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RESEARCH ARTICLE

Risk stratification system for skin and soft tissue infections after allogeneic hematopoietic stem cell transplantation: PAH risk score

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Abstract **Skin and soft tissue infections (SSTIs) refer to infections involving the skin, subcutaneous tissue, fascia, and muscle. In transplant populations with hematological malignancies, an immunocompromised status and the routine use of immunosuppressants increase the risk of SSTIs greatly. However, to date, the profiles and clinical outcomes of SSTIs in hematopoietic stem cell transplantation (HSCT) patients remain unclear. This study included 228 patients (3.67%) who developed SSTIs within 180 days after allogeneic HSCT from January 2004 to December 2019 in Peking University People's Hospital. The overall annual survival rate was 71.5%. We compared the differences between survivors and non-survivors a year after transplant and found that primary platelet graft failure (PPGF), comorbidities of acute kidney injury (AKI), and hospital-acquired pneumonia (HAP) were independent risk factors for death in the study population. A PPGF–AKI–HAP risk stratification system was established with a mortality risk score of 1×PPGF+1×AKI+1×HAP. The areas under the curves of internal and external validation were 0.833 (95% CI 0.760–0.906) and 0.826 (95% CI 0.715–0.937), respectively. The calibration plot revealed the high consistency of the estimated risks, and decision curve analysis showed considerable net benefits for patients.**

Keywords skin and soft tissue infections; hematopoietic stem cell transplantation; risk stratification system; mortality

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the most effective therapies for many hematological disorders [1]. In the past 20 years, allo-HSCT has achieved a breakthrough, namely, the expanded selection of stem cell sources from mismatched human leukocyte antigen (HLA) donors [2]. In addition, advanced prevention and treatment strategies have been proposed to address post-HSCT graft-versus-host disease (GVHD) [3,4]. However, allo-HSCT recipients are often vulnerable when exposed to pathogens, including bacteria, fungi, and viruses, which could lead to lethal diseases [5].

Skin and soft tissue infections (SSTIs) refer to infections occurring in the skin, subcutaneous tissue, fascia, and muscle [6,7]. Since the beginning of the 21st century, the incidence of SSTIs has been increasing dramatically [8]. SSTIs in immunocompromised patients should be classified as severe [9]. In the HIV-infected population, the incidence of SSTIs is approximately 15.7%, which is much higher than the incidence of SSTIs among people without HIV infection [10]. In the transplant population, the routine use of immunosuppressive agents increases the risk of SSTIs [11]. However, to date, no study has focused on SSTIs in HSCT recipients. The common pathogens, occurrence periods, anatomic locations, and clinical outcomes of SSTIs in the allo-HSCT population remain unclear.

In this work, we conducted a real-world study to

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investigate the frequency, onset time, common anatomic locations, and clinical outcomes of allo-HSCT recipients with SSTIs. A risk stratification system was developed and validated to predict patients' 12-month survival. Our risk scoring system focuses on the clinical features and comorbidities of patients with SSTIs and can be simply and conveniently used in clinical practice.

Methods

Patient selection and study designs

A real-world study was conducted to review data from 7044 recipients who underwent allo-HSCT between January 2004 and December 2019 at the Institute of Haematology, Peking University People's Hospital. Fig. 1 shows the process by which we identified the study population. For selection, patients were required to have at least one discharge diagnosis based on the International Classification of Diseases Tenth Revision (ICD-10) code for SSTIs. The specific ICD diagnosis and corresponding code are summarized in Table 1 [12,13]. Our study focused on infections that occurred from pre-treatment to 180 days after HSCT. We included 228 patients with 237 SSTI discharge diagnoses. Only the last infection per individual was used in this study. The entire study population consisted of inpatients who met our inclusion criteria.

In our study, all patients had a follow-up period of at least 12 months, during which patients returned for visits once a month and underwent routine examinations. Data, including baseline features, clinical symptoms, laboratory examinations, microbiology records, imaging results, therapies, and clinical outcomes, were recorded in detail. Two researchers extracted relevant information from electronic medical records and checked the data to ensure accuracy.

Our study was conducted in strict accordance with the *Declaration of Helsinki* and authorized by the Peking University People's Hospital Ethics Committee.

Transplant protocol

The prescribed conditioning regimens have been introduced in detail in a previous study [14]. All recipients received

