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Eosinopenia Associated with Infection is an Independent Risk Factor for 28-day Mortality in *Staphylococcus aureus* Bloodstream Infection

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Authors' contributions

This work was carried out in collaboration among all authors. Author CZ designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Authors JS and FX collected the data. Author SJ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This retrospective study aimed to evaluate the impact of eosinopenia on 28-day mortality in *Staphylococcus aureus* bloodstream infection (SABSI).
Methods: A retrospective study was designed to evaluate the impact of eosinopenia on 28-day mortality in SABSI.
Results: Patients who were ≥16 years old with SABSI at Sun Yat-Sen Memorial Hospital between January 1st 2014 and December 31st 2018 were included. The overall 28-day mortality of all patients was 14.3% (44 out of 307). Patients with eosinopenia in the onset of SABSI had a significantly higher 28-day mortality than those without eosinopenia (22.4% vs 6.5%; P<0.01). For patients who developed SABSI after the first 48 hours in the hospital, eosinophils decreased significantly from the baseline (P<0.01). Kaplan–Meier survival curve showed that patients with

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eosinopenia had a lower survival rate than those without eosinopenia (*P*<0.01). Multivariate Cox regression analysis revealed that eosinophils in the onset of SABSI were associated independently with 28-day mortality (hazard ratio [HR], 2.84; 95% confidence interval [CI], 1.36–5.91; *P*<0.01).
Conclusion: Eosinopenia associated with infection might be an independent risk factor for 28-day mortality in SABSI.

Keywords: Staphylococcus aureus; bloodstream infection; prognosis; eosinopenia.

ABBREVIATION

SABSI : Staphylococcus aureus bloodstream infection.

1. INTRODUCTION

The *Staphylococcus aureus* bloodstream infection (SABSI) is a common condition with a high fatality rate,an important cause of morbidity and mortality all over the world [1]. In North America, the incidence of SABSI has ranged between 20 and 40 cases per 100,000 population, with an increase demonstrated over the last two decades in some regions [2]. In an epidemiological study from 2011 to 2013 in Alberta of Canada, there were 299 cases of Methicillin-Resistant *Staphylococcus aureus* bloodstream infection, equating to 3.95 cases per 100,000 population [3].

So far, foreseeing the prognosis of SABSI in the early stage remains a huge challenge. Some biological parameters such as C-reactive protein and procalcitonin, have been used to determine the diagnosis of infection or bacteriaemia, but these biomarkers are not necessarily associated with the prognosis [4-6]. Moreover, as the resources are limited, the use of some biomarkers remains unavailable in some developing countries. Therefore, an ideal biomarker which is highly specific and sensitive, easy to measure and inexpensive is in urgent need.

Unlike the biological parameters mentioned above, the routine analysis of blood is economical, thus put into use extensively among patients. Eosinophils are multifunctional cells of the innate immune system linked to allergic and parasitic inflammation in the traditional perspective, and are generally interpreted as purely detrimental. Surprisingly, the intricate relationship between eosinophils and infectious diseases has been delineated detailed in recent researches, in which eosinophils have been shown to have a unique protective role in the setting of nonparasitic infectious diseases. In infectious-related asthma patients, the phago-cytosis of bacteria by eosinophils might be a dominating pathophysiological process [7]. Caroline et al. [8] confirmed that degranulating airway eosinophils promoted survival in virus infection, and activated eosinophils from both Aspergillus antigen and cytokine-driven asthma models were profoundly antiviral and promoted survival in an otherwise lethal pneumonia virus of mice infection. In mice infected with influenza A virus, eosinophils were susceptible to the virus and responded by activation, piecemeal degranulation and upregulation of antigen presentation markers. The transfer of eosinophils from lungs of allergen-sensitized and challenged mice to influenza virus-infected mice reduced morbidity and viral burden, improved lung compliance, and increased CD8(+) T cell numbers in the airways [9].

To the best of our knowledge, neither any work has investigated the incidence of eosinopenia in SABSI, nor the potential association between theosbee patients.

