


Clinical risk score for predicting invasive fungal disease after allogeneic hematopoietic stem cell transplantation: Analysis of the China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) study

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Abstract

Background and objective: Invasive fungal disease (IFD) is associated with a high mortality for patients with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). This study aimed not only to develop a proven/probable IFD risk-scoring model but to identify high-risk populations that would benefit from anti-fungal prophylaxis.

Methods: Data from the China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) study were retrieved, and all patients (n = 1053) undergoing allo-HSCT were randomly divided into the training set (n = 685) for model development and the validation set (n = 368) for model verification. A weighted risk score for proven or probable IFD was established through multivariate logistic regression analysis.

Results: The study population had a mean age of 28.95 years and the majority underwent myeloablative transplantation in complete remission 1 (53.4%). Five risk factors of IFD were identified, namely neutropenia lasting longer than 14 days, corticosteroid use, diabetes, haploidentical donor, and unrelated donor. Based on the risk score for IFD, the patients were categorized into three groups: low risk (score 0-4, 1.5%-4.0%), intermediate risk (score 5-8, 9.8%), and high risk (score >8, 24.7%-14.0%). Anti-fungal prophylaxis may provide benefits for patients with intermediate (8.5% vs. 18.5%, $P = .0085$) or high risk (19.4% vs. 30.8%, $P = .4651$) but not low risk (2.1% vs. 3.8%, $P = .6136$) of IFD.

Conclusion: A practical weighted risk score for IFD in patients receiving allo-HSCT was established, which can aid decision-making regarding the administration of anti-fungal prophylaxis.

KEYWORDS

allogeneic hematopoietic stem cell transplantation, anti-fungal therapy, invasive fungal disease, prophylaxis, risk-scoring model

1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for hematologic malignancies such as leukemias, multiple myeloma, lymphomas, and myeloproliferative neoplasms.¹ However, secondary infectious disease greatly affects the prognosis of patients receiving allo-HSCT, although various therapeutic measures have been developed to enhance transplant performance.^{1,2} Invasive fungal disease (IFD) is one of the main infective causes of morbidity and mortality in allo-HSCT patients.³⁻⁵ Prophylaxis for IFD is therefore of critical importance due to the related economic burden and dismal outcomes.

The previously reported incidence of proven IFD in allo-HSCT patients has varied from 5.4%-22.4%, with aspergillosis and candidiasis as the most common causative pathogens.^{3,5-7} Patients with heterogenous characteristics may be categorized into different risk stratification categories with varied IFD incidence. Absent or delayed prophylaxis in high-risk patients may lead to a high mortality.⁸ On the contrary, for patients at low-risk of IFD, aggressive prophylactic strategy brings an economic burden and associated adverse events.⁹ An ideal resolution for comprehensively assessing the IFD risk is to apply a quantitative predictive model. We have previously established a clinical risk score for IFD in patients with hematological malignancies undergoing chemotherapy.⁹ However, a practical model to predict the incidence of IFD in patients with hematological malignancies undergoing allo-HSCT has yet to be reported.

In the current study, by using data from the nation-wide China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) study, which evaluated the use of anti-fungal therapy in hematological diseases, we aimed not only to develop a proven/probable IFD risk-scoring model but to identify high-risk populations that would benefit from anti-fungal prophylaxis.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was based on the CAESAR study, which was a multi-center, prospective and observational study evaluating the clinical, microbiological and prognostic features of IFD in a Chinese cohort receiving chemotherapy or HSCT. All patients of any age who were hospitalized and underwent HSCT in each center were included from January 1, 2011 and October 30, 2011. The follow-up was ended on April 30, 2012 and all patients were followed for 6 months ± 7 days after transplantation.¹⁰

Proven, probable, and possible IFD were defined according to the 2008 criteria provided by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.¹⁰

Data of the patients treated with allogeneic HSCT were retrieved from the CAESAR study. These data included baseline demographical characteristics, comorbidities, hematological diagnosis, clinical features of allogeneic HSCT and IFD, laboratory results, and anti-fungal treatment. As previously reported, the average duration of antifungal prophylaxis before HSCT was 10.9 ± 6.56 days. Single antifungal agents were the most common prophylaxis regimen (736/906, 81.2%). Fluconazole and voriconazole were the most commonly applied agents for primary and secondary antifungal prophylaxis.¹¹ *Aspergillus* is the most commonly identified pathogen.¹¹ The diagnosis, prophylaxis, and treatment of IFD were performed according to usual practice based on recommendations from local clinical guidelines as described previously.¹²

The study was performed in accordance with the Declaration of Helsinki for medical research. The study protocol was reviewed and

approved by the local ethics committees of all participating institutions. Informed consent was obtained from all patients.