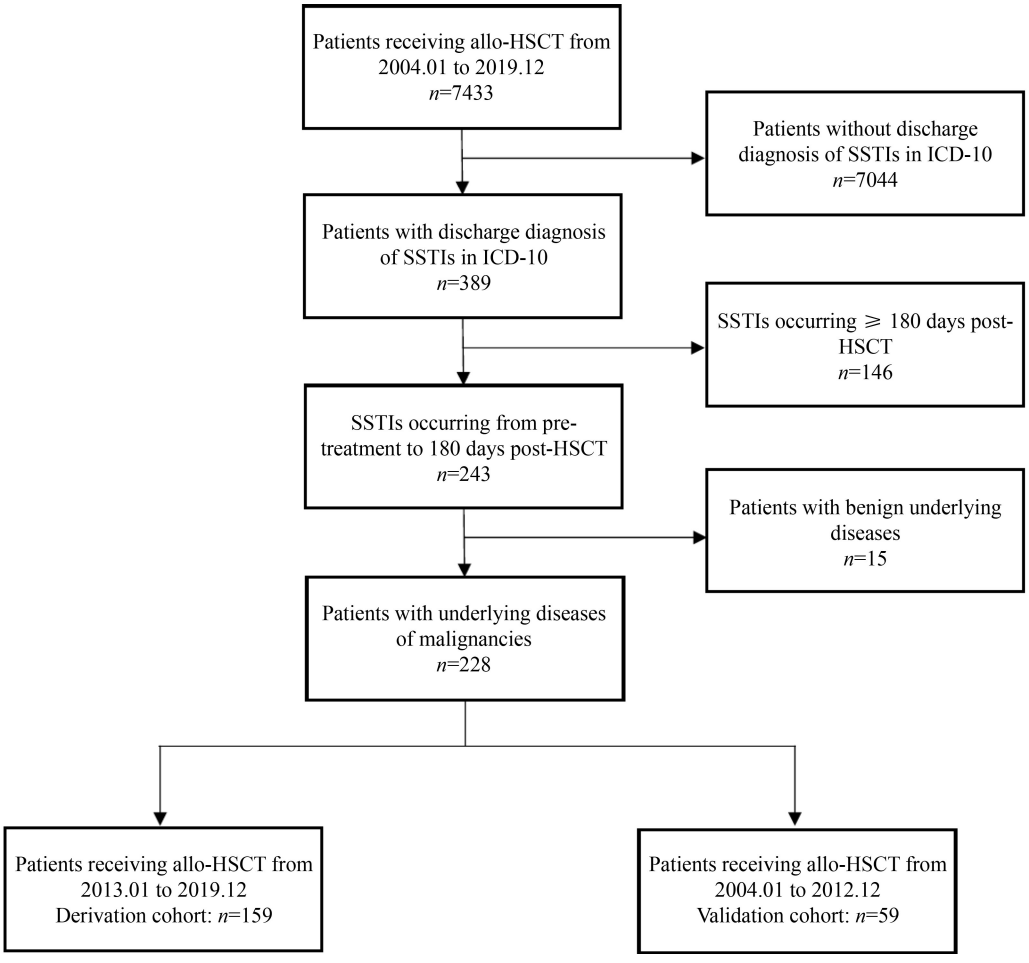

Fig. 1 Flow chart of the study population selection.

Table 1 ICD-10 diagnosis and code of SSTIs in allo-HSCT recipients

ICD diagnosis	ICD code	No. of patients (%)
Anogenital herpesvirus (herpes simplex) infection	A60.XXX	3 (1.3)
Viral infections characterized by skin and mucous membrane lesions	B00.XXX–B09.XXX	20 (8.8)
Dermatophytosis	B35.XXX	2 (0.88)
Candidiasis of skin and nail	B37.201	2 (0.88)
Anal abscess	K61.002	13 (5.7)
Perianal infection	K62.805	22 (9.6)
Cutaneous abscess, furuncle, and carbuncle	L02.XXX	4 (1.8)
Cellulitis	L03.XXX	13 (5.7)
Other local infections of skin and subcutaneous tissue	L08.XXX	110 (48.2)
Decubitus ulcer	L89.XXX	3 (1.3)
Gangrene	R02.XXX	1 (0.4)
Infection and inflammatory reaction due to vascular devices	T82.703	28 (12.3)
Infection following a procedure, not elsewhere classified	T81.XXX	2 (0.88)

busulfan-based conditioning therapy, including the administration of cytarabine (4 g/m^2/day, from −10 days to −9 days, intravenously), busulfan (BU) (3.2 mg/kg/day, from −8 days to −6 days, intravenously), cyclophosphamide (CY) (1.8 g/m^2/day, from −5 days to −4 days, intravenously), and semustine (250 mg/m^2, on day 3). In terms of antithymocyte immunoglobulin, in the HLA haplo-HSCT population, the recipients intravenously received 2.5 mg/kg/day of this medicine from −5 days to −2 days, whereas the HLA-matched patients did not receive it. In addition, the elderly (≥55 years old) and/or drug-intolerant patients received modified conditioning regimith fludarabine (FLU) (30 mg/m^2/day, from −5 days to 1 day, intravenously) in place of CY [15]. To prevent post-HSCT GVHD, all recipients were treated with mycophenolate mofetil, cyclosporine A, and short-term methotrexate [16].

Infection prevention protocol

All allo-HSCT recipients received infection prevention measures, and the specific treatment and care plan was as follows. All patients were hospitalized for 4 to 5 weeks (from −10 days until neutrophil engraftment) in a room fitted with a high-efficiency, particle-arresting air filter. All patients were given oral trimethoprim-sulfamethoxazole from −10 days to +180 days to prevent *Pneumocystis jiroveci* pneumonia. For the treatment of invasive fungal infections, fluconazole or itraconazole capsules were given from −10 days to +75 days, and herpes simplex virus and varicella-zoster virus acyclovir were used from +1 day to CSA withdrawal time. The patients also received oral antibiotics for gastrointestinal decontamination before and during neutropenia. Ganciclovir (5 mg/kg) was given two times intravenously from −9 days to −2 days to prevent cytomegalovirus (CMV) infections. CMV and Epstein–Barr virus (EBV) in plasma were detected by real-time quantitative polymerase chain reaction [17,18].