Therefore, the study designed a evaluate the impact of eosinopenia on 28-day mortality in SABSI. In this study, we showed that eosinophils were susceptible to SABSI and eosinopenia associated with infection was an independent risk factor for 28-day mortality in SABSI.

2. MATERIALS AND METHODS

2.1 Study Population

We performed a retrospective cohort study at Sun Yat-Sen Memorial Hospital between January 1st 2014 and December 31st 2018. Sun Yat-Sen Memorial Hospital is 2800-bed primary care and tertiary referral centre in South China. Patients who were ≥16 years of age with SABSI were chosen from the computerized database of the hospital's clinical microbiology laboratory. For patients who had more than one episode of SABSI, only the first episode was selected for this study. Patients with a length of stay shorter than 48 hours after the episode of SABSI were excluded.

2.2 Study Design

The study reviewed retrospectively the medical records of all the eligible patients. The data collected included demographic, clinical, microbiological data and the outcome. The main outcome was 28-day mortality. All of the patients had given their informed consent for the medical and the study was approved by the Institutional Review Board.

2.3 Definitions

SABSI was defined as the isolation of *Staphylococcus aureus* in a blood culture. Initial antibiotic therapy was considered adequate when at least one adequate antimicrobial was given within 24 hours of SABSI onset, and the dose and pattern of administration must be in accordance with current medical standards. The adequacy of the antimicrobial was determined by *in vitro* susceptibility for the causative microorganism [10]. There has been no unified standard for eosinopenia so far. The standards adopted in the previous researches were varied from 0.01×10^9/L to 0.04×10^9/L and the definition 0.02×10^9/L adopted in the present research actually was based on the distribution of eosinophils in the onset of SABSI.

2.4 Microbiological and Biochemical Testing

Blood cultures, consisting of aerobic and anaerobic samples, were processed at the clinical laboratory of the hospital. The Vietk 2 system (bioMérieux, Marcy l'Etoile, France) was used for isolate identification and antimicrobial susceptibility testing. Minimum inhibitory concentrations were classified according to the Clinical Laboratory and Standards Institute criteria used in the corresponding year. Blood counts were measured by a XE-5000 haematology analyzer (Sysmex, Kobe, Japan), and levels of serum creatinine and total bilirubin were measured by a TBA-2000FR hematology biochemical analyzer (Toshiba, Tokyo, Japan). Patients were divided into two cohorts depending on whether the SABSI was onset in the first 48 hours in the hospital or not. The data of blood counts in the onset of SABSI were collected in all patients, and data of blood counts in the first hospital day were also collected in those who had SABSI onset after the first 48 hours in the hospital.

2.5 Statistical Analysis

The main outcome was all-cause 28-day mortality. For convenience, some continuous parameters were dichotomised at the median, including leukocytes, platelets, haemoglobin, neutronphils, lymphocytes, monocytes, eosinophils, basophils, serum creatinine and total bilirubin.

Firstly, baseline differences between survivors and non-survivors were compared. Parametric variables (except the dichotomized ones) were described as mean (standard deviation, SD), while non-parametric variables as median (interquartile range, IQR). Means were executed with Student's t test or paired Student's t test when appropriate. Medians and comparative analysis were executed with Mann–Whitney U test, Kruskal–Wallis test or chi-square test when appropriate.

Secondly, the Kaplan–Meier survival curve was used to assess the association between eosinopenia and all-cause 28-day mortality and log rank test was done to compare the survival curves.

Thirdly, Cox proportional hazards regression models were performed, in which hazard ratio (HR) and 95% confidence interval (CI) were reported, to assess predictors of 28-day mortality. Variables with a $P< 0.05$ in univariate analysis, along with age and sex, were entered in the multivariate Cox regression model. All P values were 2-tailed and statistical significance was set at $P< 0.05$. All statistic analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA).