2.2 | Statistical analysis

All patients ($n = 1053$) were randomly divided into the training set (65%) for model development and the validation set (35%) for model verification. Continuous variables were compared between groups by the *t*-test. Categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test.

A two-step analytical approach was performed as previously performed.⁹ First, a multivariate logistic regression model was constructed to analyze the independent factors of proven and probable IFD in the training set. Multivariate analyses were conducted in a forward manner for factors in the univariate analyses with $P < .10$. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Points were assigned for the independent risk factors for which P remained $< .05$ in the final logistic regression analysis and were weighted approximately based on the corresponding regression β -coefficients. For each variable, the regression coefficients were divided by the minimum absolute value of all coefficients in the final multivariable model, multiplied by 2. Each patient was assigned a total score with all points of risk factors summed. Receiver operator curve (ROC) analysis with 95% CI was performed to evaluate the discrimination capacity of the risk score. Patients were classified into three different risk categories based on the risk scores. Secondly, the performance of the established model was verified in the validation dataset.

A P -value $< .05$ was considered statistically significant. All analyses were performed using SAS 9.2 (SAS Institute).

3 | RESULTS

3.1 | Study populations

The study population had a mean age of 28.95 years and the majority (53.4%) underwent myeloablative transplantation in complete remission 1. All patients ($n = 1053$) were randomly divided into the training set ($n = 685$) and the validation set ($n = 368$). The characteristics of patients were well balanced between the training and the validation groups (Table 1, Table S1). The characteristics of the donor type and preparative regimen in the training and the validation groups respectively were further displayed in Table S2.

3.2 | Risk factors associated with IFD in the training dataset

A total of 94 (8.9%) IFD episodes occurred in the overall population, with 62 (9.1%) in the training set and 32 (8.7%) in the validation

set. Univariate logistic regression was performed as previously reported,¹² followed by multivariate logistic regression analysis of the training set. This analysis identified five risk factors associated with IFD: absolute neutrophil count (ANC) $< 500/\text{mm}^3$ for more than 14 days, corticosteroid application, concomitant diabetes, haploid-matched transplantation, and unrelated donor. Weighted points for each risk factor were assigned accordingly. The total risk scores for all patients ranged from 0 to 14 (Table 2).

3.3 | IFD incidence based on risk score categories in the training and validation sets

The IFS incidence rates based on different risk score categories are displayed in Table 4. With higher risk scores, a greater incidence of IFD was observed. In the training set, patients with risk scores of 0-4, 5-8, and > 8 presented IFD incidence rates of 1.5%, 9.8%, and 24.7%, respectively. Statistical significance was observed for comparisons between every two categories (all $P < .001$). Similarly, in the validation set, a significantly higher IFD incidence was observed in the patients with risk scores > 8 (14.0%) compared to those with scores of 0-4 (4.0%, $P = .032$) (Table 3).

ROC curve analysis assessing the discrimination capacity of the risk scores showed that the area under the ROC curve (AUC) was 0.7324 for the training set and 0.6567 for the validation set (Figure 1). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for the different risk score cut-points were calculated and are shown in Table S3.

3.4 | Impact of anti-fungal prophylaxis in patients with different risk scores or risk factors

All patients were divided into three risk categories: low-risk for patients with scores 0-4, intermediate-risk for those with scores 5-8, and high-risk for those with scores > 8 .

