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Comparison of interleukin-6, interleukin-10, procalcitonin and C-reactive protein in identifying high-risk febrile illness in pediatric cancer patients: A prospective observational study

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ABSTRACT

The aim of this study is to systematically compare the performance of C-reactive protein (CRP), procalcitonin (PCT) and serum cytokines in identifying pediatric cancer patients with high-risk infection. A prospective observational study was performed from January 2014 through December 2016. Consecutive pediatric cancer patients who experienced febrile illness during hospitalization were enrolled. The CRP, PCT, interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α and interferon (IFN)-γ were determined within 6 h of fever onset. A total of 3118 episodes of febrile illness were included, with 13.1% episodes documented as bloodstream infection (BSI) and 3.5% diagnosed as septic shock. Patients with BSI presented much higher levels of PCT, IL-6, IL-10 and TNF-α than patients with other types of fever and have much higher incidence of septic shock (11.2% vs. 2.3%, $P < 0.001$). IL-6 and IL-10 showed better performance in identifying patients with gram-negative bacteremia (GNB) and septic shock than CRP and PCT, respectively. The area under the curve (AUCs) of receiver operating characteristic (ROC) curve for septic shock prediction were 0.65, 0.78, 0.89 and 0.87 for CRP, PCT, IL-6 and IL-10, respectively. Furthermore, elevation of IL-6 and IL-10 were strongly associated with the development of GNB and septic shock. Our results indicate that BSI, especially GNB, is a high-risk form of infection which results in high incidence of septic shock. IL-6 and IL-10 performance better than CRP and PCT in identifying patients with high-risk febrile illness.

1. Introduction

In recent decades, the outcome of pediatric cancer patients has been greatly improved, with up to 80% of cases having a favorable result [1]. However, intensive chemotherapy and immunosuppression make these patients more susceptible to infection, which has become one of the leading causes of mortality in this population [2].

Early identification of infectious pathogens and disease severity are essential to start timely and effective treatment and to prevent avoidable deaths in patients with sepsis, especially septic shock [3], highlighting the need for early and reliable diagnostic biomarkers for severe infection. C-reactive protein (CRP) is routinely used biomarker for infection evaluation, however, its level rises relatively slowly in cases of infection and consequently has a low initial diagnostic accuracy [4]. Procalcitonin (PCT) is widely reported as a useful biochemical marker to differentiate sepsis and non-sepsis inflammatory response and to predict severe infection [5,6]. It has become an important parameter to guide the discontinuation of antibiotic treatment in patients with presumed sepsis and even critically ill patients [7,8]. Interleukin (IL)-6 is another important mediator of the acute phase reaction in response to inflammation in sepsis, which is closely related to the severity and organ failure [9]. Furthermore, IL-10, TNF-α and IFN-γ are considered to be helpful inflammatory biomarkers as well in our previous study and others [10–13]. For example, IL-10 is a very helpful biomarker to predict gram-negative bacteremia (GNB) in pediatric hematology/oncology patients with septic shock [11]. A pediatric multiple cytokine

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; IL, interleukin; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; BSI, bloodstream infection; GNB, gram-negative bacteremia; GPB, gram-positive bacteremia; FUO, fever of unknown origin

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score which integrating IL-6, IL-10, TNF-α and IFN-γ was an independent predictive factor for fatal outcome in these patients, presenting similar discriminative power with pediatric index of mortality 2 scoring system [10]. There are many clinical studies focusing on their values for discriminating different causes of systematic inflammation and disease severity, however, the conclusions are controversial [14,15]. Such heterogeneity may be partially related to the difference of underlying diseases and age of the population. On the other hand, many studies have not yielded solid conclusions possibly due to their small sample sizes.

We conducted studies on the role of quick cytokine profile determination by flow cytometry in pediatric hematology/oncology patients who experienced febrile illness since 2005 and more than 100,000 samples from pediatric patients with variety of febrile diseases. PCT was added to be a reference biomarker for these patients from 2011. In our retrospective analysis, we found that PCT was not as effective as IL-6 and IL-10 in predicting infection and disease severity [12]. However, as the retrospective nature, selective bias (many patients had cytokine data but did not have PCT data) and the different time we took PCT and cytokine samples in many patients made the results not solid enough. Thus, we conducted a prospective observational study from January 2014 in our department. Herein we collected the data from 2014 to 2016 and systematically compare the performance of PCT and inflammatory cytokines (IL-6, IL-10, tumor necrosis factor (TNF)-α and interferon (IFN)-γ) in discriminating various types of infection and their severity, aiming to find out useful inflammatory biomarkers to identify pediatric cancer patients with fever at high-risk to develop septic shock and death.

