Analysis of risk factors and clinical indicators in bloodstream infections among patients with hematological malignancy: a retrospective study

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Abstract

Background: The incidence of bloodstream infection caused by bacteremia is more common in patients with hematological malignancy. It is important to distinguish infectious episodes from non-infectious episodes. The present study was aimed to describe epidemiology and clinical indexes for in-hospital infection of hematological malignancy patients.

Methods: Single-center retrospective research was performed on hematological malignancy patients admitted to our hospital from July 2015 to March 2018. Laboratory and clinical information from 322 febrile patients were acquired. These episodes were divided by blood culture results into two groups: (1) blood culture positive group, (2) blood culture negative group.

Results: In the 322 febrile cases, 81 (25.2%) patients were blood culture positive, and among them, Gram-negative bacteria (51.9%) were more isolated than Gram-positive bacteria (32.1%) and fungi (7.4%). Gram-negative bacteria were more likely to have a drug resistance than Gram-positive bacteria. Independent risk factors revealed that patients with complications, high levels of procalcitonin (PCT), glucose, interleukin-6 (IL-6) and d-dimer (D-D), and low concentration of albumin were correlated with occurrence of infection. PCT, IL-6 and D-D performed well in differentiating not only the infection group from the non-infection group, but also in the Gram-negative group from the Gram-positive group with the areas under the curve all above 0.75.

Conclusions: We analyzed the risk factors for bloodstream infection in patients with hematological malignancy, the distribution of bacteria, antibiotics resistance and the changes of clinical parameters. This single-center retrospective study may provide clinicians insight to the diagnosis and treatment of infection.

1. Background

Blood stream infection (BSI) remains a common concern for cancer patients, especially hematological malignancy patients who often receive chemotherapy or hematopoietic stem cell transplanting [1, 2]. Distinguishing infectious from non-infectious episodes is more complicated in hematological malignancy patients. Fever is a common symptom of infected patients and its early recognition is necessary to offer timely antibiotic therapy [3]. As a result, sufficient and immediate clinical laboratory results are critical for patients with suspected bacterial infection.

Blood culture, the gold standard of infection diagnosis, often takes 3–5 days and is limited by the relatively low positive rate, which restricts the use in early diagnosis [4]. Patients with infection are often accompanied with changes of biochemical indexes, such as albumin (ALB), glucose (GLU), alanine transaminase (ALT), and aspartate transaminase (AST). Some clinical parameters, including white blood cell (WBC), platelets (PLT), C reaction protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6) and d-dimer (D-D) are commonly used in diagnosing infection [5–9]. However, these parameters have not been widely studied in hematological malignancy patients. Therefore, in this study, the clinical characteristics, bacterial distribution, antibiotics use and resistance, inflammation biomarkers and risk factors of 322 hematologic malignancy patients with febrile episodes were systematically and retrospectively analyzed to predict bacterial infection.

2. Methods

2.1 Enrollment of patients and clinical data collection

This retrospective study was conducted at the PLA General Hospital with approval by the Ethical Committee (No.S2018-207002). All adult patients diagnosed as hematological malignancies accompanied with febrile syndrome and undergoing blood culture were recorded from July 2015 to March 2018. Totally 322 patients were included who had all clinical and laboratory data, such as WBC, PLT, CRP, PCT, IL-6, D-D, ALB, GLU, ALT, AST, blood culture results, antibiotic use and resistance. These patients suffered fevers with body temperature above 37.5 °C, and their bloods were collected for blood culture. Bacterial BSI was diagnosed with blood culture results, indicating the types of microorganisms causing the infection.

2.2 Laboratory tests

Blood samples were collected when patients had fever, cough, chill and related infection syndrome to measure WBC, PLT, CRP, PCT, IL-6, D-D, ALB, GLU, ALT, AST, blood culture results, antibiotic use and resistance. These patients suffered fevers with body temperature above 37.5 °C, and their bloods were collected for blood culture. Bacterial BSI was diagnosed with blood culture results, indicating the types of microorganisms causing the infection.