The benefit of anti-fungal prophylaxis varied for patients in the different risk categories. For low-risk patients ($n = 294$), no significant difference in the IFD incidence was observed between those who did or did not receive anti-fungal prophylaxis (2.1% vs. 3.8%, $P = .6136$). However, for the intermediate-risk group ($n = 643$), patients who received anti-fungal prophylaxis had a significantly reduced IFD incidence compared with patients who did not take prophylaxis (8.5% vs. 18.5%, $P = .0085$). An obvious numerical decrease in the incidence of IFD was observed for high-risk patients given prophylactic treatment compared with those not given prophylaxis, although statistical significance was not achieved (19.4% vs. 30.8%, $P = .4651$) (Table 4).

The differences in IFD incidence among patients categorized by risk factors are shown in Table 5. Significant less IFD episodes were observed for sibling-matched transplantations compared with other transplantations (2.1% vs. 10.7%, $P = .0082$).

TABLE 1 Characteristics of patients in the training and validation datasets

Factors	Training set (n = 685)	Validation set (n = 368)	P value
Age			
N (Nmiss)	685 (0)	368 (0)	.4151
Mean (S.D)	28.71 (12.861)	29.41 (13.755)	
Median	28.0	28.5	
Min, Max	1.0, 61.0	2.0, 63.0	
Sex			
Male	419 (61.2%)	224 (60.9%)	.9472
Female	266 (38.8%)	144 (39.1%)	
Previous IFD			
Yes	68 (9.9%)	37 (10.1%)	1.0000
No	617 (90.1%)	331 (89.9%)	
Disease			
ALL	194 (28.3%)	116 (31.5%)	.4657
CLL	2 (0.3%)	2 (0.5%)	
HD	4 (0.6%)	1 (0.3%)	
MM	3 (0.4%)	—	
AA	61 (8.9%)	21 (5.7%)	
AML	239 (34.9%)	137 (37.2%)	
CML	79 (11.5%)	47 (12.8%)	
NHL	24 (3.5%)	7 (1.9%)	
MDS	53 (7.7%)	27 (7.3%)	
Others	26 (3.8%)	10 (2.7%)	
Disease status			
Newly diagnosed			
CR1	361 (52.7%)	201 (54.6%)	.4832
CR2	45 (6.6%)	33 (9.0%)	
CR3	6 (0.9%)	2 (0.5%)	
PR	38 (5.5%)	11 (3.0%)	
NR	54 (7.9%)	34 (9.2%)	
AP	4 (0.6%)	5 (1.4%)	
BP	10 (1.5%)	3 (0.8%)	
Hematological relapse	32 (4.7%)	12 (3.3%)	
Other	62 (9.1%)	38 (10.3%)	
Donor type			
Sibling-matched	292 (42.7%)	155 (42.1%)	.7964
Haploid-matched	210 (30.7%)	120 (32.6%)	
Unrelated	182 (26.6%)	93 (25.3%)	
Total	684 (100.0%)	368 (100.0%)	
Missing	1	—	
Source of stem cells			
Total No.			
Bone marrow	28 (4.2%)	12 (3.3%)	.9409
Bone marrow and peripheral blood	251 (37.2%)	136 (37.7%)	
Peripheral blood	383 (56.8%)	206 (57.1%)	
Cord blood	12 (1.8%)	7 (1.9%)	

(Continues)

TABLE 1 (Continued)

Factors	Training set (n = 685)	Validation set (n = 368)	P value
Missing	11	7	
Myeloablative preparative regimen			
Yes	611 (89.2%)	325 (88.3%)	.6814
No	74 (10.8%)	43 (11.7%)	
Total body irradiation-based preparative regimen			
Yes	103 (15.0%)	55 (14.9%)	1.0000
No	582 (85.0%)	313 (85.1%)	
Application of ATG			
Yes	411 (60.0%)	221 (60.1%)	1.0000
No	274 (40.0%)	147 (39.9%)	

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AP, accelerated phase; ATG, antithymocyte globulin; BP, blast crisis phase; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CR, complete remission; IFD, invasive fungal disease; MDS, myelodysplasia syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, nonremission; PR, partial remission.