2. Patients and methods

2.1. Patients and definitions

This was a prospective observational study conducted from January 2014 through December 2016 in the Division of Hematology/Oncology, Children's Hospital of Zhejiang University School of Medicine. This study was approved by the Medical Ethics Committee of our hospital. Fever was defined as one ear temperature reading higher than 38.5 °C or at least two measurements of higher than 38.0 °C within 24 h. For every febrile illness, patients' blood samples were taken for CRP, PCT, Th1/Th2 cytokine (including IL-6, IL-10, TNF-α and IFN-γ) and microbiological analyses at the first time when the body temperature higher than 38.0 °C or when the patients were admitted into the department. Patients who had been treated with antibiotics before the blood sample taken were excluded. Urine, stool, sputum or specimens from other body regions were also taken for culture if relevant infection was suspected. The patients were undertaken chest radiography and/or CT scanning when the fever had not been controlled within 48 h, and laboratory evidences of viral and fungal infections were determined as well. Abdominal ultrasound was performed to exclude abdominal infection if necessary.

The febrile illnesses were assigned to the following groups based on the sources of infection: bloodstream infection (BSI), upper respiratory tract infection (URTI) and bronchitis, pneumonia, oral cavity infection, gastrointestinal tract infection, skin and soft tissue infection, genitourinary infection, central nervous system (CNS) infection, viral infection and fever of unknown origin (FUO). BSI was documented by microbiological culture. When coagulase-negative staphylococci were reported, they were considered as pathogens only when two samples from two different sites showed the same result or the same result reported from a repeated culture. URTI included the infection of nasal cavity, pharynx, and larynx. Pneumonia was diagnosed based on symptoms and signs of lung infection and (or) a new pulmonary infiltrate on the chest radiograph. Oral cavity infection refers to the dental infection and other infections including the lips, buccal mucosa, floor of the mouth and tongue. Gastrointestinal tract infection mainly refers to gastroenteritis, enteritis, appendicitis and other abdominal infections. CNS infection refers to bacterial or viral meningitis, encephalitis. Viral infection mainly referenced to viruses caused systematic symptoms, such as Epstein-Barr virus, herpes virus and influenza virus, while respiratory or gastrointestinal diseases caused by virus were not categorized into viral infection group. FUO was defined if no microbiological, radiological or clinical related evidence could be identified in patients with fever. Septic shock was defined as sepsis with cardiovascular organ dysfunction characterized by arterial hypotension with signs of decreased perfusion (decrease in blood pressure less than 5th percentile for age or systolic blood pressure less than 2 SD below normal for age) [16].

2.2. Determination of serum cytokines and PCT

Blood samples were taken at the onset of fever. Determination of IL-6, IL-10, TNF-α and IFN-γ was performed by flow cytometry with a commercially available cytometric bead array (CBA) Human Th1/Th2 Cytokine Kit II[17]. The low and upper limits of detection were 1.0 pg/mL and 5000 pg/mL for each cytokine, respectively. For values higher than 5000 pg/mL, 5000 pg/mL was used in the statistical analysis. CRP was measured with QuikRead go, a new generation of POCT testing system designed and developed by Orion Diagnostica (detection limit 1.0 mg/L and 180 mg/L). PCT was detected with Roche e411 electrochemical luminescence immunity analyzer with a detection limit of 0.02 ng/mL. The upper limit of normal reference range for PCT, IL-6, IL-10, TNF-α and IFN-γ were 0.40 ng/mL, 16.6 pg/mL, 4.9 pg/mL, 5.2 pg/mL and 17.3 pg/mL, respectively.

2.3. Statistical analysis

Categorical variables were compared between groups with the chi-square or Fisher's exact test when appropriate. Quantitative continuous variables were compared using the Student's *t* test or nonparametric Mann-Whitney *U* test when appropriate. The power of inflammatory biomarkers to predict gram-negative bacteremia (GNB) and septic shock were assessed and compared with receiver operating characteristics (ROC) curves. the area under the curve (AUC), optimal cutoff values were calculated and Z test was performed to compare the AUCs. A multivariate logistic regression model was constructed with either GNB or septic shock as dependent variables, and age, underlying disease, neutropenia, CRP, PCT, IL-6 and IL-10 levels as independent variables. All statistical analyses were performed using IBM SPSS Statistics 20.0 software. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patients' characteristics

A total of 3118 episodes of febrile illness were recorded in 1115 patients during the three years described above. These patients suffered one to five episodes of febrile illness during this period, respectively. The demographic features including gender, age and neutropenic rate were shown in Table 1. The median age of this cohort was 6.1 years old (range: one months to 17.5 years old) and male to female ratio was 1.48. Patients with neutrophil count less than 0.5×10^9/L accounted for 64.0%. The diagnoses of the underlying diseases were mainly acute lymphoblastic leukemia (n = 2222), acute myeloid leukemia (n = 580) and lymphoma (n = 179). Other diseases included Langerhans cell histiocytosis (n = 44), neuroblastoma (n = 56), myelodysplastic syndrome (n = 8), chronic myeloid leukemia (n = 13), rhabdomyosarcoma (n = 12) and others (n = 4).

Table 1
Demographic features and inflammatory biomarkers levels of patients with BSI and septic shock.

