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RESEARCH ARTICLE

Clinical risk score for invasive fungal diseases in patients with hematological malignancies undergoing chemotherapy: China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) study

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Abstract **Invasive fungal disease (IFD) is a major infectious complication in patients with hematological malignancies. In this study, we examined 4889 courses of chemotherapy in patients with hematological diseases to establish a training dataset ($n = 3500$) by simple random sampling to develop a weighted risk score for proven or probable IFD through multivariate regression, which included the following variables: male patients, induction chemotherapy for newly diagnosed or relapsed disease, neutropenia, neutropenia longer than 10 days, hypoalbuminemia, central-venous catheter, and history of IFD. The patients were classified into three groups, which had low (0–10, ~1.2%), intermediate (11–15, 6.4%), and high risk (> 15, 17.5%) of IFD. In the validation set ($n = 1389$), the IFD incidences of the groups were ~1.4%, 5.0%, and 21.4%. In addition, we demonstrated that anti-fungal prophylaxis offered no benefits in low-risk patients, whereas benefits were documented in intermediate (2.1% vs. 6.6%, $P = 0.007$) and high-risk patients (8.4% vs. 23.3%, $P = 0.007$). To make the risk score applicable for clinical settings, a pre-chemo risk score that deleted all unpredictable factors before chemotherapy was established, and it confirmed that anti-fungal prophylaxis was beneficial in patients with intermediate and high risk of IFD. In conclusion, an objective, weighted risk score for IFD was developed, and it may be useful in guiding antifungal prophylaxis.**

Keywords invasive fungal diseases; hematological malignancies; chemotherapy; risk score; prophylaxis

Introduction

Although advances in diagnostic tools, such as serum galactomannan test and high-resolution computer

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tomography, have been achieved and new antifungal agents have been developed in the past few decades, invasive fungal disease (IFD) remains as a major infectious complication for patients with hematological malignancies undergoing chemotherapy and hematopoietic stem cell transplantation (HSCT) [1,2]. To address this problem, anti-fungal prophylaxis had been evaluated in multiple clinical trials [3–5], which confirmed that it reduced IFD incidence and IFD-related mortality. To realize an effective prophylaxis strategy, the specific risk of IFD must be predicted accurately to identify the patients with significantly increased incidence of IFD who are most likely to benefit from the intensive monitoring of IFD and antifungal prophylaxis [6]. With regard to the optimal duration of antifungal therapy in patients with neutropenic fever, current guidelines recommend the empirical antifungal treatment for patients with persistent fever should last for 3–5 days after broad-spectrum antibiotic chemotherapy, whereas pre-emptive treatment was recommended as a diagnostic-driven therapy for patients with persistent fever together with diagnostic work-up showing suspicious findings prior to the initiation of antifungal treatment [7]. Moreover, empirical treatment, which may induce side effects and may be costly due to overtreatment, is recommended only for high-risk but not low-risk patients, such as in cases of anticipated duration of neutropenia (< 10 days), unless other findings indicate a suspected IFD [8]. Therefore, these risk-based approaches are feasible only with the proper assessment of risk factors of IFD in patients undergoing chemotherapy with hematological malignancies.

Although numerous factors, including diseases such as acute myeloid leukemia (AML) and myelodysplasia syndrome (MDS) [9], disease status (untreated or non-remission disease) [10], prolonged neutropenia [11], previous history of IFD [12], age [13], comorbidity such as diabetes and pulmonary disease [14,15], treatment with corticosteroid or other immune-suppression drugs [15–18], genetic factors related to host innate immunity [19,20], and environmental variables [21,22], have been reported as the main risk factors of IFD, the precise prediction of IFD incidence has remained difficult. In this study, we utilize the China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) Study database, which contain 4889 courses of chemotherapy in patients with hematological malignancies, to develop an objective risk score for proven or probable IFD [23]. We established a weighted risk score for IFD that accurately discriminated a cohort of patients with low ($< 2\%$), intermediate (5%), and high ($> 10\%$) incidence of IFD. Moreover, the benefits of anti-fungal prophylaxis were evaluated in patients with different IFD risks.

Materials and methods

Study design

As previously reported, the CAESAR study was a nationwide multicenter, prospective, observational study conducted in China to evaluate the clinical and microbiological management and outcomes of IFD in patients treated with chemotherapy or HSCT. The diagnosis of IFD was classified as proven, probable, or possible on the basis of the 2008 criteria devised 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. The collected data included baseline characteristics, hematological diagnosis, chemotherapy, clinical features, anti-fungal treatment, and the epidemiological and treatment-related potential risk factors of IFD.

The study was conducted in accordance with the *Declaration of Helsinki*, International Conference on Harmonization/Good Clinical Practice and nationally mandated ethical requirements. The study protocol and informed consent document were reviewed and approved by the ethics committee of all participating institutions.