3. RESULTS

3.1 Study Population

During the study period, a total of 307 patients with SABSI were identified. The mean age (±SD) of these patients was 56.9±17.7 years and 65.5% were male (n=201). The most common underlying disease was hypertension (n=107, 34.9%), followed by solid organ malignancy (n=94, 30.6%). Comparisons between survivors and non-survivors in the whole study population were summarized in Table 1. The disease severity in the non-survivor group was much more critical than that of the other group. Drug-resistance bacteria and receiving an inappropriate initial empirical antimicrobial therapy were more common in the non-survivors. For the routine analysis of blood in the

onset of SABSI, no significant differences in the leukocytes, neutrophils, monocytes, basohils or lymphocytes were observed between the two groups, while the reduction of platelets, haemoglobin and eosinophils in non-survivors were much more frequent. The median of eosinophil counts in the onset of SABSI was 0.02×10^9/L, which happened to be the boundary of eosinopenia according to the criterion used in the clinical laboratory. There were 101 patients who had SABSI onset in the first 48 hours in the hospital, while 206 patients developed SABSI after 48 hours. For patients who developed SABSI after 48 hours in the hospital, paired Student's t test showed that eosinophils decreased significantly after the SABSI (Difference value=0.04, $P < 0.01$).

3.2 28-day Mortality and Predictors of Mortality

The overall 28-day mortality of all patients was 14.3% (44 out of 307). Patients in the onset of SABSI had a significantly higher 28-day mortality than those without eosinopenia (22.4% vs 6.5%; P<0.01). The survival curve showed that patients with eosinopenia had a lower probability of survival than those without eosinopenia (Fig. 1, log rank test, P<0.01). In the subgroup analysis, for patients who developed SABSI after 48 hours in hospital, the survival curve showed the same trend among the prognosis and eosinopenia in the onset of SABSI (Fig. 2, log rank test, P<0.01), while eosinopenia presenting in the first day in hospital in these patients was not associated with the prognosis (P=0.09). By multivariate Cox proportional hazards regression analysis, eosinophils in the onset of SABSI were associated independently with 28-day mortality (HR, 2.84; 95% CI, 1.36–5.91; P<0.01), while the other blood hemocytes were not (Table 2). Factors associated with 28-day mortality also included male, serum creatinine, total bilirubin and inappropriate empiric antimicrobial therapy. In the subgroup analysis, for patients who developed SABSI after 48 hours in the hospital, eosinophils in the onset of SABSI were associated independently with 28-day mortality (HR, 3.20; 95% CI, 1.23–8.14; P<0.01), while eosinophils in the first day were not (Table 3).

4. DISCUSSION

Our study demonstrated that eosinopenia in the onset of SABSI might be a predictive factor of the 28-day mortality of SABSI. It was the first time to explore the relationship of evolution of eosinophil and the prognosis of SABSI. As the eosinophil count is given for each patient, it would be a great gain for no additional outlay if eosinopenia is proven to be a useful prognostic marker.

Eosinophils have been traditionally perceived largely as end-stage, cytotoxic effector cells associated with allergy and parasitic diseases [11-13]. Production of eosinophils is tightly regulated by interleukin-3, interleukin-5 and granulocyte–macrophage colony-stimulating factor [14,15]. Studies have confirmed that the decline of eosinophil count is associated with any of the three processes: peripheral sequestration of eosinophils, suppression of egress of mature eosinophils and suppression of eosinophil production [16]. By expressing specific cytokines associated with inner immunity, eosinophils might play an indispensable role in viral infection. In mouse airways *in vivo* and in isolated human eosinophils *in vitro*, eosinophils mediated the antiviral effect via the production of nitric oxide and by serving as a dead-end host for virus infection. Eosinophils produced nitric oxide in response to virus and to a synthetic agonist of the virus-sensing innate immune receptor, Toll-like receptor (TLR) 7 [17]. In another research, eosinophils were able to limit lung dysfunction associated with the respiratory syncytial virus, via surface and intracellular TLR associated with antiviral immunity and responding functionally to TLR ligands [18]. Shigeharu et al. [19] demonstrated that activated human eosinophils can undergo extracellular DNA trap cell death (ETosis) that cytolytically releases free eosinophil granules, and EETosis resulted in the generation of histone-bearing nuclear DNA extracellular nets and cell-free granules, both of which may exert biological activities for eosinophils postmortem.