Definitions and evaluations

SSTIs refer to infections involving the skin and subcutaneous tissue, fascia, or muscle [6,7]. In accordance with current guidelines, the diagnosis of SSTIs was based on clinical characteristics, laboratory test image reports, or etiological evidence [6,9,19], and established by hematologists and dermatologists at Peking University. The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) modified from the Charlson Comorbidity Index is a sensitive and reliable prognostic scoring system for the HSCT population. It gives scores of 1 point for comorbidities of arrhythmia, cardiac disease, inflammatory bowel disease, diabetes, cerebrovascular disease, psychiatric disturbance, mild hepatic disease, obesity and infection; 2 points for comorbidities of rheumatologic ulcer, peptic ulcer, moderate/severe renal disease, and moderate pulmonary disease; and 3 points for comorbidities of prior solid tumor, heart valve disease, severe pulmonary disease, and moderate/severe hepatic disease [20]. Death after HSCT includes relapse-related mortality (RRM) and transplant-related mortality (TRM) [21]. Patients who died without having achieved remission or relapse at any time post-transplant were defined as having RRM [5,22]. The main TRM causes were infections, GVHD, and toxicity [21,22]. Patients who experienced multiple complications were classified based on the main and direct causes of death [21]. The diagnosis and grading of acute GVHD (aGVHD) and chronic GVHD (cGVHD) were established in accordance with aGVHD and cGVHD consensus conferences [23,24]. Antecedent diseases, including GVHD and CMV/EBV viremia, referred to comorbidities that occurred prior to the onset of SSTIs [25]. Neutrophil engraftment referred to 3 consecutive days of absolute neutrophil counts $\geqslant 0.5 \times 10^9$/L. Platelet engraftment referred to 7 consecutive days of platelet counts $\geqslant 20 \times 10^9$/L without blood transfusion. Primary platelet graft failure (PPGF) was defined as thrombocytopenia ($< 20 \times 10^9$/L) that required platelet transfusion due to insufficient platelet recovery over 100 days after HSCT [26]. The definition of complicated SSTIs (cSSTIs) was established based on whether the infection sites required surgical intervention [27]. Comorbidities of SSTIs referred to diseases occurring during the entire course of SSTI. Hospital-acquired pneumonia (HAP) referred to lung infections

occurring at least 48 h after hospitalization without invasive mechanical ventilation. The diagnosis of HAP was confirmed by radiographic evidence on (1) a newly occurring or progressive parenchymal lung infiltrate without any known causes and (2) two items or more of the following: a temperature over 38 °C or less than 36 °C, purulent respiratory tract secretions, or a white blood cell (WBC) count over 12×10^9/L or less than 4×10^9/L [28,29]. Hepatic failure was defined as liver function in the Child–Pugh B/C class [30]. Acute kidney injury was diagnosed when serum creatinine increased to over 1.5 times the baseline, was ⩾ 0.3 mg/dL, or the urine output decreased to 0.5 mL/kg/h for more than 6 h [31].

Statistical analysis

In this study, continuous variables were compared through Mann–Whitney U tests and presented as mean or median values (ranges). The distributions of categorical variables were recorded with percentages, and Pearson's chi-square test and Fisher's exact test were used for comparisons. Statically significant differences were defined as P values < 0.05 (two-sided). Univariate logistic regression analysis was applied to determine the relationship between candidate variables and 12-month survival, and predictors with P values < 0.1 were included in further multivariate logistic regression analysis. The risk stratification system was finally established through backward stepwise logistic regression in accordance with the Akaike information criterion. Variables with P values < 0.05 were identified as independent risk factors or recipients' one-year mortality. Internal validation of the final model was conducted with the bootstrap method with 1000 repetitions. Moreover, a study cohort of different periods was used for external validation. The predictive value of the risk scoring system was examined based on discrimination power (through the area under the curve (AUC)), calibration power (through calibration plots), and net benefits (through decision curve analysis). All statistical work described above was accomplished with SPSS Statistics 26.0 for Windows and R software 4.0.3.

Results

Patients' characteristics

A total of 7433 patients underwent allo-HSCT at Peking University Institute of Haematology between January 2004 and December 2019, among whom 228 recipients (3.67%) developed SSTIs from pretreatment to 180 days after allo-HSCT. The 12-month mortality was 28.5% (61/228). The detailed clinical characteristics of these patients grouped by their one-year outcomes are recorded in Table 2. RRM accounted for the highest percentage of deaths (24/61, 39.3%) in our study. Infections were the second most common cause of death (20/61, 32.7%). In addition, five patients, accounting for 8.2% of the study population, died from GVHD. Non-survivors were older in age (P = 0.006) and much more advanced in status (P = 0.032) than survivors. No significant differences in sex, underlying diseases, HCT-CI, median time between diagnosis and HSCT, donor, disease status, donor–patient sex relationship, ABO and HLA compatibility, graft source, stem cell source, mean MNCs, and $CD34^+$ cell count were observed between the survivor and non-survivor groups. However, in the non-surviving recipients, the occurrence of aGVHD with previous SSTIs was much more frequent (P = 0.040). The rates of antecedent cGVHD, CMV viremia, and EBV viremia were similar among the survivors and non-survivors.

