |
|----------|-----|--------|
| S. epidermidis | 0.059 | 0.068 |
| S. haemolyticus | 0.059 | 0.068 |
| S. aureus | 0.059 | 0.068 |
| E. faecalis | 0.059 | 0.068 |
| E. coli | 0.059 | 0.068 |
| K. pneumoniae | 0.059 | 0.068 |
| E. cloacae | 0.059 | 0.068 |
| S. haemolyticus | 0.059 | 0.068 |
| S. enteritidis | 0.059 | 0.068 |
| C. difficile | 0.059 | 0.068 |
### Supplementary Table 1. Performance of hematological parameters in diagnosing bloodstream infection (BSI) caused by different pathogens.

| Comparison              | Hematological parameters | AUC  | 95% CI       | Sensitivity (%) | Specificity (%) | Cut-off |
|-------------------------|--------------------------|------|--------------|-----------------|-----------------|---------|
| **Negative vs. BSI**    | NEU                      | 0.620| 0.585-0.653  | 61.4            | 60.4            | 7.66    |
|                         | LYM                      | 0.635| 0.601-0.668  | 66.7            | 59.0            | 0.96    |
|                         | PLT                      | 0.653| 0.619-0.685  | 38.4            | 87.3            | 121.00  |
|                         | MPV                      | 0.644| 0.609-0.678  | 51.1            | 76.0            | 10.70   |
|                         | PDW                      | 0.589| 0.554-0.624  | 28.7            | 93.2            | 16.60   |
|                         | PCT                      | 0.607| 0.572-0.641  | 35.9            | 81.2            | 0.14    |
|                         | NLR                      | 0.674| 0.641-0.706  | 65.3            | 66.4            | 9.01    |
|                         | MPV/PLT                  | 0.653| 0.618-0.686  | 44.6            | 80.4            | 7.70    |
|                         | P-LCR                    | 0.637| 0.597-0.676  | 48.4            | 75.9            | 31.90   |
|                         | CRP                      | 0.704| 0.669-0.739  | 65.2            | 68.8            | 89.40   |
| **Negative vs. Gram-positive** | PLT                      | 0.584| 0.535-0.632  | 32.0            | 87.3            | 121.00  |
|                         | MPV                      | 0.612| 0.563-0.660  | 48.2            | 76.0            | 10.70   |
|                         | NLR                      | 0.598| 0.549-0.646  | 54.0            | 66.4            | 9.01    |
|                         | MPV/PLT                  | 0.597| 0.547-0.645  | 45.6            | 75.2            | 7.20    |
|                         | P-LCR                    | 0.597| 0.540-0.653  | 38.5            | 79.7            | 33.30   |
|                         | CRP                      | 0.650| 0.596-0.701  | 56.0            | 68.8            | 89.40   |
| **Negative vs. Candida**| LYM                      | 0.718| 0.639-0.787  | 75.0            | 66.4            | 0.84    |
|                         | NLR                      | 0.730| 0.652-0.798  | 65.0            | 80.6            | 13.38   |
| **Negative vs. Gram-negative** | NEU                      | 0.658| 0.616-0.699  | 65.6            | 63.4            | 8.02    |
|                         | LYM                      | 0.677| 0.635-0.717  | 72.8            | 59.0            | 0.96    |
|                         | PLT                      | 0.706| 0.665-0.745  | 44.0            | 86.6            | 122.00  |
|                         | MPV                      | 0.673| 0.630-0.715  | 54.0            | 75.9            | 10.70   |
|                         | PDW                      | 0.620| 0.575-0.663  | 43.8            | 82.0            | 16.30   |
|                  | MPV       | MPV       | P-LCR    | CRP       |
|------------------|-----------|-----------|----------|-----------|
| **Gram-positive vs. Gram-negative** |           |           |          |           |
| **Negative vs. S. epidermidis**       |           |           |          |           |
| MPV               | 0.674     | 0.594     | 0.579    | 0.674     |
| PLT               | 0.605     | 0.556     | 0.540    | 0.695     |
| P-LCR             | 0.670     | 0.622     | 0.721    | 0.650     |
| CRP               | 0.737     | 0.695     | 0.759    | 0.650     |
| **Negative vs. S. aureus**            |           |           |          |           |
| MPV               | 0.650     | 0.567     | 0.598    | 0.605     |
| PLT               | 0.665     | 0.546     | 0.597    | 0.698     |
| P-LCR             | 0.670     | 0.622     | 0.721    | 0.650     |
| CRP               | 0.737     | 0.695     | 0.759    | 0.650     |
| **Negative vs. E. cloacae**           |           |           |          |           |
| MPV               | 0.674     | 0.594     | 0.579    | 0.674     |
| PLT               | 0.605     | 0.556     | 0.540    | 0.695     |
| P-LCR             | 0.670     | 0.622     | 0.721    | 0.650     |
| CRP               | 0.737     | 0.695     | 0.759    | 0.650     |
| **Negative vs. S. faecal**            |           |           |          |           |
| MPV               | 0.650     | 0.579     | 0.598    | 0.605     |
| PLT               | 0.665     | 0.546     | 0.597    | 0.698     |
| P-LCR             | 0.670     | 0.622     | 0.721    | 0.650     |
| CRP               | 0.737     | 0.695     | 0.759    | 0.650     |
| **Negative vs. S. faecium**           |           |           |          |           |
| MPV               | 0.679     | 0.599     | 0.597    | 0.674     |
| PLT               | 0.666     | 0.613     | 0.597    | 0.699     |
| P-LCR             | 0.670     | 0.622     | 0.721    | 0.650     |
| CRP               | 0.737     | 0.695     | 0.759    | 0.650     |
| **Negative vs. K. pneumoniae**        |           |           |          |           |
| MPV               | 0.666     | 0.598     | 0.597    | 0.674     |
| PLT               | 0.680     | 0.613     | 0.597    | 0.699     |
| P-LCR             | 0.672     | 0.604     | 0.597    | 0.672     |
| CRP               | 0.737     | 0.672     | 0.721    | 0.672     |
| **Negative vs. E. aerogenes**         |           |           |          |           |
| MPV               | 0.859     | 0.791     | 0.720    | 0.759     |