TABLE 2 Independent risk factors associated with proven or probable IFD in the training dataset

Risk factor	Variables	Coefficient	Weight of score	Standard error	Walds	P value	OR	95% CI of OR
Intercept		-5.56		0.83	45.18	.00	—	—
ANC <500/mm ³	>14 days vs. ≤14 days	1.36	3	0.38	12.87	.00	3.90	1.8536-8.1978
Corticosteroid	Yes vs. No	1.51	3	0.74	4.13	.04	4.53	1.0546-19.432
Diabetes	Yes vs. No	1.59	3	0.65	6.03	.01	4.91	1.3789-17.508
Haploidentical donor	Haploid-matched vs. sibling-matched	1.03	2	0.39	6.88	.01	2.79	1.2967-6.0171
Unrelated donor	Unrelated donor vs. sibling-matched	1.39	3	0.41	11.43	.00	4.02	1.7937-8.9962

Note: Hosmer and Lemeshow goodness-of-fit test: chi-square (1.9954), P (0.9201).

Abbreviations: 95% CI, 95% confidence interval; ANC, absolute neutrophil count; OR, odds ratio.

TABLE 3 Risk score categories and the corresponding cumulative incidence of IFD in the training and validation datasets

Risk score	No.	IFI episodes (n)/Incidence (%)
Training dataset		
0-4	194	3 (1.5%)
5-8 [†]	418	41 (9.8%)
>8 ^{**}	73	18 (24.7%)
Validation dataset		
0-4	100	4 (4.0%)
5-8 [#]	225	22 (9.8%)
>8 [#]	43	6 (14.0%)

*P < .001 vs. the group with scores of 0-4.; **P < .001 and <.001 vs. the groups with scores of 0-4 and 5-8, respectively.

[†]P = .076 vs. the group with scores of 0-4.

[#]P = .032 and =.412 vs. the groups with scores of 0-4 and 5-8, respectively.

TABLE 4 Impact of anti-fungal prophylaxis in all patients with different risk scores

Risk score	Prophylaxis	No. of cases	IFI episode (n)/Incidence (%)	P value
0-4	Yes	241	5 (2.1%)	.6136
	No	53	2 (3.8%)	
5-8	Yes	562	48 (8.5%)	.0085
	No	81	15 (18.5%)	
>8	Yes	103	20 (19.4%)	.4651
	No	13	4 (30.8%)	

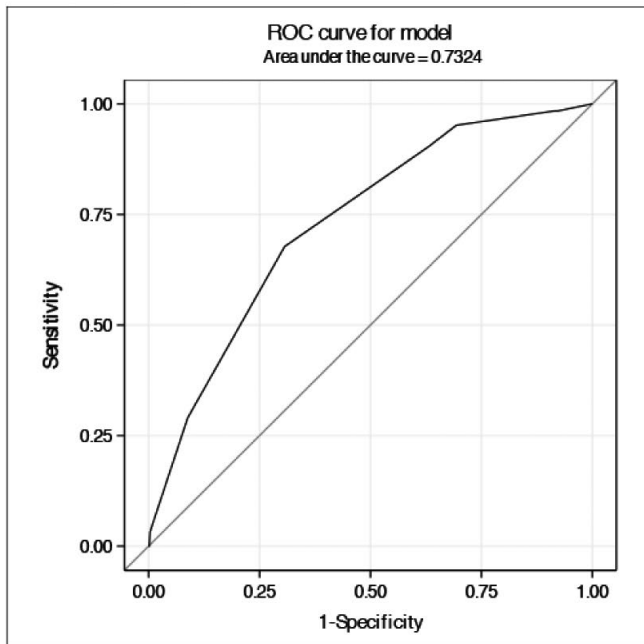
4 | DISCUSSION

The current study established a practical risk scoring model for the risk of IFD among allo-HSCT recipients that incorporates five independent risk factors for IFD, namely ANC, use of corticosteroids, diabetes, haploid-matched transplantation, and unrelated donor.

