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Development and internal validation of a model for predicting 60-day risk of invasive mould disease in patients with haematological malignancies

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SUMMARY

Objective: Our objective was to develop a model that predicts a patient's risk of developing invasive mould disease (IMD) within 60 days of admission for treatment of a haematological malignancy.
Methods: We analysed 19 risk factors for IMD in a cohort of 1944 adult patients with haematological malignancies over 4127 admissions at a haematology referral centre in Northern Italy (2007-2016). We used a multivariable logistic regression to estimate the 60-day probability of developing probable or proven IMD. The model was internally validated using a bootstrap resampling procedure.
Results: The prevalence of IMD was 3.3% (90 probable cases, 43 proven cases). Seven risk factors were retained in the final risk model: (1) uncontrolled malignancy, (2) high-risk chemotherapy regimen, (3) high-dose corticosteroids, (4) severe lymphopenia, (5) CMV reactivation or disease, (6) prolonged neutropenia, and (7) a history of previous IMD within 90 days. The model displayed good calibration and discrimination in both the derivation (aROC 0.85, 95% CI 0.84-0.86) and validation (aROC 0.83 95% CI 0.79-0.89) populations.
Conclusions: Our model differentiated with 85% accuracy whether or not patients developed IMD within 60-days of admission. Individualized risk assessment, aided by validated prognostic models, could assist IMD management and improve antifungal stewardship.

Introduction

Many decisions surrounding the management of invasive mould disease (IMD) rely on an accurate estimate of the patient's future probability for developing the infection.[1] In patients with haematological malignancies, this risk is influenced by multiple interrelated factors, including the type and status of underlying malignancy, the depth and duration neutropenia, and receipt of high-dose corticosteroids and/or the presence of graft versus host disease following allogeneic hematopoietic stem cell transplantation (HSCT).[2–4] Other risk factors include co-infections (e.g., cytomegalovirus, H1N1 influenza),[5,6] comorbidities such as diabetes mellitus, iron overload, renal impairment or acidosis, and an occupational history associated with high levels of fungal spore exposure (e.g., construction, farming).[2,3] More recently, single nucleotide polymorphisms (SNPs) in genes related to innate immune system recognition of fungal pathogens (e.g., Toll-like receptors, C-type lectin receptor, mannose binding lectins, pentraxin-3, and plasminogen) have been linked to increased risk of aspergillosis following allogeneic HSCT.[7–10]

Despite improved understanding of these risk factors, determining which individual patient is at higher risk for IMD remains challenging, especially among populations with a low overall prevalence for such opportunistic infections- i.e. patients undergoing treatment for lymphoma, chronic myelogenous leukaemia, chronic lymphocytic leukaemia, multiple myeloma. In these populations, routine serum galactomannan screening may result in frequent false-positive results leading to unnecessary follow-up radiological studies or even invasive procedures.[11] Similarly, indiscriminate use of broad-spectrum antifungal prophylaxis may not be justifiable for all patients, but only for a small subset of patients at the highest risk.

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One approach to improve individualized risk assessment for patients is to develop models that can accurately predict a patient's future risk for IMD based on objective summation of multiple clinical variables assessed at the time of admission, thereby clarifying which patients should be targeted for more aggressive monitoring or prophylaxis.[12] As a first step towards this goal, we previously proposed a prognostic risk score that estimated the probability of future development of IMD in patients with haematological malignancies.[13] This score was based on 1709 inpatient admissions from 2005 to 2008 and prospectively validated using a follow-up cohort of 1746 admissions from 2009 to 2012. However, we hypothesized that recalibration of this risk model with additional risk factors for IMD and consideration of antifungal prophylaxis could improve its prognostic utility, thereby allowing for improved prediction of which patients are at low versus high risk for IMD.

To test this hypothesis, we developed and internally validated a new prognostic multivariable risk model for use at the time of hospital admission that predicts the 60-day probability of IMD in patients undergoing treatment for a haematological malignancy. The model was then used to construct a simplified nomogram to allow for rapid, bedside calculation of IMD risk. We also explored how an individualized risk assessment using the nomogram could identify higher-risk subgroups of patients among heterogeneous populations of patients with hematologic malignancies associated with a low risk for IMD, who could benefit in the future from more intensive diagnostic workup or antifungal prophylaxis.