2.3 Statistical analysis

Continuous data were expressed as median and range or 95% confidence interval (CI), and categorical data as number and percentages. Categorical data were compared by Chi-square test, and abnormally arranged variables by Mann-Whitney U test. The independent indices
forecasting bacteremia in hematologic patients with febrile episode were identified by logistic regression. Any index with \( P < 0.2 \) in univariate analysis was sent to logistic regression. Reliability of each index for bacteremia diagnosis was assessed using receiver-operating characteristic (ROC) curve and area under the curve (AUC). Diagnostic accuracy including sensitivity and specificity was computed using cut-off values. The optimal diagnostic cutoff level was found using Youden's index. All analyses were performed on SPSS 19.0 (IBM Corp., Armonk, NY, USA) and Graphad Prism 6.0 (GraphPad Software, La Jolla, CA, USA). \( P < 0.05 \) implied significance.

3. Results

3.1 Clinical characteristics of patients with hematological malignancies

Totally 322 febrile episodes were included and separated by blood culture results into a positive (infection) group and a negative (non-infection) group. The general characteristics were shown in Table 1. There were more male patients in these two groups. Median ages were 44 and 43 years old respectively. The main primary diseases of these two groups were acute myeloid leukemia (AML), lymphoma, acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS). Infected patients intended to have more complications (88.9%) than non-infected patients (68.9%). Moreover, there were high percentages of diabetes and smoking in the infection group. The length of hospital stay was not much different between the two groups.

### Table 1
Comparison of clinical characteristics between blood culture (+) and blood culture (-) group

| Characteristics       | Blood culture (+) (n = 81) | Blood culture (-) (n = 241) |
|-----------------------|----------------------------|------------------------------|
| Sex (Male), no(%)     | 49 (60.5)                  | 148 (61.4)                   |
| Age, median (range)   | 44 (21–87)                 | 43 (18–91)                   |
| Underlying disease, no% |                           |                              |
| AML                   | 35 (43.2)                  | 98 (40.7)                    |
| ALL                   | 9 (11.1)                   | 43 (11.8)                    |
| Lymphoma              | 23 (28.4)                  | 63 (26.1)                    |
| MDS                   | 4 (4.9)                    | 16 (6.6)                     |
| MM                    | 5 (6.2)                    | 9 (3.7)                      |
| AA                    | 1 (1.3)                    | 7 (2.9)                      |
| Others                | 4 (4.9)                    | 5 (2.2)                      |
| Complications, no%    |                           |                              |
| Yes                   | 72 (88.9)                  | 166 (68.9)                   |
| No                    | 9 (11.1)                   | 75 (31.1)                    |
| Diabetes, no%         |                           |                              |
| Yes                   | 9 (11.1)                   | 21 (8.7)                     |
| No                    | 72 (88.9)                  | 220 (91.3)                   |
| Smoke, no%            |                           |                              |
| Yes                   | 25 (30.9)                  | 54 (22.4)                    |
| No                    | 56 (69.1)                  | 187 (77.6)                   |
| Days in hospital, no% |                           |                              |
| \( \leq 30 \)         | 36 (44.4)                  | 105 (43.6)                   |
| \( > 30 \)            | 45 (55.6)                  | 136 (56.4)                   |

Notes: AML acute myeloid leukemia, lymphoma, ALL acute lymphoblastic leukemia, MDS myelodysplastic syndrome, MM multiple myeloma, AA aplastic anemia; Complications: infection in respiratory system, digestive system, abdominal and perianal.
The distribution of pathogens was shown in Fig. 1. The most frequent Gram-negative bacterium in blood culture was Escherichia coli (21%), followed by Klebsiella pneumoniae (8.6%), Pseudomonas aeruginosa (6.2%) and Brucella (6.2%). The frequent Gram-positive bacteria were Staphylococci hominis (S.hominis) (12.3%), Staphylococcus epidermidis (S.epidermidis) (7.4%), Coagulase-negative Staphylococci (CNS) (3.7%), Staphylococci. capitis (S.capitis) (2.5%) and Staphylococci hemolyticus (S.hemolyticus) (2.5%). Fungemia occupied 7.4% in the infection group; multiple bacterial (≥ 2) infection occurred in 8.6% episodes. Because of the definite blood culture results, the antibiotics use was more targeted. The four major antibiotics used in the infection group were meropenem (25%), imipenem (23.4%) cephalosporins (15.6%) and vancomycin (14.1%) (Table 2). In the non-infection group, however, the results were unclear which pathogens caused infection, and empirical medication of antibiotics was implemented, including cephalosporins (33.6%), imipenem (24.2%) and meropenem (16.4%). Gram-negative bacteria were more likely to have a drug resistance than Gram-positive bacteria (Table 3). Both Gram-negative or Gram-positive bacteria were resistant against penicillins and quinolones, and especially E.coli was most resistant against quinolones. For cephalosporins resistance, it often occurred in Gram-negative bacteria. Resistance against tetracyclines, erythromycin and clindamycin occurred in most Gram-positive bacteria than Gram-negative bacteria. Fungi were likely itraconazole-resistant (Table 3).