On the contrary, in the territory of bacterial infection, the relationship between the eosinophil count and the inner immunity are poorly understood. The mechanism of eosinopenia in bacterial infectious diseases is much less reported. It is a conventional knowledge that cortisol increases leukocyte and neutrophil counts, whereas it reduces lymphocyte, monocyte and eosinophil counts. Some study suggested that eosinopenia can develop from acute severe stress of infectious or noninfectious, which is mediated by adrenal glucocorticoids and epinephrine [20-22]. Basic research showed that *Staphylococcus aureus* mediated rapid eosinophil cell death, and the cytolysin was a major contributory factor in

eosinophil death [23]. Bass showed that both the infectious and noninfectious stimuli of acute inflammation markedly suppressed eosinophilia, which suggested that eosinopenia was a

Table 1. Comparisons between survivors and non-survivors in the whole study population

Variable	Survivors (N=263)	Non-survivors (N=44)	All patients (N=307)	*P* value
Male gender	178(67.7%)	23(52.3%)	201(65.5%)	0.05
Age(Mean, ±SD)	56.3(±17.9)	60.4(±16.0)	56.9(±17.7)	0.13
LOS before BSI(Mean, ±SD)	15.2(±21.2)	16.9(±22.3)	15.2(±21.4)	0.58
Neutropeni[a]	9(3.4%)	4(9.1%)	13(4.2%)	0.19
Prior surgery or trauma[a]	84(31.9%)	19(43.2%)	103(33.6%)	0.14
With previous hospitalization in the preceding 90 days	122(46.4%)	27(61.4%)	149(48.5%)	0.07
Antibiotics therapy	121(46.0%)	30(68.2%)	151(49.2%)	<0.01
Prior chemotherapy or radiotherapy[a]	45(17.1%)	6(13.6%)	51(16.6%)	0.57
Dialysis or filtration[a]	9(4.0%)	3(7.7%)	12(4.6%)	0.55
Mechanical ventilation[b]	49(18.6%)	14(31.8%)	63(20.5%)	0.05
Indwelling central venous catheter[b]	101(38.4%)	27(61.4%)	128(41.7%)	<0.01
Indwelling nasogastric tube[b]	65(24.7%)	20(45.5%)	85(27.7%)	<0.01
Indwelling urinary catheter[b]	84(31.9%)	24(54.5%)	108(35.2%)	<0.01
Underlying disease				
Solid organ malignancy	78(29.7%)	16(36.4%)	94(30.6%)	0.37
Hematological malignancy	13(4.9%)	3(6.8%)	16(5.2%)	0.60
Chronic lung disease	14(5.3%)	1(2.3%)	15(4.9%)	0.62
Cerebrovascular disease	36(13.7%)	5(11.4%)	41(13.4%)	0.68
Chronic cardiac failure	38(14.8%)	11(25.0%)	50(13.6%)	0.09
Hypertension	90(34.2%)	17(38.6%)	107(34.9%)	0.57
Atrial fibrillation	11(4.2%)	4(9.1%)	15(4.9%)	0.31
Liver cirrhosis	18(6.8%)	6(13.6%)	24(7.8%)	0.21
Chronic renal failure	31(11.8%)	3(6.8%)	34(11.1%)	0.48
Diabetes mellitus	58(22.1%)	10(22.7%)	68(22.1%)	0.92
Autoimmune disease	36(13.7%)	8(18.2%)	44(14.3%)	0.43
Charlson score(Mean, ±SD)	1.9(±1.9)	2.7(±2.2)	2.0(±1.9)	<0.01
Pitt score(Mean, ±SD)	1.7(±2.0)	3.1(±2.8)	1.9(±2.2)	<0.01
APACHE Ⅱ score(Mean, ±SD)	11.3(±5.5)	16.3(±7.3)	12.0(±6.1)	<0.01
Drug-resistance bacteria	173(65.8%)	39(88.6%)	212(69.1%)	<0.01
MRSA	114(43.3%)	25(56.8%)	139(45.3%)	0.10
Inappropriate empiric	109(41.4%)	31(70.5%)	140(45.6%)	<0.01
antimicrobial therapy	129(49.0%)	28(63.6%)	157(51.1%)	0.07
*Serum creatinine[c]				
*Total bilirubin[c]	127(48.3%)	31(70.5%)	158(51.5%)	<0.01
*Leukocytes[c]	130(49.4%)	24(54.5%)	154(50.2%)	0.53
*Hemoglobin [c]	122(46.4%)	32(72.7%)	154(50.2%)	<0.01
*Platelets[c]	118(44.9%)	29(65.9%)	147(47.9%)	0.01
*Lymphocytes[c]	130(49.4%)	27(61.4%)	157(51.1%)	0.14
*Neutrophils[c]	127(49.0%)	22(52.4%)	149(49.5%)	0.69
*Monocytes[c]	129(49.0%)	28(63.6%)	157(51.1%)	0.07
*Basohils[c]	187(71.7%)	36(81.8%)	223(72.6%)	0.14
*Eosinophils[c]	118(44.9%)	34(77.3%)	152(49.5%)	<0.01