Statistical analysis

The study cohort of 4889 chemotherapy courses on the CAESAR database was randomly split by simple random sampling at a ratio of 2.5:1 into two datasets, of which one served as the training set for model development (n = 3500) and the other served as the validation set for model verification (n = 1389). The patients' characteristics of training and validation dataset were described and compared by t test for continuous variables or by χ^2 test for proportion variables.

To develop the risk score, we first identified the factors that were individually associated with proven and probable IFD by using univariate analysis with $P < 0.10$. The factors that demonstrated an individual association were carry-forwarded in the multivariate logistic regression with the stepwise criteria of 0.05. Points were assigned for the variables that remained statistically significant ($P < 0.05$) in the final logistic regression and were weighted approximately by 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, and rounded to the nearest whole number. Once the point values were defined, the score for each of the significant prognostic factors was summed as the total score for each individual chemotherapy course. Receiver operator curves (ROC) with 95% CI were calculated to evaluate the discrimination capacity of the risk score. We classified

patients into different risk groups with corresponding incidences of IFD as < 2%, ~5%, and > 10%. Once the model was defined, it was tested using the independent validation dataset to confirm its performance in predicting the IFD incidence. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Study populations and incidence of IFD

The CAESAR study included 4889 chemotherapy courses from 4192 patients with variable hematological malignant diseases. The documented IFD episodes were 407, of which 19 were proven, 84 were probable, and 304 were possible IFD cases, and the overall incidence of proven/probable IFD was 2.1%. The documented pathogens consisted mostly of candida (n = 31) and aspergillus (n = 24), as well as a few cases of mucor (n = 1) and *Cryptococcus neoformans* (n = 1). The overall mortality of all patients was 1.5%, which increased significantly in proven/probable (11.7%) and possible IFD (8.2%), as previously reported [23].

A total of 3500 chemotherapy courses were selected from the CAESAR database by simple random sampling to form the training dataset, and the remaining 1389 courses comprised the independent validation dataset. The patients' characteristics of both training and validation datasets were balanced in all aspects, as shown in Table 1.

Table 1 Patients' characteristics in training and validation dataset

Factors		Training set	Validation set	*P* value
Sex	Male	2072 (59.2%)	818 (58.9%)	0.8566
	Female	1428 (40.8%)	571 (41.1%)	
Age	Mean (S.D.)	40.69 (20.665)	40.93 (20.691)	0.7239
	Median	43.0	43.0	
	Min, Max	1.0, 90.0	1.0, 89.0	
Eastern Cooperative Oncology Group score	0	1555 (44.4%)	601 (43.3%)	0.9975
	1	1379 (39.4%)	587 (42.3%)	
	2	399 (11.4%)	144 (10.4%)	
	3	124 (3.5%)	44 (3.2%)	
	4	43 (1.2%)	13 (0.9%)	
Diabetes	Yes	211 (6.0%)	77 (5.5%)	0.5449
	No	3289 (94.0%)	1312 (94.5%)	
Previous IFD	Yes	191 (5.5%)	74 (5.3%)	0.8888
	No	3309 (94.5%)	1315 (94.7%)	
Disease*	ALL	703 (20.1%)	262 (18.9%)	0.5101
	CLL	68 (1.9%)	28 (2.0%)	
	MM	324 (9.3%)	119 (8.6%)	
	AML	961 (27.5%)	397 (28.6%)	
	CML	33 (0.9%)	8 (0.6%)	
	NHL	943 (26.9%)	403 (29.0%)	
	MDS	59 (1.7%)	22 (1.6%)	
	AHL	15 (0.4%)	6 (0.4%)	
	HPS	2 (0.1%)	0	
	LCH	6 (0.2%)	1 (0.1%)	
	Plasma cell disease other than MM	19 (0.5%)	8 (0.6%)	
	Others	367 (10.5%)	135 (9.7%)	
Disease status**	Newly-diagnosed	664 (19.0%)	286 (20.6%)	0.6838
	CR1	1547 (44.2%)	635 (45.7%)	
	CR2	119 (3.4%)	44 (3.2%)	
	CR3	42 (1.2%)	12 (0.9%)	
	CR4	0	1 (0.1%)	
	PR	599 (17.1%)	220 (15.8%)	
	NR	190 (5.4%)	72 (5.2%)	
	AP	14 (0.4%)	6 (0.4%)	
	BP	7 (0.2%)	1 (0.1%)	
	CP	0	1 (0.1%)	

(*Continued*)