| Antibiotics use | Blood culture (+) (n = 81) | Blood culture (-) (n = 241) |
|-----------------|-----------------------------|-----------------------------|
| Antibiotics use all | 64                          | 128                         |
| Meropenem, no% | 16 (25)                     | 21 (16.4)                   |
| Imipenem, no%  | 15 (23.4)                   | 31 (24.2)                   |
| Cephalosporins, no% | 10 (15.6)               | 43 (33.6)                   |
| Moxifloxacin, no% | 4 (6.3)                    | 3 (2.3)                     |
| Vancomycin, no% | 9 (14.1)                    | 6 (4.7)                     |
| Levofoxacin, no% | 3 (4.7)                    | 3 (2.3)                     |
| Teicoplanin, no% | 0 (0)                      | 10 (7.8)                    |
| Antifungal drugs, no% | 2 (3.1)                 | 9 (7.1)                     |
| Others, no%     | 5 (7.8)                     | 2 (1.6)                     |
### Table 3
Resistance of antibiotics in different pathogens in infection group

| Antibiotics resistance | Gram negative bacteria | Gram positive bacteria | Fungi |
|------------------------|------------------------|------------------------|-------|
|                        | E. coli (19)           | K. Pneumoniae (8)      |       |
|                        |                        | P. Aeruginosa (6)      |       |
|                        |                        | Others (13)            |       |
|                        |                        | S. Hominis (11)        |       |
|                        |                        | S. Epidermidis (6)     |       |
|                        |                        | Other Staphylococcus (7) |     |
|                        |                        | Others (5)             |       |
|                        |                        | Candida Albicans (5)   |       |
| Penicillins, no%       | 9 (47.4)               | 3 (37.5)               | 3 (28.6) | 1 (20) | NA |
| Cephalosporins, no%    | 8 (42.1)               | 2 (25)                 | 4 (66.7) | 1 (9.1) | 0  |
| Quinolones, no%        | 12 (63.2)              | 1 (12.5)               | 0       | 1 (7.7) | 6 (54.5) | 3 (50) | 2 (28.6) | 2 (40) | NA |
| Sulbactam, no%         | 2 (10.5)               | 0                      | 0       | 0       | 0       | 0  | NA |
| Aztreonam, no%         | 3 (15.8)               | 1 (12.5)               | 0       | 2 (15.4) | 0       | 0  | 0  | 0  | NA |
| Gentamicin, no%        | 8 (42.1)               | 0                      | 0       | 1 (7.7) | 0       | 0  | 0  | 0  | NA |
| Sulfonamides, no%      | 3 (15.8)               | 1 (12.5)               | 1 (16.7) | 0 | 1 (9.1) | 1 | 0 | 1 (20) | NA |
| Furadantin, no%        | 0  | 0 | 2 (33.3) | 1 (7.7) | 0 | 0 | 0 | 0  | NA |
| Tetracyclines, no%     | 0  | 0 | 0 | 0 | 5 (45.5) | 1 (16.7) | 0 | 1 (20) | NA |
| Erythromycin, no%      | 0  | 0 | 0 | 0 | 7 | 4 (66.7) | 1 (14.3) | 0 | NA |
| Clindamycin, no%       | 0  | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (14.3) | 0 | NA |
| Itraconazole, no%      | NA | NA | NA | NA | NA | NA | NA | NA | 1 (20) |