Parameters	Total	BSI	Non-BSI	P-value	Septic shock	Without septic shock	
Gender (male to female)	1860/1258	251/159	1609/1099	0.488	74/35	1786/1223	0.074
Age (median and range, year)	6.1 (0.1–17.5)	5.5(0.6–16.1)	6.2(0.1–17.5)	0.008	9.9(1.5–16.1)	6.0(0.1–17.5)	< 0.001
Neutrophil count ($\times 10^9$/L)	0.16(0–228.5)	0.08(0–32.4)	0.20(0–228.5)	< 0.001	0.05(0–17.55)	0.18(0–228.5)	< 0.001
Neutropenia (%)	64.0% (1995/3118)	76.8% (315/410)	62.0% (1680/2708)	< 0.001	80.7% (88/109)	63.4% (1907/3009)	< 0.001
Underlying diseases							
Acute lymphoblastic leukemia	2222 (71.2%)	318 (78.3%)	1904 (70.1%)	0.006	86 (74.8%)	2136 (71.1%)	0.753
Acute myeloid leukemia	580 (18.6%)	62 (15.3%)	518 (19.1%)		22 (19.1%)	558 (18.5%)	
Lymphoma	179 (5.7%)	11 (2.7%)	168 (6.2%)		3 (2.6%)	176 (5.9%)	
Others	140 (4.5%)	15 (3.7%)	125 (4.6%)		4 (3.5%)	136 (4.5%)	
Inflammatory biomarkers (median and range)							
CRP (mg/L)	34 (1–180)	34 (1–180)	34 (1–180)	0.255	62 (1–180)	33 (1–180)	< 0.001
PCT (ng/mL)	0.22 (0.02–275.80)	0.31 (0.02–275.80)	0.21 (0.02–84.85)	< 0.001	1.23 (0.08–275.80)	0.22 (0.02–80.86)	< 0.001
IL-6 (pg/mL)	58.8 (1.5–5000)	179.3 (2.3–5000)	52.9 (1.5–5000)	< 0.001	718.7 (13.8–5000)	55.3 (1.5–5000)	< 0.001
IL-10 (pg/mL)	6.9 (1.0–5000)	22.3 (1.5–5000)	6.3 (1.0–5000)	< 0.001	161.5 (2.3–5000)	6.6 (1.0–5000)	< 0.001
TNF-α (pg/mL)	2.3 (1.0–5000)	2.7 (1.0–5000)	2.3 (1.0–1104.6)	< 0.001	3.0 (1.5–5000)	2.3 (1.5–2779.7)	< 0.001
IFN-γ (pg/mL)	7.7 (1.0–2475.8)	8.3 (1.0–2475.8)	7.7 (1.0–1817.4)	0.146	9.6 (1.0–1817.4)	7.7 (1.0–2475.8)	0.009

3.2. Distribution of the sources of fever

The distribution of the sources of fever was shown in Fig. 1. About one third of the patients experienced FUO, which was mainly suspected infection and drug fever. Of the remaining 2028 episodes of fever, respiratory tract infections were the most common type of diseases, with URT infection/bronchitis and pneumonia accounting for 18.6% and 23.6%, respectively. BSI was documented in 13.1% of episodes. Of the 2438 episodes of fever in 870 patients who had a central line in place, the central lines from 116 patients were removed when catheter-associated bloodstream infection was suspected. Other origins of fever such as oral cavity, gastrointestinal tract, soft tissue, CNS, genitourinary and viral infection were less common, only accounting for about 10% of episodes totally. Septic shock was documented in 109 (3.5%) episodes of fever in this cohort, with BSI presenting much higher rate of shock than other types of fever (11.2% vs. 2.3%, $P < 0.001$). Twelve patients died in this cohort, eight of whom developed septic shock and four due to severe pneumonia without shock.