Methods

Source of data

The population sample used for model development was from a prospectively-collected data registry at a major haematology centre in Northern Italy. The registry included 4694 consecutive hospital admissions lasting more than 5 days of 2187 adult patients with haematological malignancies during 2007-2016. Methods concerning data collection and adjudication were previously described.[13] All admission episodes including re-admissions with complete data were included in the analysis to maximize the power and generalizability of the results and applicability to clinical care. Data collection was conducted in accordance with guidelines outlined by the Declaration of Helsinki. A full ethics review was waived by the institutional ethics committee based on the observational nature of the study.

In addition to data concerning the underlying malignancy and treatment, comorbidities, infections and medical complications, we collected data on 19 candidate risk factors for IMD selected *a priori* based on consensus of treating physicians and prior literature review.[13] These predictive risk factors included: (1) Age over 40 years; (2) Patient occupation associated with high spore exposure (e.g., farmer, construction worker); (3) Smoker; (4) Previous documented episode of IMD within 90 days of the admission date; (5) Type I or II diabetes mellitus; (6) Receipt of high-dose corticosteroids within 30 days of admission ($>$ 0.5 mg/kg prednisone equivalent); (7) Underlying high-risk malignancy (acute myeloid leukaemia, myelodysplastic syndrome, or bone marrow aplasia); (8) Uncontrolled malignancy status (not in complete or partial remission); (9) Ongoing or planned high-risk chemotherapy within 30 days (myeloablative conditioning for allogeneic HSCT, high-dose ARA-C, fludarabine plus cytarabine and idarubicin (FLAI), or ifosfamide, carboplatin, etoposide (ICE) induction chemotherapy; (10) Ongoing or imminent (chemotherapy-associated) prolonged neutropenia defined as PMN $<$ 100 cells/mm^3 for greater than 10 days; (11) Severe lymphopenia defined as total lymphocyte count $<$ 50 cells/mm^3; (12) Grade II-IV acute GVHD defined according to criteria proposed by Glucksberg et al.[14]; (13) Extensive chronic GVHD defined according to criteria proposed by Shulman et al.[15]; (14) Mucositis Grade III-IV defined according to WHO criteria[16]; (15) CMV reactivation detected by plasma CMV DNA $\geq$ 1000 IU/mL or development of CMV disease requiring antiviral treatment; (16) Admission to a non-high-efficiency particulate air (HEPA) filtered room; and (17) Admission to an inpatient room during a period of hospital construction affecting the same unit. We also systematically collected data on (18) receipt of any mould-active therapy within 30 days of admission as well as (19) receipt of posaconazole prophylaxis.

Study endpoints

The primary outcome of interest was the development of proven or probable IMD within 60 days of admission as defined by 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 (EORTC/MSG) Consensus criteria.[17] Patients were followed for the duration of their hospitalization up to 90 days or until death. Patients who were discharged without fever or infectious symptoms before day 90 and did not require readmission for infection were considered to not have developed probable or proven IMD within 60 days. Each admission was analysed as a separate episode, and risk factors were re-recorded an analysed as a unique record in the database.

Statistical analysis

Because of the ongoing nature of the registry, a formal sample size calculation was not performed. We assumed that at least 10 outcome events (proven or probable IMD) were needed per variable analysed by multivariable regression to obtain stable coefficient estimates.[18] For descriptive analysis of the study population, continuous variables were reported as medians with interquartile ranges. The Mann-Whitney U test was used to compare continuous variables. Binary and categorical data were expressed as frequencies and analysed with the Fisher's exact test.