| PLT               | 0.722     | 0.657     | 0.657    | 0.697     |
| P-LCR             | 0.759     | 0.679     | 0.721    | 0.697     |
| CRP               | 0.737     | 0.679     | 0.721    | 0.697     |
| **Negative vs. E. cloacae**           |           |           |          |           |
| MPV               | 0.645     | 0.563     | 0.679    | 0.605     |
| P-LCR             | 0.634     | 0.551     | 0.721    | 0.679     |
| CRP               | 0.674     | 0.596     | 0.721    | 0.679     |
| **Negative vs. P. aeruginosa**        |           |           |          |           |
| MPV               | 0.675     | 0.592     | 0.679    | 0.587     |
| P-LCR             | 0.675     | 0.594     | 0.679    | 0.587     |
| CRP               | 0.675     | 0.594     | 0.679    | 0.587     |
| **Negative vs. Candida**              |           |           |          |           |
| MPV               | 0.654     | 0.582     | 0.679    | 0.574     |
| P-LCR             | 0.654     | 0.582     | 0.679    | 0.574     |
| CRP               | 0.654     | 0.582     | 0.679    | 0.574     |
| **S. epidermidis vs. S. aureus**      |           |           |          |           |
| MPV               | 0.675     | 0.621     | 0.726    | 0.675     |
| P-LCR             | 0.675     | 0.621     | 0.726    | 0.675     |
| CRP               | 0.675     | 0.621     | 0.726    | 0.675     |
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| Comparison                        | Hematological parameters | Standard β value | OR     | 95% CI Lower bound | 95% CI Upper bound | P value |
|-----------------------------------|--------------------------|------------------|--------|--------------------|--------------------|---------|
| **Negative vs. BSI**              |                          |                  |        |                    |                    |         |
|                                  | NEU                      | -0.002           | 0.998  | 0.942              | 1.057              | 0.938   |
|                                  | LYM                      | -0.020           | 0.980  | 0.927              | 1.060              | 0.920   |
|                                  | PLT                      | <0.001           | 0.999  | 0.979              | 1.020              | 0.925   |
|                                  | MPV                      | 0.184            | 1.202  | 0.267              | 5.414              | 0.810   |
|                                  | PDW                      | -0.021           | 0.979  | 0.847              | 1.131              | 0.775   |
|                                  | PCT                      | 6.026            | 41.424 | <0.001             | 94.541             | 0.620   |
|                                  | NLR                      | 0.040            | 1.041  | 1.005              | 1.077              | **0.025** |
|                                  | MPV/PLT                  | 19.955           | 46.378 | 7.590              | 283.316            | **0.029** |
|                                  | P-LCR                    | -0.019           | 0.981  | 0.806              | 1.195              | 0.894   |
|                                  | CRP                      | 0.008            | 1.008  | 1.005              | 1.011              | **<0.001** |
| **Negative vs. Gram-positive**   |                          |                  |        |                    |                    |         |
|                                  | PLT                      | 0.005            | 1.005  | 1.001              | 1.009              | **0.023** |
|                                  | MPV                      | 0.829            | 2.292  | 0.665              | 7.898              | 0.189   |
|                                  | NLR                      | 0.026            | 1.026  | 1.001              | 1.052              | **0.043** |
|                                  | MPV/PLT                  | 16.851           | 20.817 | 10.467             | 41.381             | **0.023** |
|                                  | P-LCR                    | -0.099           | 0.906  | 0.762              | 1.078              | 0.265   |
|                                  | CRP                      | 0.006            | 1.006  | 1.003              | 1.009              | **<0.001** |
| **Negative vs. Candida**         |                          |                  |        |                    |                    |         |
|                                  | LYM                      | -0.852           | 0.427  | 0.112              | 1.630              | 0.213   |
|                                  | NLR                      | 0.035            | 1.036  | 0.988              | 1.086              | 0.146   |
| **Negative vs. Gram-negative**   |                          |                  |        |                    |                    |         |
|                                  | NEU                      | 0.023            | 1.024  | 0.956              | 1.096              | 0.502   |
|                                  | LYM                      | -0.068           | 0.935  | 0.577              | 1.515              | 0.784   |
|                                  | PLT                      | 0.004            | 1.004  | 0.980              | 1.029              | 0.723   |
|                                  | MPV                      | -0.096           | 0.909  | 0.177              | 6.674              | 0.909   |
|                                  | PDW                      | -0.068           | 0.934  | 0.786              | 1.109              | 0.436   |
|                                  | PCT                      | -2.605           | 0.074  | <0.001             | 74.321             | 0.853   |
| BS1: bloodstream infection; CRP: C-reactive protein; LYM: lymphocyte count; MPV: mean platelet volume; MPV/PLT: mean platelet volume-to-platelet count ratio; NEU: neutrophil count; NLR: neutrophil-to-lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; PLT: platelet count; P-LCR: platelet larger cell ratio; AUC: the area under the curve; CI: confidence intervals.