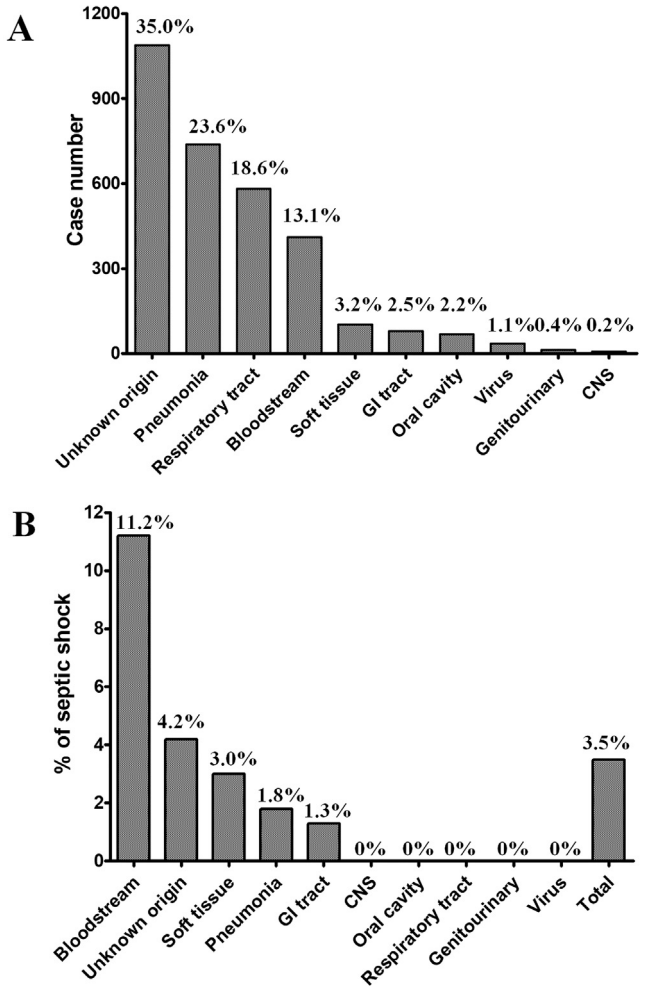

Fig. 1. Distribution of sources of fever and the incidence of septic shock. The upper figure showed the case numbers and percentages of patients with various types of fever, while the lower figure showed the incidences of septic shock in each type of fever.

3.3. Bloodstream infection (BSI)

Of the 410 episodes of BSI, gram-positive bacteremia (GPB), GNB, fungemia and polymicrobial infection were accounted for 43.7%, 52.9%, 1.5% and 2.2% respectively. *Escherichia coli* (35.9%), *Klebsiella pneumoniae* (15.2%) and *Pseudomonas aeruginosa* (11.5%) were the predominant organisms in GNB while coagulase-negative staphylococci (39.1%), *Streptococcus* (16.8%), *Staphylococcus aureus* (6.1%) and *Corynebacterium parvum* (6.7%) were the leading types in GPB. For polymicrobial infection, five episodes were due to the mix of gram-positive and negative bacteria, four episodes were two isolates of gram-negative bacteria (thus assigned as GNB), one episode was two isolates of gram-positive bacteria (thus assigned as GPB). The incidence of septic shock was much higher in patients with GNB when compared to those with GPB (16.5% (36/218) vs. 5.5% (10/181), $P < 0.001$), indicating that patients with GNB presented much higher risk of developing septic shock than patients with other types of fever. We thus considered GNB and septic shock as high-risk form of infection.

3.4. Serum levels of inflammatory biomarkers in different infection groups

Among the inflammatory biomarkers, CRP, IL-6 and IL-10 were increased in 82.6%, 85.2% and 63.9% episodes of fever, while PCT, TNF-α and IFN-γ were elevated in only 29.9%, 10.2% and 31.6% episodes, respectively. The serum levels of the above biomarkers in BSI and non-BSI, septic shock and non-septic shock groups were shown in Table 1. Patients with BSI presented much higher levels of CRP, PCT, IL-6, IL-10 and TNF-α when compared to those with non-BSI, and patients with septic shock showed very higher levels of the above biomarkers and IFN-γ than those without it as well.

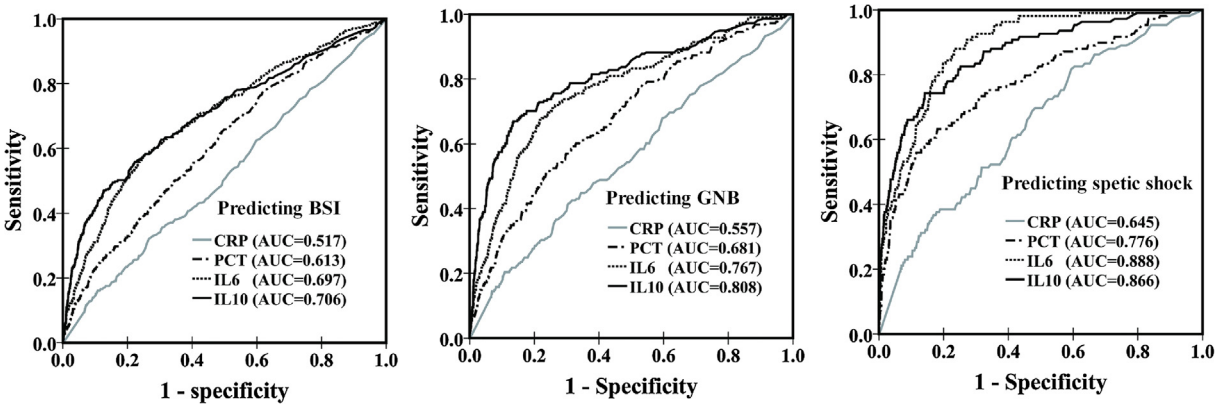

Fig. 2. Discriminative performance of biomarkers to identify BSI, GNB and septic shock. The receiver operating characteristic (ROC) curves illustrated the performance of CRP, PCT, IL-6 and IL-10 to predict BSI, GNB and septic shock.