For multivariable analysis, candidate risk factors for IMD with a $P < 0.10$ in univariable analysis were analysed in multivariable model. Antifungal prophylaxis/therapy and posaconazole prophylaxis were included in the multivariable model irrespective of P values in univariable analysis. We applied a backward selection approach during multivariable logistic regression to ensure all correlations between predictors were considered using a P cutoff of 0.05. Missing values were excluded from the analysis. The prediction equation was derived using coefficients obtained from the multivariate regression model. Model discrimination was assessed by area under the receiver operating characteristics (aROC). Model goodness of fit was assessed by plot of predicted versus observed rates of IMD plotted using a Loess smoothing algorithm,[19] and by septile of grouped risk - a graphical illustration of the Hosmer-Lemeshow goodness-of-fit test.[20] The final prediction model was internally validated using a bootstrap resampling procedure with 100 repetitions from the original database (IMD incidence ranging from 2 to 9%) to assess model bias.[18] A simplified nomogram for risk score calculation was generated from the final logistic regression model using the Nomolog program for STATA.[21] All analysis was performed using STATA/IC 13 (STATA Corp LP, College Station, TX).

Table 1
Patient demographic characteristics of hospital admissions.

Characteristic	No invasive fungal disease ($n = 3994$)	EORTC/MSG Proven/probable fungal disease ($n = 133$)	*P* value[a]
Median age-years (IQR)	55 (16-86)	52 (15-85)	.13
Sex- male (%)	60	62	.92
Median no. of hospitalizations- (IQR)	2 (1-3)	1 (1–3)	.67
Underlying malignancy-no. (%)			
Acute myeloid leukaemia/ myelodysplastic syndrome	1031 (25.0)	69 (51.9)	<0.001
Acute lymphoblastic leukaemia	455 (11.4)	27 (20.3)	<0.001
Chronic myelogenous leukaemia	34 (0.9)	1 (0.8)	.88
Chronic lymphocytic leukaemia	92 (2.3)	7 (5.2)	.04
Lymphoma	1379 (34.5)	21 (15.8)	<0.001
Multiple myeloma/amyloidosis	912 (22.8)	3 (3.0)	<0.001
Aplastic anaemia	57 (2.1)	2 (2.2)	.74
Non-neoplastic haematological disease	34 (0.9)	1 (0.8)	.20
Reason for admission-no. (%)			
Induction chemotherapy	744 (18.6)	20 (15.0)	.29
Consolidation chemotherapy	1003 (25.1)	13 (9.8)	<0.001
Salvage chemotherapy	493 (12.3)	29 (21.8)	<0.001
Allogeneic HSCT	248 (6.2)	44 (33.1)	<0.001
Autologous HSCT	833 (21.0)	5 (3.8)	<0.001
PBSC mobilization	272 (6.8)	1 (0.8)	.006
Radiotherapy	14 (0.03)	0 (0)	.49
Admission for medical complication	267 (6.7)	10 (7.8)	.04
At initial malignancy diagnosis	120 (3.0)	6 (4.7)	.32

[a] Fischer's exact test or Mann Whitney *U* test.

Results

Participants

We screened 4694 patient admission episodes in 2187 patients admitted with a diagnosis of haematological malignancy from 2007 to 2016. Approximately 10% of admissions in the registry ($n = 502$) had missing data for one or more IMD risk factors that could not be correlated to any study variables or endpoints, or patient death. Therefore, these missing data were considered to missing completely at random and these cases were excluded from further analysis.[18] Among the remaining 4127 admissions in 1944 patients, the overall prevalence of EORTC/MSG defined probable or proven IMD was 3.3% (90 probable cases, 43 proven cases). Galactomannan antigen was detected in serum or bronchoalveolar lavage fluid in 69% of these cases. Moulds were documented by culture or histopathology in 32% of the cases and included, *Aspergillus flavus* ($n = 14$), *A. fumigatus* ($n = 10$), *Aspergillus* hyphae ($n = 11$); *Aspergillus niger* ($n = 1$); *Fusarium* spp. ($n = 5$), and Mucorales hyphae ($n = 1$). The median time to onset for IMD was 22 days (IQR 13-28 days). The median duration of hospital admission in patients without IMD was 20 days (IQR 14-28), and 40 days (IQR 29-57) for patients with probable or proven IMD.