Abbreviation: LOS=length of sta; Values are n (%) unless otherwise noted; [a]Within 30 days preceding infection onset; [b]Within 48 hours preceding infection onset

MRSA= Methicillin Resistant Staphylococcus Aureus; Values are n (%) unless otherwise noted;

[c]Data in the onset of Staphylococcus aureus Bloodstream Infection; Parameters dichotomised at the median; Values are n (%) unless otherwise noted

The numbers were patients' numbers with leukocytes, haemoglobin, platelets, neutrophils, lymphocytes, monocytes, basophils or eosinophils under the median, and patients' numbers with serum creatinine total bilirubin above the median

Table 2. Cox proportional hazards regression analysis for mortality in *Staphylococcus aureus* bloodstream infection

Variable	Univariate HR(95%CI)	*P* value	Multivariate HR(95%CI)	*P* value
Male gender	0.54(0.30-0.97)	0.04	0.43(0.22-0.81)	0.01
Age, +10 years	1.11(0.94-1.31)	0.24	1.00(0.83-1.18)	0.91
Neutropenia[a]	2.43(0.87-6.80)	0.09		
With previous hospitalization in the preceding 90 days	1.80(1.00-3.30)	0.06		
Antibiotics therapy	2.32(1.23-4.38)	0.01		
Mechanical ventilationa[b]	1.92(1.02-3.62)	0.04		
Indwelling central venous catheter[b]	2.33(1.27-4.28)	<0.01		
Indwelling nasogastric tube[b]	2.28(1.26-4.12)	<0.01		
Indwelling urinary catheter[b]	2.35(1.30-4.25)	<0.01		
APACHE □score, +1 score	1.11(1.07-1.15)	<0.01		
Pitt score, +1 score	1.22(1.11-1.34)	<0.01		
Charlson score, +1 score	1.18(1.04-1.35)	0.01		
Drug-resistance bacteria	3.61(1.42-9.17)	<0.01		
Inappropriate empiric antimicrobial therapy	2.96(1.55-5.66)	<0.01	4.01(2.04-7.92)	<0.01
Total bilirubin	2.32(1.22-4.44)	0.01	2.20(1.13-4.29)	0.02
Serum creatinine	1.75(0.95-3.24)	0.07	2.08(1.07-4.02)	0.03
Monocytesc	1.74(0.94-3.21)	0.08		
Eosinophils[c]	3.98(1.97-8.06)	<0.01	2.84(1.36-5.91)	<0.01