3.5. Performance of inflammatory biomarkers to identify GNB and septic shock

As patients with GNB presented high incidence of septic shock which caused high mortality, GNB and septic shock were considered as high-risk forms of infection. We thus investigated the diagnostic powers of CRP, PCT, IL-6, IL-10 and TNF-α and IFN-γ to identify GNB and septic shock by ROC analysis. CRP, TNF-α and IFN-γ were not very helpful to identify GNB and septic shock, with AUCs of 0.557 (95% CI, 0.516–0.597), 0.663 (95% CI, 0.626–0.701) and 0.533 (95% CI, 0.494–0.572) for GNB and of 0.645 (95% CI, 0.593–0.697), 0.651 (95% CI, 0.594–0.707) and 0.574 (95% CI, 0.517–0.630) for septic shock, respectively; While PCT, IL-6, IL-10 were better biomarkers to predict GNB and septic shock compared with CRP, TNF-α and IFN-γ. As shown in Fig. 2, the AUCs for IL-10, IL-6 and PCT, IL-6 and IL-10 to predict GNB were 0.681 (95% CI, 0.644–0.719), 0.767 (95% CI, 0.733–0.801) and 0.808 (95% CI, 0.774–0.843), respectively. IL-10 and IL-6 performed better than PCT when AUCs were statistically compared (IL-10 vs. IL-6, $P = 0.098$; IL-10 vs. PCT, $P < 0.001$; IL-6 vs. PCT, $P < 0.001$). The AUCs for septic shock prediction was 0.776 (95% CI, 0.726–0.826), 0.888 (95% CI, 0.861–0.914) and 0.866 (95% CI, 0.828–0.903) for PCT, IL-6 and IL-10, respectively. Similarly, IL-10 and IL-6 were much better to predict septic shock than PCT as well (IL-10 vs. IL-6, $P = 0.351$; IL-10 vs. PCT, $P = 0.004$; IL-6 vs. PCT, $P < 0.001$). As shown in Table 2, when the above biomarkers identified septic shock with specificities of about 80%, the sensitivities of PCT, IL-6 and IL-10 were 63.3% (54.0–71.8), 84.4% (76.4–90.0) and 77.1% (68.3–84.0), respectively.

We then investigated whether the above biomarkers were still powerful to predict septic shock among patients with BSI. As shown in Fig. 3, there were 46 episodes of shock in 410 patients with BSI. By using the cut-off values in Table 2, CRP, PCT, IL-6 and IL-10 could screen out 13 (28.3%), 30 (65.2%), 40 (87.0%) and 40 (87.0%) episodes of shock, respectively, indicating IL-6 and IL-10 were still powerful to identify relative severe cases among those diagnosed with BSI. The combination of IL-6 and IL-10 was the most powerful to identify low-risk patients as well. The rate of septic shock was only 0.7% among patients with IL-6 less than 185 pg/mL and IL-10 less than 20 pg/mL together, while the septic shock rate was 6.7% among patients with low PCT and low CRP combination.

3.6. Performance of inflammatory biomarkers in multivariate analysis

There were many parameters, including inflammatory biomarkers and patients' features, related to the development of GNB and septic shock, which could be used as predictors of these diseases. We thus investigated which parameters were the most powerful predictors in multivariate analysis using Logistic regression models. As shown in Table 3, older patients (≥6 years old) were more likely to develop septic shock while patients with ALL presented more susceptible to GNB. Of inflammatory cytokines, IL-6 and IL-10 were independent predictors of GNB and septic shock, while CRP was not related to either one of them. PCT, which was elevated mostly in patients with severe diseases, was a predictor for septic shock but did not predict GNB.

Table 2
Diagnostic performance of CRP, PCT, IL-6 and IL-10 in identifying patients with severe forms of infection.