#### 3.3 Risk factors for BSI in hematological malignancies patients

In univariate analysis (Table 4), some significant variables (P < 0.2) were involved and adjusted in the multivariate analysis. Age, diabetes, inpatient days, ALT and AST were insignificant in infection, which may be due to the number of patients or the statistic analysis. Multivariate analysis confirmed six variables were significantly associated with infection: having complications (OR [95% CI]: 3.459 [1.183–10.109]; P = 0.023), PCT (1.29 [1.107–1.503]; P = 0.001), ALB (0.885 [0.795–0.92]; P < 0.001), GLU (1.297 [1.092–1.539]; P = 0.003), IL-6 (1.048 [1.025–1.07]; P < 0.001) and D-D (1.048 [1.025–1.07]; P < 0.001) (Table 5). No such association was observed in sex, smoke, CRP or PLT in multivariate analysis.
Table 4
Univariate analysis of the risk factors for infection and non-infection among 322 episodes in patients with hematologic malignancies

| Variables   | Blood culture (+) (n = 81) | Blood culture (-) (n = 241) | P-value |
|-------------|-----------------------------|-------------------------------|---------|
|             | N   | %     | N    | %     |         |
| Age, year   |     |       |     |       | 0.884   |
| < 60        | 67  | 82.7  | 213 | 88.4  |         |
| ≥ 60        | 14  | 17.3  | 28  | 11.6  |         |
| Sex         |     |       |     |       | 0.193   |
| Male        | 49  | 60.5  | 148 | 61.4  |         |
| Female      | 32  | 39.5  | 93  | 38.6  |         |
| Diabetes    |     |       |     |       | 0.522   |
| Yes         | 9   | 11.1  | 21  | 8.7   |         |
| No          | 72  | 88.9  | 220 | 91.3  |         |
| Smoke       |     |       |     |       | 0.128   |
| Yes         | 25  | 30.9  | 54  | 22.4  |         |
| No          | 56  | 69.1  | 187 | 77.6  |         |
| Complications|    |       |     |       | 0.001   |
| Yes         | 72  | 88.9  | 166 | 68.9  |         |
| No          | 9   | 11.1  | 75  | 31.1  |         |
| Days in hospital | | | | | 0.891   |
| ≤ 30        | 36  | 44.4  | 105 | 43.6  |         |
| > 30        | 45  | 55.6  | 136 | 56.4  |         |

| Variables   | Blood culture (+) (n = 81) (median ± quantile) | Blood culture (-) (n = 241) (median ± quantile) | P-value |
|-------------|-----------------------------------------------|-----------------------------------------------|---------|
| WBC         | 1.24 (0.27–16.15)                             | 2.71 (0.78–62.23)                             | 0.036   |
| PLT         | 31 (19–233)                                   | 39 (22–339)                                   | 0.016   |
| CRP         | 8 (4.16–11.32)                                | 4.35 (1.75–8.93)                              | < 0.001 |
| PCT         | 2.65 (1.1–5.12)                               | 0.23 (0.13–0.67)                              | < 0.001 |
| ALB         | 31.5 (27.45–35.1)                             | 35.3 (32.4–39.2)                              | < 0.001 |
| GLU         | 6.95 (5.24–8.99)                              | 5.3 (4.75–6.64)                               | < 0.001 |
| ALT         | 19.5 (9.95–46.4)                              | 18.7 (11.25–31.25)                            | 0.475   |
| AST         | 16.2 (10.5–31.7)                              | 17.1 (11.65–30.2)                             | 0.679   |
| IL-6        | 32.1 (12.2–72.4)                              | 7.58 (4.2–15.22)                              | < 0.001 |
| D-D         | 3.1 (1.36–5.37)                               | 0.61 (0.41–1.1)                               | < 0.001 |
Table 5
Multivariate analysis of the risk factors for infection/non-infection among 322 episodes in patients with hematologic malignancies

| Variables | Infection/non-infection | OR       | 95%CI       | P-value |
|-----------|--------------------------|----------|-------------|---------|
| Complications |                          | 3.459    | 1.183–10.109 | 0.023   |
| PCT       |                          | 1.29     | 1.107–1.503  | 0.001   |
| ALB       |                          | 0.885    | 0.795–0.92   | <0.001  |
| GLU       |                          | 1.297    | 1.092–1.539  | 0.003   |
| IL-6      |                          | 1.048    | 1.025–1.07   | <0.001  |
| D-D       |                          | 1.19     | 1.06–1.335   | 0.003   |

3.4 Diagnostic accuracy of indicators for bacteremia detection

ROC curves of WBC, PLT, CRP, PCT, IL-6, D-D, ALB, GLU, ALT and AST levels were plotted to diagnose bacteremia in the 322 febrile episodes (Figure. 2). Among these indicators, the AUCs of PCT, IL-6 and D-D were 0.8473, 0.7937 and 0.8613 respectively, indicating higher diagnostic accuracy. Table 6 showed the diagnostic sensitivity and specificity of these indexes with the best cut-off value. When we analyzed WBC, CRP, PCT, IL-6 and D-D in differentiating Gram-negative and Gram-positive infection, PCT, IL-6 and D-D all demonstrated high diagnostic accuracy, with AUC of 0.7834, 0.8182 and 0.8951, respectively. However, neither WBC nor CRP can effectively differentiate these two groups (Fig. 3).