Factors		Training set	Validation set	*P* value
	Hematological relapse	248 (7.1%)	91 (6.6%)	
	PD	15 (0.4%)	4 (0.3%)	
	Non evaluable	51 (1.5%)	16 (1.2%)	
	Other	4 (0.1%)	0	
Type of chemotherapy	Induction	701 (20.0%)	289 (20.8%)	0.1389
	Consolidation	1783 (50.9%)	727 (52.3%)	
	Re-induction	687 (19.6%)	262 (18.9%)	
	Chemo-relapse/refractory disease	329 (9.4%)	111 (8.0%)	
Nadir ANC***($\times 10^9$/L)	$\geqslant 1.5$	1964 (56.1%)	748 (53.9%)	0.1870
	$1.0 \leqslant$ and < 1.5	81 (2.3%)	37 (2.7%)	
	$0.5 \leqslant$ and < 1.0	260 (7.4%)	102 (7.3%)	
	$0.1 \leqslant$ and < 0.5	430 (12.3%)	187 (13.5%)	
	< 0.1	765 (21.9%)	315 (22.7%)	
Duration of neutropenia	$\leqslant$10 days	641 (19.5%)	278 (21.4%)	0.2933
	11 – 14 days	144 (4.4%)	48 (3.7%)	
	>14 days	205 (6.2%)	89 (6.8%)	
Corticosteroid	Yes	1864 (53.3%)	760 (54.7%)	0.3733
	No	1636 (46.7%)	629 (45.3%)	
Broad-stream antibiotics for 7 days	Yes	358 (10.2%)	144 (10.4%)	0.8756
	No	3141 (89.8%)	1245 (89.6%)	
EBV viremia	Yes	28 (0.8%)	12 (0.9%)	0.2566
	No	876 (25.0%)	317 (22.8%)	
	NA	2595 (74.2%)	1060 (76.3%)	
CMV viremia	Yes	16 (0.5%)	6 (0.4%)	0.0529
	No	892 (25.5%)	309 (22.2%)	
	NA	2591 (74.0%)	1074 (77.3%)	
Liver function	Abnormal	222 (6.3%)	80 (5.8%)	0.4692
	Normal	3278 (93.7%)	1309 (94.2%)	
Renal function	Abnormal	88 (2.5%)	41 (3.0%)	0.3754
	Normal	3412 (97.5%)	1348 (97.0%)	
Central venous catheter	Yes	1584 (45.3%)	650 (46.8%)	0.3397
	No	1916 (54.7%)	739 (53.2%)	
Respiratory support	No	3481 (99.5%)	1381 (99.4%)	0.8809
	Non-invasive	12 (0.3%)	6 (0.4%)	
	Invasive	6 (0.2%)	2 (0.1%)	
Hypoalbuminemia	Yes	544 (15.5%)	211 (15.2%)	0.7924
	No	2956 (84.5%)	1178 (84.8%)	
Parenteral nutrition	Yes	75 (2.1%)	36 (2.6%)	0.3396
	No	3423 (97.9%)	1353 (97.4%)	
ICU	Yes	7 (0.2%)	1 (0.1%)	0.4538
	No	3491 (99.8%)	1388 (99.9%)	
Anti-fungal prophylaxis	Yes	571 (16.3%)	256 (18.4%)	0.0758
	No	2929 (83.7%)	1133 (81.6%)	

* ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; NHL: non-Hodgkin lymphoma; MDS: myelodysplasia syndrome; AHL: amyloid heavy or light chain amyloidosis; HPS: hemophagocytic syndrome; LCH: Langerhans cell histiocytosis.
** CR: complete remission; PR: partial remission; NR: non remission; AP: accelerated phase; BP: blast crisis phase; CP: chronic phase; PD: progression disease.
*** ANC: absolute neutrophil count.

Risk score associated with proven or probable IFD in training dataset

Univariate analysis (with $P < 0.10$) of the training data identified 13 factors that were associated with IFD incidence, namely, age, gender, diagnosis of hematological disease, higher Eastern Cooperative Oncology Group (ECOG) performance score, history of previous IFD, occurrence of neutropenia, duration of neutropenia (< 10, 11–14, and > 14 days), concomitant diseases, hematological disease status (newly diagnosed disease, complete remission, partial remission, and relapse or disease progression), hepatic impairment, use of parenteral nutrition, type of chemotherapy (induction or re-induction chemotherapy and consolidation), and hypoalbuminemia after chemotherapy. The variables such as male patients, patients with central-venous catheter, history of previous IFD, hypoalbuminemia, chemotherapy for newly diagnosed or relapsed disease, neutropenia after chemotherapy (absolute neutrophils count, ANC $< 0.5 \times 10^9$/L), and prolonged neutropenia for > 10 days or > 14 days remained significant in the stepwise multivariate logistic regression analysis, and weighted points were assigned accordingly (Table 2).