Incidence and profiles of SSTIs

The diagnoses and corresponding ICD codes of the patients are summarized in Table 1. The most common SSTIs were diagnosed as "other local infections of skin and subcutaneous tissue" with an ICD code of L08. XXX, the detailed anatomical distribution of which is summarized in Table S1. Definite diagnoses of viral infections (B00.XXX–B09.XXX) accounted for 8.8% of the study population. Thirteen recipients developed cellulitis, and one recipient developed gangrene. The specific anatomic locations of the SSTIs are summarized in Table 3. Maxillofacial infection was the most common (20.6%, 47/228), followed by infection due to vascular devices (18.0%, 41/228) and anal infection (17.5%, 40/228). Two patients (0.9%, 2/228) developed multiple systemic infections due to varicella-herpes zoster virus (VZV) or *Aspergillus fumigatus*. The median onset time of the SSTIs was 12 days after transplant (from −9 days to 179 days). The specific median onset times of maxillofacial infections, infections due to vascular devices, and anal infections were 20 days (from −3 days to 168 days), 11 days (from −8 days to 167 days), and 8 days (from −5 days to 111 days), respectively. Additionally, 55 patients were pathologically diagnosed in our study. Among them, bacteria, fungi, and viruses accounted for 18 (32.7%), 12 (21.8%), and 25 (45.5%) of the diagnoses, respectively. The specific records of the pathogens are summarized in Table S2.

In our study, two patients (2/228, 0.8%) died from uncontrolled SSTIs. One patient had poor graft function (absolute neutrophil count ⩽ 0.5×10^9/L, platelet count ⩽ 20×10^9/L, and hemoglobin level ⩽ 80 g/L with the presence of complete donor hematopoiesis) [32–34] and developed maxillofacial infection 154 days after transplant. Then, on the third day, he passed away due to septic shock. The other patient who died of an SSTI developed a recurrent abscess in her left thigh 125 days

Table 2 Baseline characteristics of surviving and dead allo-HSCT patients with SSTI

Characteristics	Survivors	Non-survivors	*P*
No. of patients	167	61	
Gender, *n* (%)			0.980
Male	118 (70.7%)	43 (70.5%)	
Female	49 (29.3%)	18 (29.5%)	
Age (diagnosed with pneumonia), year, mean ± SD	32.68 ± 13.733	38.28 ± 12.731	0.006*
Underlying diseases, *n* (%)			0.467
AML	53 (31.7%)	16 (26.2%)	
ALL	71 (42.5%)	27 (44.3%)	
CML	9 (5.4%)	1 (1.6%)	
MDS	27 (16.2%)	11 (18.0%)	
NHL	2 (1.2%)	2 (3.3%)	
Others	5 (3.0%)	4 (6.6%)	
HCT-CI, *n* (%)			0.316
0	130 (77.8%)	46 (75.4%)	
1	29 (17.4%)	8 (13.1%)	
2	6 (3.6%)	6 (9.8%)	
3	2 (1.2%)	1 (1.6%)	
Median time from diagnosis to HSCT, month (range)	6 (2–144)	6 (2–240)	0.863
Disease status, *n* (%)			0.032*
CR	137 (82.0%)	42 (68.9%)	
Advanced disease	30 (18.0%)	19 (31.1%)	
Donor, *n* (%)			0.232
MRD	4 (2.4%)	2 (3.3%)	
MUD	43 (25.7%)	15 (24.6%)	
HID	119 (71.3%)	41 (67.2%)	
CB	1 (0.6%)	3 (4.9%)	
Gender relationship, *n* (%)			0.874
M−M	78 (46.7%)	33 (54.1%)	
M−F	38 (22.8%)	11 (18.0%)	
F−M	37 (22.2%)	12 (19.7%)	
F−F	14 (8.4%)	5 (8.2%)	
ABO compatibility, *n* (%)			0.467
Match	102 (61.1%)	34 (55.7%)	
Mismatch	66 (38.9%)	27 (44.3%)	
HLA compatibility, *n* (%)			0.433
Match	47 (28.1%)	17 (23.0%)	
Haplo-identical	120 (71.9%)	44 (77.0%)	
Graft source			0.149
BM + PB	158 (94.6%)	56 (91.8%)	
BM	2 (1.2%)	0	
PB	6 (3.6%)	2 (3.3%)	
CB	1 (0.6%)	3 (4.9%)	
MNCs ($\times 10^8$/kg, mean ± SD)	8.21 ± 1.67	8.04 ± 1.72	0.481
$CD34^+$($\times 10^6$/kg, mean ± SD)	2.67 ± 1.37	2.79 ± 1.46	0.558

(*Continued*)