Baseline demographic characteristics

Baseline demographic characteristics of the study population are presented in Table 1. We observed significantly higher frequencies of probable or proven IMD among patients admitted with a diagnosis of acute myeloid leukaemia/ myelodysplastic syndrome (AML/MDS), acute lymphoblastic leukaemia (ALL), and chronic lymphocytic leukaemia (CLL). Admissions associated with the administration of salvage chemotherapy or an allogeneic HSCT were also associated with a higher IMD frequency. Baseline characteristics associated with lower frequency of IMD included, hospital admissions for treatment of lymphoma, multiple myeloma/amyloidosis, or admission for consolidation chemotherapy or autologous HSCT.

IMD risk model

The association of 19 *a priori* selected candidate risk variables for proven or probable IMD within 60 days of admission are shown in Table 2. In univariable analysis, 12/19 risk factors were associated with the development of IMD at a $P < 0.1$. When these 12 variables were analysed by multivariable logistic regression, uncontrolled malignancy, receipt of high-risk chemotherapy, receipt of high-dose corticosteroids, severe lymphopenia, CMV reactivation or disease, prolonged neutropenia, and a history of IMD within 90 days of admission were independently associated with the development of probable or proven IMD (Table 3). Prior mould-active antifungal therapy or posaconazole prophylaxis were not retained in the final multivariable model. Using coefficients obtained from the multivariable logistic regression analysis, we derived the following prediction equation for calculating the log odds of proven or probable IMD where outcomes are coded as "1" if present and "0" if absent:

$$Risk = (0.68 \times \textit{uncontrolled malignancy}) + (0.79 \times \textit{high-risk chemotherapy}) + (0.80 \times \textit{high-dose corticosteroids}) + (0.89 \times \textit{severe lymphopenia}) + (1.14 \times \textit{CMV reactivation}) + (1.52 \times \textit{prolonged neutropenia}) + (1.64 \times \textit{previous mould disease}) - 5.45.$$

To calculate the 60 day probability from the formulae, the result from the calculation above is converted from log odds to odds (e^{Risk}), then odds must be converted to probability using the formulae: Risk/(1+Risk).

The model was well-calibrated up to a risk rates of 40% in both the derivation and bootstrapped resampled validation population with IMD incidence ranging from 2 to 9% (Fig. 1), with a bias to overestimation of IMD risk at rates above 40%. The prediction model based on the equation above had an aROC of 0.85 (95% CI 0.84-0.86) (Fig. 2). Internal validation using the bootstrapping technique with 100 repetitions resulted in a similar aROC of 0.83 (95% CI 0.79-0.87, bias 0.002).

A Youden-index defined cut-off of 5% was used to explore the potential clinical application of the model. At this cut-off, the risk model correctly identified the 60-day IMD outcomes in 85.12% of admissions while predicting a low probability in 43 admissions as-

Table 2
Risk factors evaluated in the prediction model.