On the basis of the multivariate logistic regression analysis, IFD risk scores ranging from 0 to 23 were generated (Table 3) and calculated for each chemotherapy course in the training dataset. The distribution of the risk scores and the cumulative incidence of proven or probable IFD were calibrated, as shown in Table 4. Overall, the patients with risk scores of 0–5 and 6–10 presented low incidences of IFD at 0.3% and 1.2%, respectively ($P =$

Table 2 Risk factor analysis by multivariate analysis (stepwise) in the training dataset

Risk factor	Variables	Coefficient	Weight of score	Standard error	Walds	*P* value	OR	95% CI of OR
Intercept		−6.66		0.44	225.76	–		–
Hypoalbuminemia	Yes vs. No	1.49	5	0.27	30.06	0.00	4.45	2.6088 – 7.5827
Chemotherapy	(Re) Induction vs. consolidation	1.05	4	0.34	9.66	0.00	2.85	1.4731 – 5.5308
Neutropenia	ANC$<0.5\times10^9$/L, $\leqslant$10 days vs. $\geqslant 0.5\times10^9$/L	1.18	4	0.34	11.71	0.00	3.25	1.6549 – 6.3871
Neutropenia	ANC$<0.5\times10^9$/L , 11 – 14 days vs. $\geqslant 0.5\times10^9$/L	1.86	6	0.41	20.28	0.00	6.43	2.8604 – 14.449
Neutropenia	ANC$<0.5\times10^9$/L, >14 days vs. $\geqslant 0.5\times10^9$/L	1.86	6	0.36	26.67	0.00	6.42	3.1686 – 12.991
Central-venous catheter	Yes vs. No	0.57	2	0.28	4.22	0.04	1.77	1.0267 – 3.0625
Sex	Male vs. Female	0.61	2	0.28	4.58	0.03	1.83	1.0523 – 3.1874
History of IFD	Yes vs. No	1.24	4	0.38	10.80	0.00	3.47	1.6517 – 7.2811

* Hosmer and Lemeshow Goodness-of-Fit Test: Chi-Square (10.4748), *P* (0.2333). SLE = 0.05, SLS = 0.05.

Table 3 Risk scores for proven and probable IFD

Factors	Variables	Scores
Sex	Male	2
	Female	0
Hypoalbuminemia	Yes	5
	No	0
Chemotherapy	Induction/re-induction	4
	Consolidation	0
Neutropenia	ANC$<0.5\times10^9$/L	4
	No	0
Duration of neutropenia	ANC$<0.5\times10^9$/L, >10 days	2
	No	0
Central-venous catheter	Yes	2
	No	0
History of IFD	Yes	4
	No	0

Table 4 Distribution of risk scores versus the cumulative incidence of proven or probable IFD in the training and validation datasets

Risk score	Chemotherapy courses (*n*)	IFD episodes (*n*) /Incidence (%)
Training dataset		
0 – 5	1446	4 (0.3%)
6 – 10*	1432	17 (1.2%)
11 – 15**	502	32 (6.4%)
>15***	120	21 (17.5%)
Validation dataset		
0 – 5	560	2 (0.4%)
6 – 10$^{\#}$	587	8 (1.4%)
11 – 15$^{\#\#}$	200	10 (5.0%)
>15$^{\#\#\#}$	42	9 (21.4%)

* $P = 0.004$ vs. the group with scores of 0–5; ** $P < 0.001$ and 0.003 vs. the groups with scores of 0–5 and 6–10, respectively; *** $P < 0.001$ vs. the groups with scores of 0–5, 6–10, and 11–15.
$^{\#}$ $P = 0.067$ vs. the group with scores of 0–5; $^{\#\#}$ $P < 0.001$ and 0.002 vs. the groups with scores of 0–4 and 5–9, respectively; $^{\#\#\#}$ $P < 0.001$ vs. the groups with scores of 0–4, 5–9, and 10–15.

0.004), whereas those with risk scores of 11–15 manifested a significantly higher IFD incidence of 6.4% ($P < 0.001$ and $P = 0.003$ vs. the groups with scores of 0–5 and 6–10, respectively). An overwhelmingly high IFD incidence of up to 17.5% was observed in the group of patients with risk score of > 15 ($P < 0.001$ vs. the groups with scores of 0–5, 6–10, and 11–15).

The discrimination capacity of the IFD risk scores was analyzed by the ROC with an area under the ROC curve (aROC) of 0.84 (95% CI: 0.80–0.89), as shown in Fig. 1 (left). We also tested the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of different cut-points of the risk score at 5, 10, and 15, as shown in Table S1 (Supplementary Material).

Confirmation of risk score associated with proven or probable IFD in the validation dataset

The IFD risk score was calculated for each chemotherapy course in the validation dataset, and the results confirmed a low IFD incidence of 0.4% and 1.4% in the patients with risk scores of 0–5 and 6–10 ($P = 0.067$), whereas those with risk scores of 11–15 presented a significantly increased IFD incidence of 5.0% ($P < 0.001$ and $P = 0.002$ vs. the groups with scores of 0–5 and 6–10, respectively). The IFD incidence was overwhelmingly high (up to 21.4%) for patients with risk scores of > 15, as shown in Table 4 ($P < 0.001$ vs. the groups with scores of 0–5, 6–10, and 11–15).