Risk factor of IFD		Prophylaxis	No. of cases	IFD episode (n)/ Incidence (%)	P value
Duration of ANC<500/ mm ³	≤10 days	Yes	100	6 (6.0%)	1.0000
		No	18	1 (5.6%)	
	11-14 days	Yes	134	2 (1.5%)	.0764
		No	39	3 (7.7%)	
	>14 days	Yes	341	40 (11.7%)	.1802
		No	53	10 (18.9%)	
Corticosteroids	Yes	Yes	467	44 (9.4%)	.1336
		No	93	14 (15.1%)	
	No	Yes	108	4 (3.7%)	1.0000
		No	16	0	
Diabetes	Yes	Yes	14	4 (28.6%)	1.0000
		No	3	1 (33.3%)	
	No	Yes	561	44 (7.8%)	.1836
		No	107	13 (12.1%)	
Donor	Sibling-matched	Yes	236	5 (2.1%)	.0082
		No	56	6 (10.7%)	
	Haploid-matched	Yes	183	24 (13.1%)	.5479
		No	27	5 (18.5%)	
	Unrelated	Yes	155	19 (12.3%)	1.0000
		No	27	3 (11.1%)	

TABLE 5 Impact of anti-fungal prophylaxis in all patients with different risk factors

Training set



Validation set

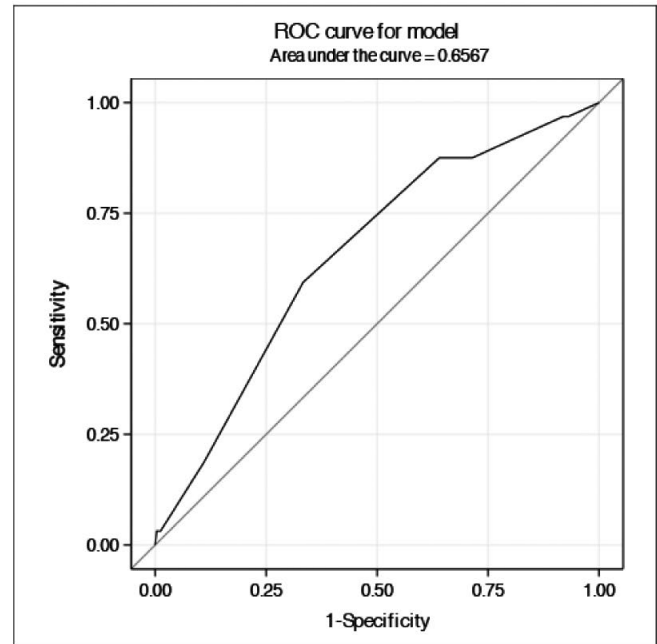


FIGURE 1 Receiver-operator curve (ROC) analysis of the risk score in the training and validation datasets

We found that anti-fungal prophylaxis reduced the incidence of IFD among intermediate- and high-risk patients, defined by a risk score ≥ 5 .

The cumulative annual incidence of IFD according to a previous analysis of a large-scale database varied depending on the type of transplantation,⁵ with allo-HSCT associated with a greater

IFD incidence than autologous HSCT. The CAESAR study reported a proven/probable IFD incidence of 8.9%, which was consistent with data from other allo-HSCT populations.^{3,5-7} Invasive aspergillosis and candidiasis were the most frequently identified invasive fungal pathogens in previous studies of IFD in allo-HSCT recipients.^{5,13,14} Notably, there has been a gradual shift from *C albicans* to non-albicans candida strains, which may vary across different regions and populations.¹⁵

According to previous studies, haploidentical HSCT is associated with a greater risk of IFD compared to sibling-matched HSCT.¹⁶⁻¹⁹ This concept was confirmed in our study, with 13.8% haploid-matched and only 3.8% sibling-matched HSCT developing IFD. A similar phenomenon is that unrelated donor (12.1%) cases had a comparable incidence of IFD with haploidentical donor cases. The increased incidence of graft-versus-host disease (GVHD) or prolonged immunosuppression during the process of T-cell depletion might possibly explain the difference in the IFD incidence among cases with different donor types. Our multivariate logistic regression analysis also identified donor type as an independent risk factor for IFD in allo-HSCT patients, and haploidentical and unrelated donor cases were assigned a risk score in the predictive model.

Diabetes, especially poorly controlled diabetes, is a risk factor for developing IFD following allo-HSCT.^{15,20} A significantly greater IFD incidence was observed in diabetic patients (29.4%) compared with non-diabetic patients (8.5%) in the present study. However, we noticed that diabetic patient who received sibling-matched allo-HSCT had a significantly reduced IFD incidence from 10.7% to 2.1% if anti-fungal prophylaxis was administered, which indicated the beneficial effect of prophylaxis in this population.