Characteristics	Survivors	Non-survivors	*P*
Median WBC engraftment time, day (range)[a]	14 (10–28)	14 (9–23)	0.361
Median PLT engraftment time, day (range)[b]	16 (6–170)	15 (10–153)	0.684
Antecedent aGVHD, *n* (%)			0.040*
None	151 (90.4%)	47 (77.0%)	
I–II	11 (6.6%)	9 (14.8%)	
III–IV	5 (3.0%)	5 (8.2%)	
Antecedent cGVHD, *n* (%)	3 (1.8%)	3 (4.9%)	0.403
Antecedent CMV viremia	27 (16.2%)	14 (23%)	0.238
Antecedent EBV viremia	4 (2.4%)	2 (3.3%)	0.718

Notes: AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; HCT-CI, hematopoietic cell transplantation specific comorbidity index; CR, complete remission; MRD, matched-related donors; MUD, matched-unrelated donors; HID, haploidentical donors; CB, cord blood; M, male; F, female; HLA, human leukocyte antigen; BM, bone marrow; PB, peripheral blood; MNCs, mononuclear cells; WBC, white blood cell; PLT, platelet; GVHD, graft versus host diseases; CMV, cytomegalovirus; EBV, Epstein–Barr virus.
[a]Four non-survivors died before WBC engraftment. [b]Six survivors and 25 non-survivors underwent primary platelet graft failure. *$P < 0.05$.

after transplant. Puncture and drainage culture revealed an *Escherichia coli* infection. On the 179th day after transplant, the patient's subcutaneous abscess had grown to 30 cm × 10 cm, combined with symptoms of septic shock. She passed away after several days.

Risk factors for death in HSCT recipients with SSTIs

A total of 159 recipients who underwent allo-HSCT after January 2013 were enrolled in the derivation cohort, and the 69 other patients were grouped as the validation cohort. Univariate analysis was conducted in the derivation cohort to identify potential associations between the patients' clinical features and their one-year outcomes. History of diabetes mellitus, PPGF, combined HAP, combined hepatic failure, and combined acute kidney injury (AKI) were revealed to be associated factors. Then, we conducted a multivariate analysis of the derivation cohort and confirmed the predictors of the one-year prognosis of allo-HSCT recipients with SSTIs. PPGF ($P < 0.001$), combined HAP ($P < 0.001$), and combined AKI ($P = 0.004$) were proven to be independent risk factors with statistical significance (Table 4).

Establishing the risk stratification system

On the basis of the regression coefficient of the independent risk factors described above, we realized the value assignment of the risk stratification system for allo-HSCT recipients with SSTIs (Table 5). A risk scoring system using PPGF, AKI, and HAP (PAH) was established to predict patients' one-year survival. According to the value assignment, the risk score of the PAH system equaled 1 × PPGF + 1 × AKI + 1 × HAP. Patients with scores of 0, 1, and ⩾2 were grouped into low-, medium-, and high-risk groups, respectively. The overall 12-month mortality of the allo-HSCT recipients with SSTIs increased significantly as the risk score increased ($P < 0.001$). A total of 66.7% of the patients (152/288) had a score of 0, with a 12-month mortality rate of 8.6% (13/152). A total of 21.1% of the patients (48/228) had a score of 1, with a 12-month mortality rate of 50% (24/48). The remaining 12.3% of the patients (28/228) with a risk score ⩾2 had a 12-month mortality rate of 85.7% (24/28). In the derivation and validation cohorts, the average death rates of the three groups also continuously increased at a similar magnitude. The specific one-year mortality of the low-, intermediate-, and high-risk groups in the derivation and validation cohorts is presented in Table 6.

Internal and external validation of the risk stratification system

The AUC was 0.833 (95% CI 0.760–0.906) in the derivation cohort, indicating that the model had good discriminatory power for predicting the one-year mortality of allo-HSCT recipients with SSTIs (Fig. 2A). In the validation cohort, the AUC was 0.826 (95% CI 0.715–0.937), which further illustrated the good discrimination power of the risk scoring system (Fig. 2B). In addition, the calibration plot demonstrated a high degree of consistency between the estimated and observed risks of 12-month mortality in the derivation and validation cohorts (Fig. 3A and 3B), and this further proves the efficacy of the prognostic model. Furthermore, the decision curve analysis indicated that the PAH risk stratification system could help improve treatment strategies and provide considerable clinical benefits to patients in the derivation and validation cohorts (Fig. 4A and 4B). In summary, the entire validation process revealed the high clinical value of the PAH risk stratification system.

Table 3 Anatomic profiles of SSTIs in patients following allo-HSCT

Locations of SSTIs	No. of patients (%)
Maxillofacial infection	47 (20.6%)
Infection due to vascular devices	41 (18.0%)
Anal infection	40 (17.5%)
Lower limbs infection	29 (12.7%)
Upper limbs infection	11 (4.8%)
Back infection	11 (4.8%)
External genital infection	9 (3.9%)
Front trunk infection	9 (3.9%)
Hip infection	8 (3.5%)
Hands infection	8 (3.5%)
Feet infection	8 (3.5%)
Neck infection	3 (1.3%)
Perineum infection	2 (0.9%)
Multiple systemic infections	2 (0.9%)

Discussion

SSTIs are common complications in HSCT recipients. For immunocompromised patients, SSTIs are always severe and require broad-spectrum antibiotics or surgical operations for treatment [9]. The skin is the largest organ of human beings; hence, patients with cutaneous and underlying infections might be susceptible to infection.