The IFD risk scores in the validation set were also analyzed by the ROC with an area under the ROC (aROC) of 0.83 (95% CI: 0.76–0.90), as shown in Fig. 1 (right). The sensitivity, specificity, PPV, and NPV of different risk score cut-points (5, 10, and 15) were documented in the validation dataset, as shown in Table S2 (Supplementary Material).

Basing on these data, we classified the patients into three major groups: patients with risk scores of 0–10 were considered low-risk patients; those with risk scores of 11–15 were regarded as intermediate-risk patients, and those with risk scores of > 15 were regarded as high-risk patients.

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

Overall, antifungal prophylaxis significantly reduced the incidence of IFD. However its benefit varied significantly in the different group of patients with different risk scores, as shown in Table 5. For low-risk patients ($n = 3945$), the IFD incidence was not reduced but was even increased from 0.6% to 2% ($P = 0.004$). For intermediate-risk patients ($n = 745$), the IFD incidence was reduced from 6.6% to 2.1% ($P = 0.007$) with anti-fungal prophylaxis. For high-risk patients ($n = 199$), the IFD incidence decreased significantly from 23.3% to 8.4% ($P = 0.007$).

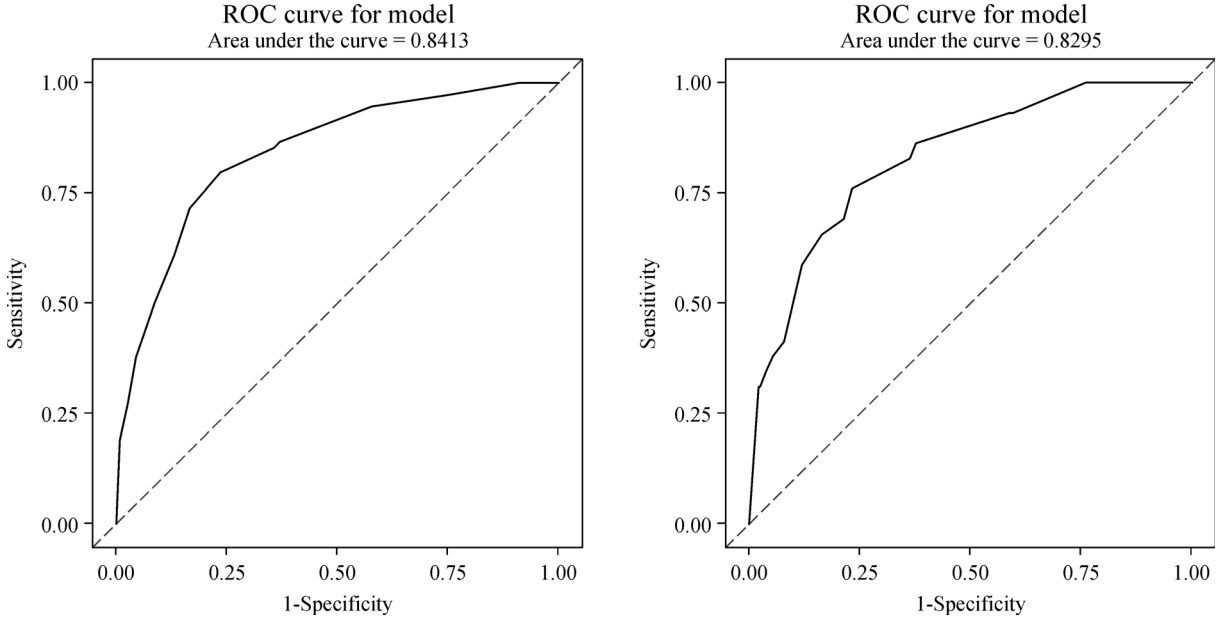

Fig. 1 Receiver-operator curve (ROC) analysis of the risk score in the training and validation datasets. (Left) ROC analysis plot of the true positives plotted as a function of false positives (100 specificity) at different cut-offs of the risk score in the training set. The dotted line represents a reference line without discrimination for IFD (aROC = 0.5). (Right) ROC analysis plot of the true positives plotted as a function of false positives (100 specificity) at different cut-offs of the risk score in the validation set. The dotted line represents a reference line without discrimination for IFD (aROC = 0.5).

Table 5 Impact of anti-fungal prophylaxis in patients with different risk score

Risk score	Prophylaxis	No. of chemotherapy courses (*n*)	IFD episode (*n*) / Incidence (%)	*P* value
0 – 10	Yes	501	10 (2.0%)	0.004
	No	3444	21 (0.6%)	
11 – 15	Yes	243	5 (2.1%)	0.007
	No	502	33 (6.6%)	
>15	Yes	83	7 (8.4%)	0.007
	No	116	27 (23.3%)	