[a]Within 30 days preceding infection onset; [b]Within 48 hours preceding infection onset; [c]Data in the onset of infection

Table 3. Cox proportional hazards regression analysis for mortality in *Staphylococcus aureus* bloodstream infection developed after 48 hours in hospital

Variable	Univariate HR(95%CI)	*P* value	Multivariate HR(95%CI)	*P* value
Male gender	0.58(0.29-1.15)	0.12	0.55(0.27-1.13)	0.10
Age, +10 years	1.08(0.88-1.32)	0.46	1.06(0.85-1.33)	0.61
Antibiotics therapy	1.92(0.92-4.02)	0.09		
Mechanical ventilationa[a]	1.82(0.91-3.67)	0.09		
Indwelling central venous catheter[a]	2.14(1.02-4.49)	0.05		
Indwelling nasogastric tube[a]	2.20(1.11-4.36)	0.02		
Indwelling urinary catheter[a]	2.26(1.11-4.59)	0.02		
Chronic cardiac failure	2.46(1.11-5.46)	0.03		
Liver cirrhosis	2.39(1.00-5.80)	0.05	3.17(1.23-8.14)	0.02
Charlson score, +1 score	1.21(1.04-1.39)	0.01		
APACHE αscore, +1 score	1.12(1.07-1.17)	<0.01		
Pitt score, +1 score	1.22(1.10-1.36)	<0.01		
Serum creatinine	2.29(1.09-4.81)	0.03	2.56(1.18-5.56)	0.02
Total bilirubin	2.24(1.04-4.82)	0.04		
Eosinophilsb	3.02(1.43-6.34)	<0.01	3.20(1.23-8.14)	<0.01

[a]Within 48 hours preceding infection onset. [b]Data in the onset of infection

response to the acute inflammatory process rather than to a specific type of pathogen [16]. Erica et al. [24] found an essential role for eosinophils in the immune response that reduces pathology associated with Clostridium difficile infection. In this process, the eosinophil number increased via microbiota-regulated interleukin-25. In the present study, eosinopenia in the onset of SABSI was found to be an independent risk factor of 28-day mortality. For patients who developed SABSI after 48 hours in the hospital, eosinophils in the onset of SABSI decreased significantly from the baseline values in the first day and the subgroup analysis shows that only eosinopenia associated with the infection was an independent risk factor of mortality. Therefore,

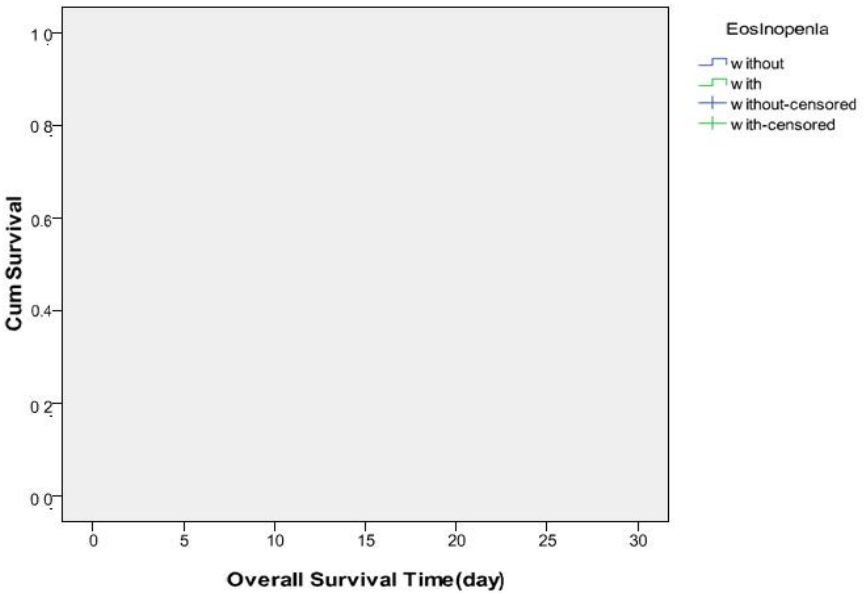

Fig. 1. Survival curve for patients with eosinopenia and patients without eosinopenia (log rank test, *p*<0.01)