**Supplementary Table 2.** Univariate odds ratios of hematological parameters in diagnosing bloodstream infection (BSI) caused by different pathogens.
|                | CRP  | NEU  | LYM  | PLT  | PCT  | NLR  | MPV/PLT | P-LCR | CRP  | 1.009 | 1.006 | 1.013 |    |
|----------------|------|------|------|------|------|------|---------|-------|------|-------|-------|-------|----|
| **Gram-positive vs. Gram-negative** |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. S. epidermidis** |      |      |      |      | -10.210 | -1.384 | -0.016 | 24.860 | 0.009 | 62.276 | < 0.001 | 0.002 |    |
| **S. epidermidis vs. P. aeruginosa** |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **S. epidermidis vs. E. cloacae** |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **S. epidermidis vs. K. pneumoniae** |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. S. haemolyticus** |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. S. aureus**     |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. S. faecalis**   |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. S. faecium**    |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. E coli**        |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. K. pneumoniae** |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. E. aerogenes**  |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. E. cloacae**    |      |      |      |      |      |      |         |       |      |       |       |       |    |
| **Negative vs. P. aeruginosa** |      |      |      |      |      |      |         |       |      |       |       |       |    |

Note: The table above compares hematological parameters (NEU, LYM, PLT, MPV, MPV/PLT, NLR, P-LCR, CRP, MPV) between different bacterial strains in patients with bloodstream infections (BSI). The statistical significance of the differences is indicated by p-values (p < 0.001, p < 0.0001).
## Hematological Parameters in Patients with BSI

|                                | PCT      | NLR      | MPV/PLT  | P-LCR    | S. epidermidis vs. E. aerogenes | S. haemolyticus vs. E. coli | S. haemolyticus vs. E. aerogenes | S. aureus vs. E. coli | S. aureus vs. K. pneumoniae | Candida vs. E. coli | Candida vs. K. pneumoniae |
|--------------------------------|----------|----------|----------|----------|---------------------------------|------------------------------|---------------------------------|------------------------|----------------------------|---------------------|--------------------------|
|                                | -25.161  | < 0.001  | < 0.001  | 1.612    |                                 |                              |                                 |                        |                            |                     |                          |
|                                | 0.029    | 1.030    | 0.995    | 1.066    |                                 |                              |                                 |                        |                            |                     |                          |
|                                | -2.488   | 0.083    | < 0.001  | 6.233    |                                 |                              |                                 |                        |                            |                     |                          |
|                                | 0.192    | 1.211    | 0.934    | 1.570    |                                 |                              |                                 |                        |                            |                     |                          |
|                                |          |          |          |          | **0.007**                          |                              |                                 |                        |                            |                     |                          |
|                                |          |          |          |          | **0.003**                          |                              |                                 |                        |                            |                     |                          |
|                                |          |          |          |          | **0.011**                          |                              |                                 |                        |                            |                     |                          |
|                                |          |          |          |          | **0.004**                          |                              |                                 |                        |                            |                     |                          |
|                                |          |          |          |          | **0.058**                          |                              |                                 |                        |                            |                     |                          |
|                                |          |          |          |          | **0.023**                          |                              |                                 |                        |                            |                     |                          |

BSI: bloodstream infection; CRP: C-reactive protein; LYM: lymphocyte count; MPV: mean platelet volume; MPV/PLT: mean platelet volume-to-platelet count ratio; NEU: neutrophil count; NLR: neutrophil-to-lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; PLT: platelet count; P-LCR: platelet larger cell ratio; OR: odds ratios; CI: confidence intervals.