Parameters	AUC (95% CI)	Cut-off	Sensitivity	Specificity	PLR	NLR
BSI						
CRP	0.52 (0.49–0.55)	90 mg/L	24.2% (20.3–28.5)	79.4% (77.8–80.9)	1.17 (0.97–1.41)	0.96 (0.90–1.01)
PCT	0.61 (0.58–0.64)	0.58 ng/mL	32.9% (28.6–37.6)	80.0% (78.4–81.4)	1.64 (1.40–1.92)	0.84 (0.78–0.90)
IL-6	0.70 (0.66–0.72)	173 pg/mL	51.0% (46.2–55.8)	80.0% (78.4–81.4)	2.60 (2.30–2.95)	0.62 (0.57–0.69)
IL-10	0.701 (0.68–0.74)	18.5 pg/mL	51.2% (46.4–56.0)	80.0% (78.4–81.4)	2.71(2.39–3.07)	0.61 (0.55–0.67)
GNB						
CRP	0.56 (0.52–0.60)	90 mg/L	28.5% (23.0–34.8)	79.5% (78.0–80.9)	1.39 (1.12–1.73)	0.90 (0.83–0.98)
PCT	0.68 (0.64–0.72)	0.58 ng/mL	44.8% (38.4–51.4)	80.0% (78.5–81.4)	2.24 (1.90–2.64)	0.69 (0.61–0.78)
IL-6	0.77 (0.73–0.80)	185 pg/mL	63.4% (56.8–69.4)	80.0% (78.6–81.5)	3.18 (2.81–3.59)	0.46 (0.39–0.55)
IL-10	0.81 (0.77–0.84)	18.5 pg/mL	70.6% (64.3–76.2)	79.4% (77.9–80.8)	3.67 (3.28–4.19)	0.37 (0.30–0.45)
Septic shock						
CRP	0.65 (0.59–0.70)	90 mg/L	38.5% (30.0–47.9)	79.6% (78.1–81.0)	1.89 (1.47–2.41)	0.77 (0.67–0.90)
PCT	0.78 (0.73–0.83)	0.58 ng/mL	63.3% (54.0–71.8)	79.8% (78.3–81.2)	3.13 (2.67–3.67)	0.46 (0.36–0.59)
IL-6	0.89 (0.86–0.91)	185 pg/mL	84.4% (76.4–90.0)	79.3% (77.7–80.6)	4.06 (3.65–4.51)	0.20 (0.13–0.30)
IL-10	0.87 (0.83–0.90)	20.0 pg/mL	77.1% (68.3–84.0)	79.3% (77.8–80.7)	3.72 (3.28–4.21)	0.29 (0.21–0.41)

BSI, bloodstream infection; GNB, gram-negative bacteremia; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

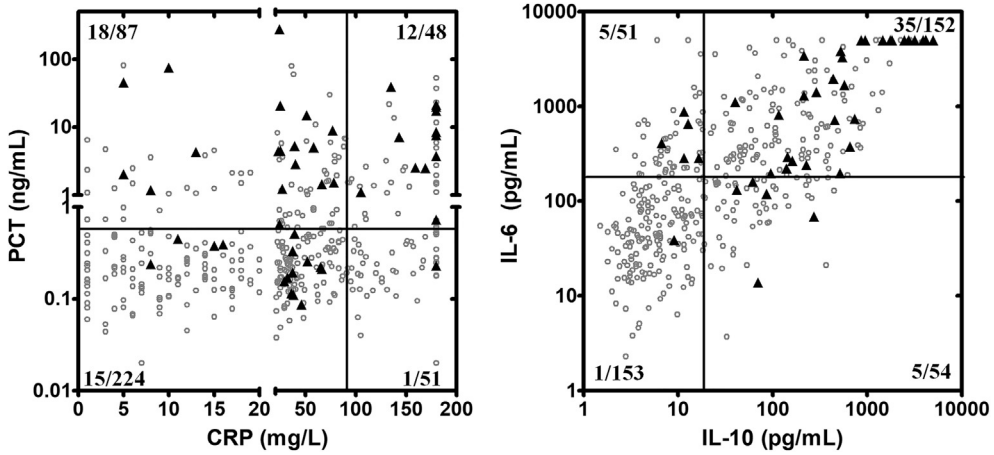

Fig. 3. Performance of biomarkers to identify septic shock in patients with BSI. the scatter plots showed the distribution of cases with BSI (blank circle) and septic shock (filled triangle). The numbers in the plot represented the case numbers of septic shock (numerator) and BSI (denominator), respectively.

4. Discussion

Septic shock is a serious medical condition with high mortality, especially in patients with underlying diseases such as hematological or neoplastic disorders. The primary cause of septic shock is bacterial infection. BSI represented one of the most severe infections in patients with cancer, with reported mortality rate reaching up to 40% [18,19]. GPB and GNB are the main types of BSI. As shown in the present study, the incidence of shock in patients with GPB is significantly lower than that in patients with GNB. We consider that GNB, but not GPB, is a high-risk form of infection among pediatric cancer patients which should be intervened early. As we reported in previous study, the mortality of septic shock in our department is relatively low with only eight patients died due to shock and four due to severe pneumonia in this cohort. Thus, we consider septic shock but not death as an endpoint in the present study.

Inflammatory cytokines play critical roles in the development of severe infection and are closely related to the outcome. Patients with higher IL-6 and IL-10 present much higher incidences of septic shock and mortality [9]. High serum IL-6 concentration causes hemodynamic disorder [10]. Corticosteroid has been proven to be the effective treatment of controlling septic shock by reducing pro-inflammatory cytokine levels [13,20]. As shown in this study, we have documented that IL-6 and IL-10 are the better biomarkers than others to identify GNB and septic shock in pediatric cancer patients with fever. As TNF-α is increased only in about 10% of episodes and IFN-γ levels are comparable among various types of infection, they are not the useful parameters for risk stratification. Although CRP was sensitive in febrile diseases, its discriminative performance to predict GNB and shock is not good.