The blue solid line indicates the survival curve for patients without eosinopenia, and the green dotted line indicates the survival curve for patients with eosinopenia

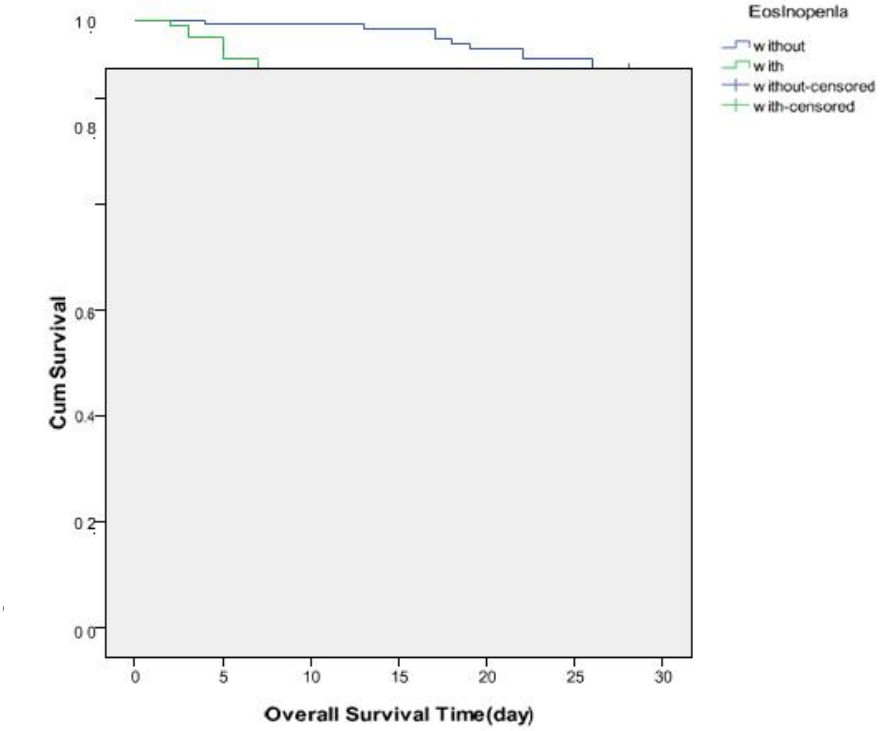

Fig. 2. For patients who developed *Staphylococcus aureus* bloodstream infection after 48 hours in hospital, survival curve for patients with eosinopenia and patients without eosinopenia (log rank test, *P*<0.01)

The blue solid line indicates the survival curve for patients without eosinopenia, and the green dotted line indicates the survival curve for patients with eosinopenia

given that patients were under severe stress of the bloodstream infection, we assume that there might be a powerful stimulation of adrenal glucocorticosteroid produced by the stress of the infection, though the level of patients' glucocorticosteroid had not been detected. As an acute physiological reaction to the SABSI, eosinopenia did harm to the SABSI in turn. Although eosinophils are not usually considered to play a crucial role in immune defences against bacteria, some studies have shown they possess anti-bacterial capabilities, mediated by granule contents [25,26] or release of mitochondrial DNA [27]. A retrospective study also found that eosinophil behaved as a protective cell in patients with ventilator-associated pneumonia caused by *Staphylococcus aureus* [28].

5. CONCLUSION

In conclusion, the decline of eosinophils is an early message associated with the severity of SABSI, and eosinopenia associated with infection might be an independent risk factor for mortality in SABSI. Further studies are needed to demonstrate how the infection and eosinopenia interact with each other.

CONSENT

All authors declare that written informed consent was obtained from the patients for publication of this report. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

The study protocol has been approved by the research institute's committee on human research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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