Pre-chemotherapy risk score

Basing on the analysis, we demonstrated that a risk score is helpful in identifying the patients with high-risk of IFD and who may benefit most likely from anti-fungal prophylaxis. In the risk score model, four independent risk factors, namely, male patients, induction chemotherapy for patients with newly diagnosed or relapsed disease, central-venous catheter, and history of previous IFD, were pre-determined before chemotherapy, whereas development of neutropenia and neutropenia for > 10 days were predicted at least partially based on the intensity of chemotherapy and the hematological toxicity of previous cycles of chemotherapy. The only factor that can neither be determined nor predicted was the hypoalbuminemia after chemotherapy thus making the evaluation of IFD unfeasible before the start of chemotherapy. To address this question, a new risk score was built-up that excluded all risk factors that were potentially related to IFD but were unpredicted before chemotherapy, such as hypoalbuminemia, liver function damage, and parenteral nutrition required after chemotherapy, in the multivariate logistic regression analysis. The new pre-chemo risk score included only six factors and a total score of 0–21, as shown in Table 6. Further analysis confirmed that the pre-chemo score could also differentiate patients into groups with increasing incidence of IFD: low-risk patients with pre-chemo risk scores of 0–9 (IFD 0%–1.3%), intermediate-risk patients with scores of 10–15 (IFD ~4.5%), and high-risk patients with scores of > 15 (IFD > 10%), as shown in Table 7. We verified that the prophylaxis was useful in the intermediate- and high-risk groups but not in the low-risk group even when a slightly increased IFD incidence was documented (Table 8).

Table 6 Pre-chemo risk scores for prediction of proven/probable IFD

Factors	Variables	Scores
Sex	Male	2
	Female	0
ECOG	⩾3	3
	<3	0
Chemotherapy	Induction/Re-induction	4
	Consolidation	0
Neutropenia	ANC<0.5×10^9/L	4
	No	0
Duration of neutropenia	ANC<0.5×10^9/L, >10 days	3
	No	0
History of IFD	Yes	5
	No	0

Table 7 Distribution of pre-chemo risk scores versus the cumulative incidence of proven/probable IFD in the training and validation datasets

Risk score	Chemotherapy courses (*n*)	IFI episodes (*n*) /Incidence (%)
Training dataset		
0 – 4	531	2 (0.4%)
5 – 9 *	2255	26 (1.2%)
10 – 15 **	577	26 (4.5%)
>15 ***	137	20 (14.6%)
Validation dataset		
0 – 4	218	0
5 – 9 #	894	12 (1.3%)
10 – 15 ##	216	10 (4.6%)
>15 ###	61	7 (11.5%)

* $P = 0.104$ vs. the group with scores of 0–4; ** $P<0.001$ vs. the groups with scores of 0–4 and 5–9, respectively; *** $P<0.001$ vs. the groups with scores of 0–4, 5–9, and 10 – 15.
# $P = 0.085$ vs. the group with scores of 0–4; ## $P<0.001$ and $P<0.002$ vs. the groups with scores of 0–4 and 5–9, respectively; ### $P<0.001$ vs. the groups with scores of 0–4 and 5–9; and $P = 0.049$ vs. the group with scores of 10–15.

Discussion

Fungal infection is one of the leading causes of lethal infectious complications in patients with hematological malignancy receiving either chemotherapy or HSCT [10,24,25]. The incidence of IFD and potentially IFD-related mortality can be reduced by anti-fungal prophylaxis and early treatment [3,26,27]. However, the significant benefits of antifungal prophylaxis was mostly observed in high-risk patients with IFD incidence of 10%–15%, whereas the benefit was minimal if the IFD incidence was < 5% [6,28–31]. Moreover, researchers argue

Table 8 Impacts of anti-fungal prophylaxis in patients with different pre-chemo risk scores

Risk score	Prophylaxis	No. of chemotherapy courses (*n*)	IFD episode (*n*) / Incidence (%)	*P* value
0 – 9	Yes	456	10 (2.2%)	0.01
	No	3442	30 (0.9%)	
10 – 15	Yes	284	6 (2.1%)	0.01
	No	509	30 (5.9%)	
>15	Yes	87	6 (6.9%)	0.02
	No	111	21 (18.9%)	

whether empirical or pre-emptive therapy should be applied in cases of persistent fever in patients with prolonged neutropenia after chemotherapy. Although pre-emptive treatment definitely reduced the potentially unnecessary use of anti-fungal treatment, empirical anti-fungal treatment seems to guarantee a better outcome in terms of the reduced incidence of IFD and IFD-related mortality [32]. Recent guidelines suggest a risk-based approach that recommends empirical therapy for high-risk patients and anti-fungal treatment for low-risk patients except in cases of additional findings that indicate a suspected IFD [8]. Therefore, the starting point of an optimal anti-fungal strategy is a more reliable risk assessment of patient at high risk of IFD.

In the literature, numerous risk factors have been reported to be associated with IFD [6,9–21]. The most commonly reported variables included hematological disease (AML/MDS vs. others), disease status (newly diagnosed and relapse/refractory vs. clinical remission), type of treatment (chemotherapy vs. transplantation or induction vs. consolidation chemotherapy), development of neutropenia and its duration, graft versus host diseases (GVHD) with steroid treatment in case of allogeneic HSCT, and previous history of IFD. Genetic factors related to host innate immunity and environmental variables have also been reported to be important [33]. Therefore, the precise evaluation of IFD incidence has become extremely complex because all of these risk factors must be considered and weighed for each patient.