In contrast to CRP, PCT was found to be elevated in only about 20%-30% of patients with localized infection, 42.4% with bacteremia, 68.8% with septic shock, indicating that PCT is mostly increased in patients with severe diseases. Thus, PCT is not clinically useful enough to identify patients with localized infection, while it is a more valuable biomarker for severe infectious diseases than CRP, which is in consistent with previous studies [21–23]. IL-6 is an inflammatory biomarker frequently used in the diagnosis of sepsis. Our previous study has demonstrated that it is very useful in discriminating Gram positive from negative bacteremia, evaluating the severity of infection and predicting the patients' outcome [10,11]. Compared with CRP, PCT and IL-6, IL-10 is an inflammatory biomarker less studied, however, it is a very useful tool to identify Gram negative bacteria and to judge the severity of infection or febrile neutropenia [11,24]. In the present study, compared with IL-6, IL-10 presents similar accuracy to predict GNB and septic shock, which is much higher than that of CRP and PCT. In order to make IL-10 a common biomarker used in clinical practice, the role of IL-10 to predict the organisms and severity of infection should be validated in more centers.

Although this is the largest cohort to systematically assess the role of inflammatory biomarkers such as PCT, IL-6 and IL-10 up to now, there are some drawbacks in this study. Firstly, the generalizability of the results may be limited because it was a single-center study and it focused on pediatric patients with cancer. Secondly, the biomarkers were measured only at the onset of fever, and the different kinetics of these markers relative to infection onset was not considered. Their performances to identify bacteremia in this study may not be the best one for each biomarker. For example, the dynamic change of PCT is more important than the absolute value to predict postoperative infection [25]. Thirdly, if the concentration of CRP, IL-6 or IL-10 reached the upper limit, we cannot get the true number, which has impact on the accuracy of the result, especially the performance of CRP.

5. Conclusions

BSI, especially GNB, is a high-risk form of infection which results in

Table 3
Multivariate analysis of related factors for GNB and septic shock.

Parameters	GNB		Septic shock	
	RR (95% CI)	P-value	RR (95% CI)	P-value
Age ≥ 6 year	1.08 (0.80–1.46)	0.614	2.73 (1.72–4.30)	< 0.001
Acute lymphoblastic leukemia	1.64 (1.13–2.38)	0.009	1.15 (0.71–1.88)	0.565
Neutropenia	1.92 (1.35–2.73)	< 0.001	1.74 (1.04–2.92)	0.034
CRP ≥ 90 mg/L	1.20 (0.85–1.70)	0.292	1.47 (0.94–2.32)	0.094
PCT ≥ 0.58 ng/mL	1.32 (0.95–1.83)	0.105	2.24 (1.41–3.56)	0.001
IL-6 ≥ 185 pg/mL	3.02 (2.16–4.23)	< 0.001	8.21 (4.58–14.72)	< 0.001
IL-10 ≥ 20.0 pg/mL	5.77 (4.11–8.10)	< 0.001	4.28 (2.56–7.15)	< 0.001

high incidence of septic shock. CRP, IL-6 and IL-10 are sensitive biomarkers for fever while PCT is elevated mostly in patients with severe diseases. IL-6 and IL-10 at the onset of fever present better performance than CRP and PCT in identifying patients with GNB and septic shock.