	Risk factor			Univariable analysis		Multivariable analysis	
		No fungal disease ($n=3994$)	Proven/probable fungal disease ($n=133$)	OR (95% CI)	*P* value[a]	AOR (95% CI)	*P* value[b]
1	Age > 40 years-no.(%)	3074 (77.0)	102 (76.7)	1.02 (0.67-1.53)	.92		
2	At risk profession	292 (7.3)	17 (12.8)	1.85 (1.10-3.13)	.03		
3	Smoker	934 (23.4)	39 (29.3)	1.35 (0.93-1.99)	.12		
4	Previous episode of invasive mould disease within 90 days of admission	87 (2.2)	20 (15.4)	7.94 (4.72-13.40)	<0.001	5.17 (2.89-9.25)	<0.0001
5	Diabetes mellitus	293 (7.3)	11 (8.2)	1.13 (0.61-2.14)	.61		
6	High dose corticosteroids[b]	437 (11.0)	30 (22.6)	2.38 (1.56-3.60)	<0.001	2.21 (1.37-3.57)	.001
7	High-risk malignancy[c]	1117 (28.0)	82 (61.7)	4.14 (2.90-5.91)	<0.001		
8	Uncontrolled malignancy[d]	1621 (40.6)	78 (58.7)	2.07 (1.46-2.95)	<0.001	1.96 (0.34-2.90)	.001
9	High-risk chemotherapy[e]	777 (19.5)	85 (63.9)	7.33 (5.10-10.53)	<0.001	2.20 (1.40-3.46)	.001
10	PMN < 100 cells/mm^3 for > 10 days	1098 (27.5)	106 (79.7)	10.35 (6.75-15.89)	<0.001	4.56 (2.69-7.73)	<0.001
11	Total lymphocyte count < 50 mm^3	462 (11.6)	65 (48.9)	7.31 (5.13-10.41)	<0.001	2.43 (1.60-3.69)	<0.001
12	Acute graft versus host disease, grade II-IV[f]	51 (1.3)	13 (9.7)	8.38 (4.44-15.81)	<0.001		
13	Chronic graft versus host disease, extensive[g]	19 (0.4)	2 (1.5)	3.91 (0.74-13.86)	.10		
14	Mucositis, grade III-IV[h]	250 (6.3)	31 (23.3)	4.55 (2.99-6.94)	<0.001		
15	CMV reactivation or disease[i]	95 (2.4)	17 (12.8)	6.01 (3.48-10.41)	<0.001	3.12 (1.63-5.96)	.001
16	Admission to a non-HEPA filtration room	1193 (29.9)	48 (36.1)	1.29 (0.90-1.85)	.28		
17	Admission during hospital construction	1766 (44.2)	51 (38.5)	1.27 (0.89-1.82)	.18		
18	Receipt of mould-active therapy[j]	650 (14.3)	22 (23.2)	1.29 (0.73-2.31)	.45		
19	Receipt of posaconazole prophylaxis[k]	349 (7.7)	14 (16.5)	3.61 (0.56-23.14)	.42		

OR, odds ratio.
AOR, adjusted Odds ratio.
[a] Fischer's exact test.
[b] 0.5 mg/kg prednisone equivalent within 30 days.
[c] Acute myeloid leukemia, myelodysplastic syndrome or bone marrow aplasia.
[d] Underlying malignancy not in complete or partial remission.
[e] Any conditioning regimen for allogeneic HSCT, high-dose ARA-C, Fludarabine, cytarabine and idarubicin (FLAI), ICE (iphosphamide, carboplatin, etoposide).
[f] According to criteria proposed by Glucksberg criteria[14]
[g] According to criteria proposed by Shulman et al.[15]
[h] According to WHO criteria[16]
[i] Detection of plasma CMV DNA≥1000 IU/mL or development of CMV disease requiring antiviral therapy.
[j] Patient received itraconazole capsules or solution, voriconazole, posaconazole, or other antifungal therapy within 30 days of admission.
[k] Patient received posaconazole antifungal prophylaxis as part of a planned standard chemotherapy protocol.

Table 3
Estimated risk score performance characteristics at 5% cut-off for defining high versus low risk admissions.