To overcome this challenge and make the assessment as simple as possible, a prognostic model or risk score can complement the clinical assessment by providing an objective summation of multiple risk factors to identify the patients with high risk of IFD and who are most likely to benefit from anti-fungal prophylaxis. In a previous study, Stanzani *et al*. [34] reported a single institution study that aimed to develop and validate an unconditional risk model for IFD in a heterogeneous population of patients with hematological malignancies undergoing both chemotherapy and allogeneic HSCT. The risk model included four major risk factors with a cut-off value of six identified patients with low vs. high risk of IFD. This study demonstrated that posaconazole prophylaxis was not associated with a reduced IFD in low-risk patients (scores < 6), whereas benefits were documented in high-risk patients (scores > 6). The major limitation of this study is the mixture of patients undergoing chemotherapy and allogeneic HSCT, which included patients with GVHD and corticosteroids treatment.

In this study, we utilized the multiple-center-based CAESAR study, which included 4192 patients, to perform a risk model study for IFD in patients with hematological malignancies undergoing chemotherapy only. The risk factors included in the analysis were routinely available in "real-life" clinical settings. After multivariate analysis, six variables, namely, age, diagnosis of disease, ECOG score, concomitant diseases, hepatic impairment, and use of parental nutrition, lost significance, thereby leaving seven clinical variables to be considered independently associated with IFD, as shown in Table 2. A score system was built up accordingly. We confirmed the discriminative performance of the IFD risk score system in both the training and validation datasets. The patients with scores of > 10 predicted an IFD incidence of over 5%, whereas higher scores of > 15 presented IFD of up to 20%. The patients with lower scores (6–10) were associated with a low IFD incidence of $< 2\%$, whereas those with scores of 0–5 presenting an extremely low risk of IFD ($< 0.5\%$).

The meta-analyses for the anti-fungal prophylaxis recommended the use of prophylaxis for patients with the highest risk of IFD, such as allogeneic HSCT recipients and those treated for acute leukemia or MDS, whose IFD incidence was likely to exceed 5% without prophylaxis, whereas the most significant benefit was recorded when the IFD incidence was above 10%–15% [6,28–30]. Reports have shown that prophylaxis was not considered cost-effective if the baseline IFD incidence rate was assumed to be 3%; thus, a threshold of 5% was often used in the clinical decision-making process [6,35]. When these independent risk factors of IFD in patients undergoing chemotherapy were considered individually, few factors could identify a group of patients with an IFD incidence of above 5% without prophylaxis, and the benefit of prophylaxis was demonstrated only in patients with either hypoalbuminemia ($n = 544$) or prolonged neutropenia (> 14 days, $n = 195$, Table 9).

Table 9 Impacts of anti-fungal prophylaxis in patients with different IFD risk factors

Risk factors of IFD		Prophylaxis	No. of chemotherapy courses (*n*)	IFD episode (*n*) / Incidence (%)	*P* value
Hypoalbuminemia	Yes	Yes	127	4 (3.1%)	0.0348
		No	417	38 (9.1%)	
	No	Yes	444	11 (2.5%)	0.0050
		No	2512	21 (0.8%)	
Chemotherapy	Induction/re-induction	Yes	281	8 (2.8%)	0.7190
		No	1436	50 (3.5%)	
	Consolidation	Yes	290	7 (2.4%)	0.0085
		No	1493	9 (0.6%)	
Neutropenia	Yes	Yes	348	10 (2.87%)	<0.001
		No	642	38 (5.9%)	
	No	Yes	156	4 (2.6%)	0.0293
		No	2149	14 (0.7%)	
Duration of neutropenia	<10 days	Yes	205	3 (1.5%)	0.2037
		No	436	15 (3.4%)	
	11 – 14 days	Yes	58	5 (8.6%)	0.7562
		No	86	6 (7.0%)	
	>14	Yes	85	2 (2.4%)	0.0033
		No	120	17 (14.2%)	
Central-venous catheter	Yes	Yes	391	10 (2.6%)	0.7314
		No	1193	37 (3.1%)	
	No	Yes	180	5 (2.8%)	0.1022
		No	1736	22 (1.3%)	
History of IFD	Yes	Yes	93	5 (5.4%)	1.0000
		No	98	6 (6.1%)	
	No	Yes	478	10 (2.1%)	0.7177
		No	2831	53 (1.9%)	