Table 6
Sensitivity and specificity of parameters in differentiating bacteremia group from non-bacteremia group

| Variables | Cut-off | Sensitivity (%) | Specificity (%) |
|-----------|---------|-----------------|-----------------|
| WBC       | 0.895   | 44.44           | 73.44           |
| PLT       | 58.5    | 80.25           | 39              |
| CRP       | 5.30    | 67.9            | 60.58           |
| PCT       | 0.99    | 77.78           | 81.33           |
| ALB       | 31.75   | 51.85           | 79.67           |
| GLU       | 6.780   | 53.09           | 77.59           |
| ALT       | 44.50   | 25.93           | 85.06           |
| AST       | 20.95   | 41.98           | 63.49           |
| IL-6      | 18.15   | 66.67           | 80.08           |
| D-D       | 0.8850  | 88.89           | 70.95           |

4. Discussion

Hematological patients are more vulnerable to pathogen infection because of long-term hospitalization, chemotherapy-induced immune suppression and antibiotic exposure, which lead to higher mortality. The common symptom of infection is fever, though noninfectious febrile episodes are often seen [2]. The gold standard of infection test is blood culture, but its application in early diagnosis is limited by huge time-consumption and low positive rate. Therefore, it is important to distinguish infectious episodes from noninfectious patients, which provides appropriate and immediate antibiotic therapy. This retrospective study was aimed to analyze the differences in clinical characteristics, pathogens distribution, antibiotics use and resistance, clinical common indicators and diagnostic efficiency between bacterial positive patients and bacterial negative patients.

We enrolled 322 patients with hematological malignancy, including 81 bacteremia (+) and 241 bacteremia (-) patients. The positive rate of 25.2% was higher than other reports from different studies, which may be due to our objects were hematological patients who were more likely to have infection because of their lower immunity [10, 11]. AML, lymphoma and ALL were the most common basic diseases in the two groups,
In summary, G- bacteria are more prevalent in febrile patients with hematological malignancy and often develop antibiotics resistance. Empirical antibiotic use may help anti-infection, but also form resistance. Meropenem, imipenem and cephalosporins show higher activity for the infection. Moreover, our findings demonstrated the risk factors for bacteremia in hematological diseases, including complications, low ALB concentration, high GLU, PCT, IL-6 and D-D levels, which may indicate the occurrence of infection. PCT, IL-6 and D-D are valuable indicators to aid infection diagnosis. Further studies are needed to validate these parameters in patients with prognosis of different conditions.

5. Conclusion

In summary, G- bacteria are more prevalent in febrile patients with hematological malignancy and often develop antibiotics resistance. Empirical antibiotic use may help anti-infection, but also form resistance. Meropenem, imipenem and cephalosporins show higher activity for the infection. Moreover, our findings demonstrated the risk factors for bacteremia in hematological diseases, including complications, low ALB concentration, high GLU, PCT, IL-6 and D-D levels, which may indicate the occurrence of infection. PCT, IL-6 and D-D are valuable indicators to aid infection diagnosis. Further studies are needed to validate these parameters in patients with prognosis of different conditions.
**Abbreviations**

BSI: Bloodstream infection; ALB: albumin; GLU: glucose; ALT: alanine transaminase; AST: aspartate transaminase; WBC: white blood cell; PLT: platelets; CRP: C reaction protein; PCT: procalcitonin; IL-6: interleukin-6; D-D: d-dimer

**Declarations**

**Ethics approval and consent to participate**

This study was conducted at the PLA General Hospital with approval by the Ethical Committee (No.S2018-207002).

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the study are available from the corresponding author on reasonable request.

**Competing interests**

There are no conflicts of interest to declare.

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**Authors' contributions**

Yating Ma did collection and analysis of data and prepared the manuscript. Ming Yang collected clinical data. Jinfeng Bao did final check about data analysis and original work. Chengbin Wang did methodology designing and reviewing final check about manuscript. All authors have provided final approval for the final version of the manuscript.

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