Allo-HSCT patients with neutropenia or receiving corticosteroids have been shown to be especially vulnerable to IFD.^{21,22} In the CAESAR study, over 90% of the overall population had profound neutropenia with an ANC $<500/\text{mm}^3$ for a median of 14 days.¹² This proportion (97.9%) was strikingly high in the present study focusing on allo-HSCT patients. Not surprising, a long duration of neutropenia >14 days was associated with an elevated risk of IFD. Corticosteroids exert complex immunosuppressive effects, which increase host susceptibility to IFD.²¹ In patients with neutropenia or those given high-dose corticosteroids, IFD was often neglected due to the absence of fever.²³

Some studies have demonstrated that patients with a prior IFD history are at high-risk for recurrent IFD after transplantation, but this was not observed in the current study.^{20,24} We speculate that heterogenous characteristics of different study populations, for example, the low proportion of proven or probable cases of prior IFD (10.0%) in the present study, may explain this discrepancy. In addition, active broad-spectrum anti-fungal prophylaxis may contribute to differences in study results as well.

We established a practical and quantified risk scoring model not only to predict the incidence of IFD but to aid the application of anti-fungal prophylaxis as well. Five risk factors including prolonged neutropenia, use of corticosteroids, diabetes, haploidentical donor, and unrelated donor were assigned risk scores. Patients with a risk score >5 were defined as intermediate- or high-risk patients. More

importantly, prophylaxis benefited patients with an intermediate or high risk of IFD, although statistical significance was not reached in high-risk patients, probably due to the limited sample size. The IFD incidence was reduced by approximately 10% for both intermediate- or high-risk patients who received anti-fungal prophylaxis, but was not significantly affected for patients at low risk. This finding is in line with the proposal that a threshold of IFD incidence of 5% can be used in clinical decision-making.^{4,25} A simplified application in the clinical setting would be to calculate the number of risk factors, with prophylaxis likely beneficial if two or more risk factors exist.

To the best of our knowledge, the present study provides the first risk scoring system for predicting IFD in patients following allo-HSCT. Although some scoring models have been established for patients receiving allo-HSCT, Forcina et al's model was designed to predict infection-related mortality and survival and Chien et al's model was specific for patients with acute leukemia.^{26,27}

For a better understanding of the clinical applicability of this risk score model, some limitations of this study should be considered. First, the timing at which IFD occurred was not classified in this study, and situations of early and late IFD might be different. Second, we did not further evaluate the risk factors for different species of fungi. Third, long-term mortality was not analyzed in the current study. Fourth, genetic risk factors and factors related to the immune response, which may further optimize the risk stratification, were not all included in the current study. Fifth, the majority of the study population were young patients receiving myeloablative transplantation in 1st remission. Whether this study's finding that mainly based on younger patients under ongoing myeloablative transplantation and myeloablative preparative regimen are applicable in the reduced intensity setting is worthy of further evaluation.

In conclusion, we developed an IFD risk scoring model based on a large-scale Chinese cohort of hematological malignancies undergoing allo-HSCT. This predictive model could not only reliably assess the risk of IFD incidence but also serve as a practical tool for guiding the use of anti-fungal prophylaxis. Further confirmation of our findings in a prospective study is needed.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design: YS, XJH. Administrative support: YS, XJH. Provision of study materials or patients: YS, JH, HH, JC, JYL, JM, JL, YML, JMW, YL, KY, JDH, JJ, CW, DPW, YX, XJH. Collection and assembly of data: YS. Data analysis and interpretation: YS. Manuscript writing: YS, XJH. Final approval of manuscript: YS, JH, HH, JC, JYL, JM, JL, YML, JMW, YL, KY, JDH, JJ, CW, DPW, YX, XJH.

ETHICAL APPROVAL

The study was performed in accordance with the Declaration of Helsinki for medical research. The study protocol was reviewed and approved by the local ethics committees of all participating institutions. Informed consent was obtained from all patients.

INFORMED CONSENT

Written informed consent was obtained from all individual participants included in the study.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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