Considering that our risk score system integrated multiple independent risk factors of IFD, we confirmed that a group of patients had an extremely low risk of IFD ($< 1\%$) and another group of patients ($n = 944$) had a high risk of IFD of above 5%. Moreover, the risk score also discriminated a group of patients ($n = 199$) with an extra high incidence of IFD above 15%. We also confirmed that the anti-fungal prophylaxis presented no significant benefits in the patients with low risk scores (0–10), whereas the benefits in the patients with intermediate (11–15) and high scores (> 15) were prominent with reduction of the total IFD incidence at 4.5% and 15%, respectively. To maximize the risk score model in guiding the anti-fungal prophylaxis, we further established a pro-chemo risk score with risk factors that can be easily determined or predicted before chemotherapy. All of these data confirmed that by using the risk score, we could divide the patients into three groups of low, intermediate, and high risk of IFD with predictable IFD incidences of $< 1.5\%$, ~5%, and $> 10\%$, respectively. More importantly, the benefit of anti-fungal prophylaxis was documented in intermediate and particularly high-risk patients, thus making the risk score a suitable tool in evaluating the risk of IFD and guiding the anti-fungal prophylaxis in clinical settings.

Several interesting points remains to be clarified. In the patients with low-risk IFD (either by risk score 0–10 or patients undergoing consolidation chemotherapy or without hypoalbuminemia), anti-fungal prophylaxis led to an overall IFD incidence of around 2%, which was even higher than that of the patients without prophylaxis (0.6%). We further analyzed the outcome of anti-fungal prophylaxis in patients with respect to individual risk factors (Table 9). Although anti-fungal prophylaxis was beneficial in patients with prolonged neutropenia for more than 14 days or hypoalbuminemia, i.e., the patients who were considered to be of low risk for IFD with consolidation chemotherapy or without hypoalbuminemia or no neutropenia, the incidence of IFD was low ($< 1\%$) without prophylaxis but increased to around 2% with anti-fungal prophylaxis.

One possible explanation is the observational nature of the CAESAR study. The use of anti-fungal prophylaxis was based on the hematologists' decision. The prevailing trend was to administer anti-fungal prophylaxis to patients with high-risk features, such as patients with previous history of IFD, elderly patients, or patients with decreased

performance status, whereas prophylaxis was usually spared in younger, fit patients without previous IFD even if these patients satisfied the criteria of low risk based on the score system. For example, 48.7% (93/191) of the patients with previous documented or suspected IFD received anti-fungal prophylaxis, whereas only 14.5% with no previous IFD history received the treatment (Table 9) even though the impact of the previous history of IFD was significant particularly in patients with low risk scores. The other possible explanation is that key factors associated with IFD, were not selected by the analysis either due to statistic power or exclusion in the original design. For example, although the evaluation of IFD risk based on clinical variables is feasible and easy to perform in clinical settings, genetic immunological factors and environmental factors, such as patients receiving chemotherapy without high efficiency particulate air (HEPA) filtration or admission to the hospital with ongoing construction, were excluded as risk factors [36–38]. Environmental factors are significant when patients have few or no other IFD risk factors, whereas its impact on IFD may lose significance in patients with multiple prominent IFD risk factors, such as prolonged neutropenia, previous history of IFD, and hypoalbuminemia. In clinical settings, the prevailing trend was to administer anti-fungal prophylaxis to patients receiving chemotherapy in a high-risk environment, whereas prophylaxis was spared for patients in a more protective scenario. Although the underlying cause of the observation remains unclear, we may conclude based on our data that anti-fungal prophylaxis is not beneficial for patients with low risk of IFD.

Another interesting point is the impact of gender on the IFD incidence, which was not identified in previous studies [13,14,34]. First, an imbalanced distribution of clinical features were observed between male and female patients in the CAESAR study, and the impact of any imbalance can be overcome by multivariate analysis. Secondary, the number of patients included in the score building-up procedure also exerts an impact. In our patients' series based on more than 4000 patients (largest for an IFD study), gender had the smallest individual weights among all factors. The low-weighted factors can stand out only with a large number of patients, and a lower number of patients may lead to the loss of its statistical significance in multivariate analysis. Finally, we may speculate that the gender issue may be associated with smoking history or smoking exposure. Although no documentation is available for smoking as a risk factor of IFD, cases of pulmonary IFD due to smoking fungal-contaminated marijuana have been reported [39,40]. The other possibility is that patients with heavy smoking history may have more severe pulmonary diseases, which may contribute to the increased risk of IFD in hematological patients — which is beyond the scope of our study.

Conclusions

In conclusion, our study attempted for the first time to develop an IFD risk score system based on a large patient population that is specifically targeted for patients with hematological malignancies receiving chemotherapy only. We established an objective, weighted risk score for IFD that could reliably discriminate the incidence of IFD. The precise risk assessment of IFD may provide a basis for risk-based anti-fungal treatment in patients with hematological malignancies. The score system should be implemented with caution because some IFD-associated factors (such as environmental factors) were excluded, and further confirmation is required in prospective study particularly with well-defined diagnostic procedure and definite anti-fungal strategy.

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Compliance with ethics guidelines

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