According to the median onset time, the SSTIs usually occurred approximately 12 days after allo-HSCT, suggesting a high incidence of SSTIs shortly after transplant. In this period, skin cleaning and care, especially in the wound area, should be given special attention. A total of 53.5% of the SSTIs occurred before neutrophil engraftment. Notably, nearly half of the SSTIs occurred after gradual immune function recovery. Generally, although recipients achieve white blood cell (WBC) engraftment, they might have leukopenia. Additionally, patients are often transferred to general wards from wards with clean laminar air

Table 4 Risk factors of the death of HSCT recipients with SSTI in the derivation cohort

Features	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age > 60 years	0.897	0.091–8.862	0.926			
Disease status	1.852	0.832–4.118	0.131			
History of diabetes mellitus, *n* (%)	3.565	1.125–11.298	0.031*	4.250	0.914–19.766	0.065
ABO matched	1.189	0.588–2.403	0.630			
HLA matched	1.146	0.489–2.686	0.754			
Primary platelet graft failure	24.348	7.606–77.941	<0.001*	11.726	3.202–42.941	<0.001*
CMV viremia	1.244	0.497–3.116	0.641			
EBV viremia	2.227	0.582–8.911	0.237			
aGVHD	1.960	0.877–4.382	0.101	1.216	0.474–3.120	0.685
cGVHD	5.610	0.495–63.516	0.164			
SSTIs at multiple locations	0.940	0.317–2.788	0.911			
Complicated SSTIs	2.135	0.457–9.965	0.335			
Hospital-acquired pneumonia	11.667	5.140–26.479	<0.001*	5.765	2.223–14.952	<0.001*
Hepatic failure	19.594	4.130–92.947	<0.001*	6.116	0.858–43.594	0.071
Acute kidney injury	12.948	3.405–49.230	<0.001*	9.948	2.040–48.512	0.004*

Notes: HLA, human leukocyte antigen; OR, odd ratio; ABO, ABO blood type; CMV, cytomegalovirus; EBV, Epstein−Barr virus; GVHD, graft versus host diseases.
*P<0.05.

Table 5 Coefficients and points for the PAH risk stratification system for SSTIs in allo-HSCT recipients by using independent variables in the derivation cohort

Variables	Multivariable analysis			Point
	OR (95% CI)	*P*	Coefficients	
Primary platelet graft failure	9.849 (3.293–29.459)	<0.001	2.462	1
Acute kidney injury	10.618 (3.093–36.455)	0.004	2.397	1
Hospital-acquired pneumonia	6.654 (3.015–14.682)	<0.001	1.752	1

Table 6 Mortality of allo-HSCT recipients with SSTIs in derivation and validation cohorts

	Derivation cohort (n = 159)			Validation cohort (n = 69)		
	Low	Intermediate	High	Low	Intermediate	High
Risk score	0	1	2–3	0	1	2–3
Survivor	97	17	3	43	7	1
Non-survivor	9	15	19	4	9	5
Mortality	8.5%	46.9%	86.4%	8.5%	56.3%	83.3%

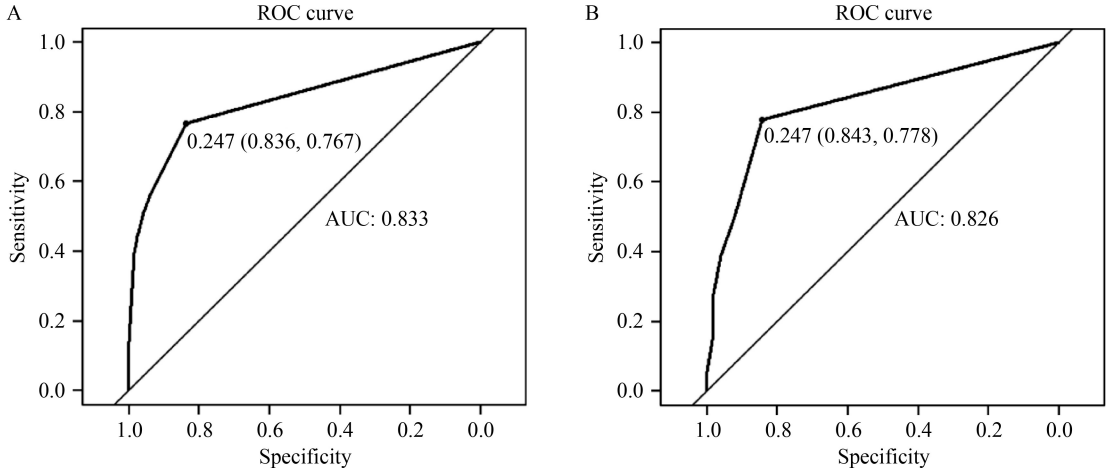

Fig. 2 Receiver operating characteristic (ROC) curve of the PAH risk stratification system in the derivation and validation cohorts. (A) ROC curve of the PAH risk stratification system for the derivation cohort. The area under the curve (AUC) was 0.833 (95% CI 0.760–0.906). (B) ROC curve of the PAH risk stratification system for the validation cohort. The AUC was 0.826 (95% CI 0.715–0.937).