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Conflicts of interest

No potential conflicts of interest to declare.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA: Cancer J. Clinic. 67 (2017) 7–30.
[2] J.D. Pole, P. Gibson, M.C. Ethier, T. Lazor, D.L. Johnston, C. Portwine, et al., Evaluation of treatment-related mortality among paediatric cancer deaths: a population based analysis, Br. J. Cancer 116 (2017) 540–545.
[3] A. Kumar, D. Roberts, K.E. Wood, B. Light, J.E. Parrillo, S. Sharma, et al., Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock, Crit. Care Med. 34 (2006) 1589–1596.
[4] M. Plesko, J. Suvada, M. Makohusova, I. Waczulikova, D. Behulova, A. Vasilenkova, et al., The role of CRP, PCT, IL-6 and presepsin in early diagnosis of bacterial infectious complications in paediatric haemato-oncological patients, Neoplasma 63 (2016) 752–760.
[5] M.B. Mat-Nor, A. Md Ralib, N.Z. Abdulah, J.W. Pickering, The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality, J. Crit. Care 33 (2016) 245–251.
[6] K. Milcent, S. Faesch, C. Gras-Le Guen, F. Dubos, C. Poulalhon, I. Badier, et al., Use of procalcitonin assays to predict serious bacterial infection in young febrile infants, JAMA Pediatr. 170 (2016) 62–69.
[7] E. de Jong, J.A. van Oers, A. Beishuizen, P. Vos, W.J. Vermeijden, L.E. Haas, et al., Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial, Lancet. Infect. Dis 16 (2016) 819–827.
[8] A. Rhodes, L.E. Evans, W. Alhazzani, M.M. Levy, M. Antonelli, R. Ferrer, et al., Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016, Crit. Care Med. 45 (2017) 486–552.
[9] Y. Tang, C. Liao, X. Xu, H. Song, S. Shi, S. Yang, et al., Evaluation of Th1/Th2 cytokines as a rapid diagnostic tool for severe infection in paediatric haematology/oncology patients by the use of cytometric bead array technology, Clinic. Microbiol. Infect.: Off. Publ. Eur. Soc. Clinic. Microbiol. Infect. Dis. 17 (2011) 1666–1673.
[10] X.J. Xu, Y.M. Tang, H. Song, S.L. Yang, W.Q. Xu, S.W. Shi, et al., A multiplex cytokine score for the prediction of disease severity in pediatric hematology/oncology patients with septic shock, Cytokine 64 (2013) 590–596.
[11] X.J. Xu, Y.M. Tang, C. Liao, H. Song, S.L. Yang, W.Q. Xu, et al., Inflammatory cytokine measurement quickly discriminates gram-negative from gram-positive bacteremia in pediatric hematology/oncology patients with septic shock, Intens. Care Med. 39 (2013) 319–326.
[12] T. Xia, X. Xu, N. Zhao, Z. Luo, Y. Tang, Comparison of the diagnostic power of cytokine patterns and procalcitonin for predicting infection among paediatric haematology/oncology patients, Clinic. Microbiol. Infect.: Off. Publ. Eur. Soc. Clinic. Microbiol. Infect. Dis. 22 (2016) 996–1001.
[13] D. Keh, T. Boehnke, S. Weber-Cartens, C. Schulz, O. Ahlers, S. Bercker, et al., Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study, Am. J. Respir. Crit. Care Med. 167 (2003) 512–520.
[14] R.S. Phillips, R. Wade, T. Lehrnbecher, L.A. Stewart, A.J. Sutton, Systematic review and meta-analysis of the value of initial biomarkers in predicting adverse outcome in febrile neutropenic episodes in children and young people with cancer, BMC Med. 10 (2012) 6.
[15] L. Ma, H. Zhang, Y.L. Yin, W.Z. Guo, Y.Q. Ma, Y.B. Wang, et al., Role of interleukin-6 to differentiate sepsis from non-infectious systemic inflammatory response syndrome, Cytokine 88 (2016) 126–135.
[16] The Group of Emergency Medicine, Chinese Pediatric Society, Chinese Medical Association, The Group of Pediatrics, Chinese Society of Emergency Medicine, Chinese Medical Association, The Editorial Board of Chinese Journal of Pediatrics, Recommended protocol for diagnosis and treatment of septic shock in children, Chin. J. Pediatr. 44 (08) (2006) 596-596.
[17] Y. Tang, X. Xu, H. Song, S. Yang, S. Shi, J. Wei, et al., Early diagnostic and prognostic significance of a specific Th1/Th2 cytokine pattern in children with haemophagocytic syndrome, Br. J. Haematol. 143 (2008) 84–91.
[18] H. Wisplinghoff, H. Seifert, R.P. Wenzel, M.B. Edmond, Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States, Clinic. Infect. Dis.: Off. Publ. Infect. Dis. Soc. Am. 36 (2003) 1103–1110.
[19] C. Gudiol, M. Bodro, A. Simonetti, F. Tubau, E. Gonzalez-Barca, M. Cisnal, et al., Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients, Clinic. Microbiol. Infect.: Off. Publ. Eur. Soc. Clinic. Microbiol. Infect. Dis. 19 (2013) 474–479.
[20] X.J. Xu, Y.M. Tang, H. Song, S.L. Yang, W.Q. Xu, S.W. Shi, Corticosteroid administration is associated with improved outcome of patients presenting high inflammatory cytokine levels during septic shock, Pediatr. Blood Cancer 61 (2014) 2243–2248.
[21] A.J. Lautz, A.C. Dziorny, A.R. Denson, K.A. O'Connor, M.R. Chilutti, R.K. Ross, et al., Value of procalcitonin measurement for early evidence of severe bacterial infections in the pediatric intensive care unit, J. Pediatr. 179 (2016) 74–81 e2.
[22] C. Rey, M. Los Arcos, A. Concha, A. Medina, S. Prieto, P. Martinez, et al., Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children, Intens. Care Med. 33 (2007) 477–484.
[23] S. Gaini, O.G. Koldkjaer, C. Pedersen, S.S. Pedersen, Procalcitonin, lipopolysaccharide-binding protein, interleukin-6 and C-reactive protein in community-acquired infections and sepsis: a prospective study, Crit. Care 10 (2006) R53.
[24] G. Matera, R. Puccio, A. Giancotti, A. Quirino, M.C. Pulicari, E. Zicca, et al., Impact of interleukin-10, soluble CD25 and interferon-gamma on the prognosis and early diagnosis of bacteremic systemic inflammatory response syndrome: a prospective observational study, Crit. Care 17 (2013) R64.
[25] X. Li, X. Wang, S. Li, J. Yan, D. Li, Diagnostic value of procalcitonin on early postoperative infection after pediatric cardiac surgery, Pediatr. Crit. Care Med.: J. Soc. Crit. Care Med. World Fed. Pediatr. Intens. Crit. Care Soc. 18 (2017) 420–428.