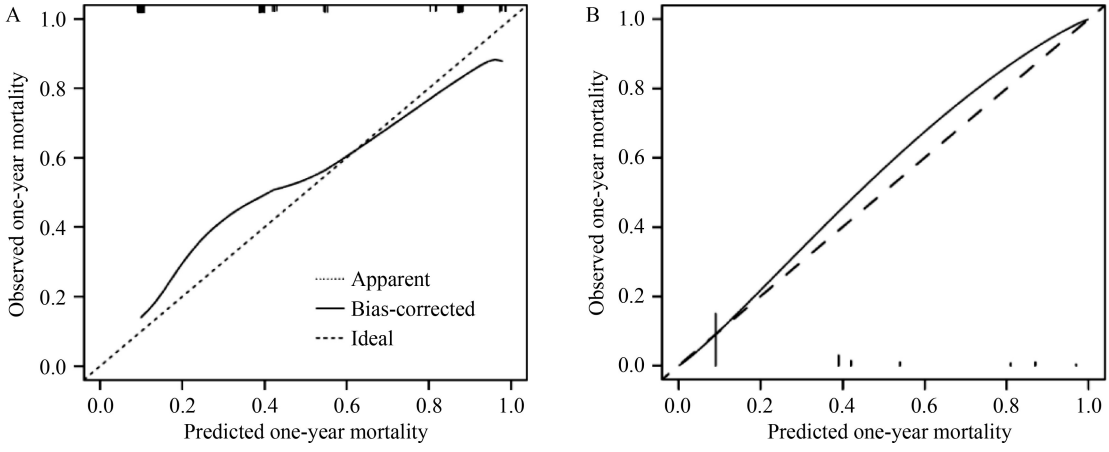

Fig. 3 Calibration plot of the PAH risk stratification system in the derivation and validation cohorts. (A) Calibration plot of the PAH risk stratification system for the derivation cohort. (B) Calibration plot of the PAH risk stratification system for the validation cohort. The x-axis plots the predicted one-year mortality of allo-HSCT recipients with SSTIs; the y-axis plots the observed one-year mortality in our study. The 45 diagonal line stands for the ideal calibration plot.

flow after WBC engraftment. A low level of hygiene conditions could increase the risk of infections. Thus, skin cleaning and care should not be neglected even though neutrophils have been grafted successfully.

Forty-seven patients developed maxillofacial SSTIs in our study, which is the most common anatomic site of infection. Among them, eight patients were diagnosed with a herpes simplex virus (HSV) infection. A previous study found that delayed platelet engraftment is an independent risk factor for the incidence of HSV infections after haploidentical HSCT [35]; thus, PPGF might be a predictive factor for the onset of and death from SSTIs after allo-HSCT. Infections due to vascular devices are the most common SSTIs due to iatrogenic

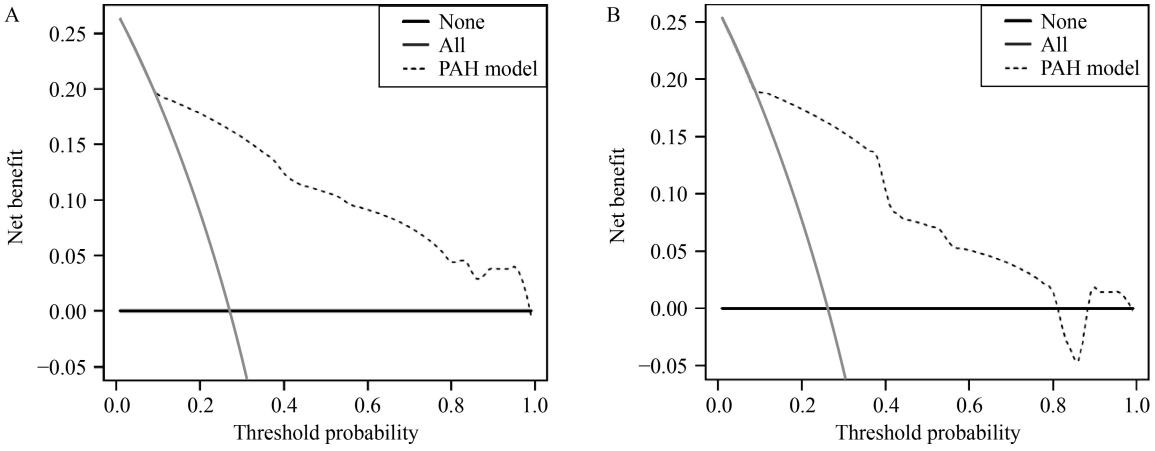

Fig. 4 Decision curve analysis of the PAH stratification system in derivation and validation cohorts. (A) Decision curve analysis of the PAH risk stratification system for the derivation cohort. (B) Decision curve analysis of the PAH risk stratification system for the validation cohort. Black line: assuming no patient died within one year. Gray line: assuming all patients died within one year. The two lines serve as references.

procedures. For HSCT recipients, a central venous catheter (CVC) is an indispensable care management tool and often indwelling for a long time. A CVC is an important infection source in patients receiving HSCT and likely to be associated with catheter-related bloodstream infections [36]. In our study, perianal infections were another type of SSTI with a high incidence in the HSCT recipients. A previous study has confirmed that pre-engraftment perianal infections increase the incidence of post-HSCT anal infections but do not affect the clinical outcomes of patients [18]. One patient with a perianal abscess was diagnosed with cSSTI and underwent surgical operation in our study. In addition, severe perianal abscess has often been reported to occur in autologous HSCT (auto-HSCT) in former studies [37]. Therefore, perianal care should be regularly taken, and once SSTIs occur in perianal regions, careful care could be adopted to prevent recurrence.

According to previous study results, prophylactic use of antibiotics (fluoroquinolones) [38,39], antifungals (voriconazole, posaconazole, micafungin, etc.) [40,41], and antivirals for HSV and VZV (acyclovir) [42,43] should be applied to prevent SSTIs. Our results showed that 24 patients developed HSV or VZV infections. Thus, in accordance with previous research and guideline recommendations [40,43,44], we regarded the appropriate extension of acyclovir duration to 100 days as reasonable. In addition, 12 patients were diagnosed with fungal SSTIs. Previous studies assumed that itraconazole can be used up to 180 days when GVHD is diagnosed [45–47]. Thus, we believe that the antifungal infection prophylaxis in our department after transplant can be adjusted depending on whether the patient has GVHD.

Thirty-one recipients (13.6%) who underwent PPGF after allo-HSCT were included in our study. Among them, 25 patients (80.6%) died within one year after transplant. A previous study confirmed that thrombocytopenia is associated with the incidence of bacterial infections, especially the *Streptococcus* species [48]. Furthermore, bacterial infection with the *Staphylococcus aureus* species has also been confirmed as an independent risk factor for death [49]. On the one hand, platelets are essential in the wound healing process [50] because they probably increase the invasion of pathogenic microorganisms to the skin and soft tissue. On the other hand, a previous study showed that platelet-related parameters are also related to the severity of the inflammatory response [51].

In our study, over a quarter of the patients (59/228) developed HAP during the SSTI period, and they accounted for a large portion of the population. Among them, 25 cases had bacterial infection (42.4%), 14 cases had fungal infection (23.7%), 7 cases had viral infection (11.9%), 11 cases had mixed bacterial and fungal infections (18.6%), and 2 cases had mixed bacterial, fungal, and viral infections (3.4%). Thirty-eight patients passed away within one year after transplant. Post-HSCT pneumonia has been confirmed to be a common complication and an independent predictive factor for the survival of recipients [52], and this finding is supported by our research outcomes. However, a previous study reported that fungal pathogens are associated with the death of patients with pulmonary infections [53]. In our study, no significant difference in one-year post-HSCT mortality was observed among the four groups with three different pathogens and mixed infections, which might be related to the small sample size.

A previous systematic review reported that combined AKI is associated with the mortality of SSTI inpatients [54], which is in line with our study results. Furthermore, according to Liu's study [55], AKI is the most common targeted organ damage among HSCT recipients, and serum creatinine level ⩾ 2× the baseline (⩾ Grade 2 AKI) [31] is an independent risk factor for patient

mortality. On the basis of these consistent research results, we conclude that AKI can predict the prognosis of SSTIs, especially in immunocompromised patients.

This study still has several limitations. First, due to the single-center retrospective nature of this study, data incompleteness and inaccuracy could not be avoided. Second, selection bias resulting from limitations in the number of patients should be considered. Etiological evidence is missing to a certain extent due to the incomplete etiological examinations for SSTIs and early use of antibiotics in HSCT recipients. Although we summarized the recorded pathogens in Table S2, the proportion is probably not in accordance with reality. While bacteria and fungi can only be identified under a microscope or by culture, viruses can often be diagnosed based on clinical manifestations. Third, interspatial data were not used to further validate the PAH risk stratification system. A prospective multicenter study should be performed to obtain full validation of the PAH risk stratification system in allo-HSCT recipients with SSTIs.

SSTIs are common complications in allo-HSCT recipients. To the best of our knowledge, this study, which is based on a large sample size and long timespan, is the first to focus on SSTIs after HSCT. According to our data, primary platelet graft failure, combined acute kidney injury, and hospital-acquired pneumonia together can predict patients' one-year prognoses. We developed and validated the PAH risk stratification system to estimate the one-year mortality of allo-HSCT recipients with SSTIs. The system could help in the development of treatment strategies and could provide clinical benefits to patients.

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Compliance with ethics guidelines

Shan Chong, Yun He, Yejun Wu, Peng Zhao, Xiaolu Zhu, Fengrong Wang, Yuanyuan Zhang, Xiaodong Mo, Wei Han, Jingzhi Wang, Yu Wang, Huan Chen, Yuhong Chen, Xiangyu Zhao, Yingjun Chang, Lanping Xu, Kaiyan Liu, Xiaojun Huang, and Xiaohui Zhangy have no conflicts of interest to declare. This study was conducted in accordance with *Declaration of Helsinki* strictly and authorized by Peking University People's Hospital ethics committee.

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