Patient group	Overall IMD prevalence,% (*n*=admissions)	IMD prevalence "high-risk,"% (*n*=admissions)	IMD prevalence "low-risk,"% (*n*=admissions)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
AML/MDS	6.7 (1100)	13.4 (388)	2.4 (712)	0.75 (0.64–0.85)	0.62 (0.59–0.65)	0.11 (0.05–0.07)	0.98 (0.96–0.99)
ALL	5.9 (482)	14.6 (103)	3.2 (379)	0.44 (0.25–0.66)	0.73 (0.69–0.77)	0.08 (0.04–0.14)	0.96 (0.94–0.98)
CML	2.9 (35)	16.7 (6)	0.0 (29)	1.00 (0.88–1)	0.73 (0.56–0.85)	0.08 (0.002–0.38)	1.0 (0.88–1)
CLL	7.6 (99)	20.0 (30)	1.4 (69)	0.86 (0.42–0.99)	0.62 (0.52–0.71)	0.13 (0.05–0.25)	0.99 (0.92–1.0)
Lymphoma	1.5 (1400)	13.2 (84)	0.8 (1316)	0.52 (0.30–0.74)	0.85 (0.83–0.86)	0.04 (0.02–0.08)	0.99 (0.98–1.0)
Myeloma	0.4 (916)	6.5 (31)	0.2 (886)	0.50 (0.07–0.93)	0.84 (0.82–0.87)	0.01 (0.001–0.009)	0.99 (0.99–1)
Aplastic anaemia	5.3 (60)	15.8 (19)	3.0 (41)	1.0 (0.29–1)	0.48 (0.37–0.59)	0.06 (0.013–0.18)	1.00 (0.91–1)
Allogeneic HSCT	8.0 (261)	10.7 (159)	3.9 (102)	0.81 (0.58–0.95)	0.33 (0.28–0.39)	0.08 (0.05–0.12)	0.96 (0.90–0.99)

sociated with IMD. However. In 32/43 (74%) of these patients, the estimated risk was within 1.5% of the 5% cut-off.

The operating characteristics at a 5% cut-off are also presented in Table 3. Overall the model effectively differentiated higher risk (≥5%) versus lower risk (<5%) patients across different populations with varying prevalence of IMD ranging from 0.4% to 8%. Notably, the model identified a substantial number of admissions in high-risk populations (e.g., 65% in AML/MDS) that were at lower risk for IMD (<3%). Similarly, the risk model also discriminated a subset of admissions associated with high risk of IMD (13.2%) in a small subset (6%) of non-transplanted low-risk lymphoma patients. The positive predictive value of the risk score at a 5% cut-off was generally low (1–13%) given the low overall prevalence of probable or proven IMD in the study cohort (3.3%). Negative predictive values, ranged between 96 and 100% across all patient groups.

Nomogram for IMD risk assessment

A graphical representation of the original mathematical regression formula was prepared as a nomogram (Fig. 3). We can

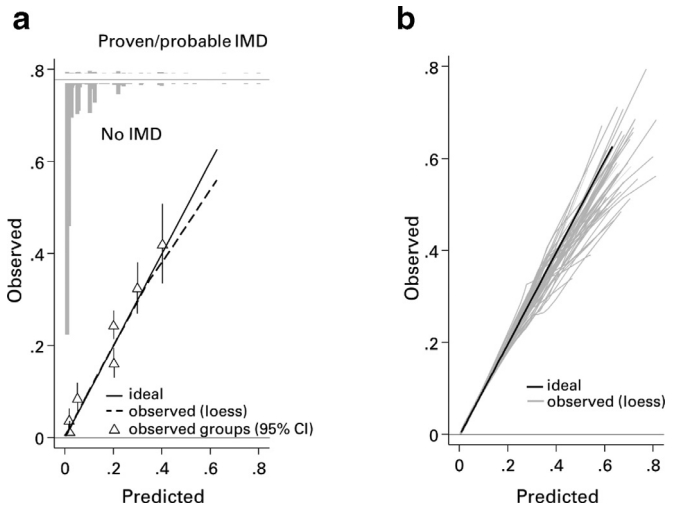

Fig. 1. Risk model calibration for the original (a) and (b) bootstrapped resampled population. Panel (a) shows the relationship between a perfectly calibrated model (solid line) and the observed incidence of EORTC/MSG proven, or probable mould disease plotted using the loess algorithm (dashed line). The observed incidence or proven or probable mould disease grouped per septile of predicted risk (a visual representation of the Hosmer–Lemeshow test) is plotted as triangles with associated 95% confidence intervals. Grey bars on the x-axis show the relative risk distribution of admissions without IMD (downward pointing spikes) or with proven or probable IMD (upward pointing spikes). Panel (b) shows observed incidence of proven or probable mould disease in 100 bootstrapped resampled datasets (overall incidence 2-9%) (grey lines) in relation to the ideal (perfectly calibrated) model.

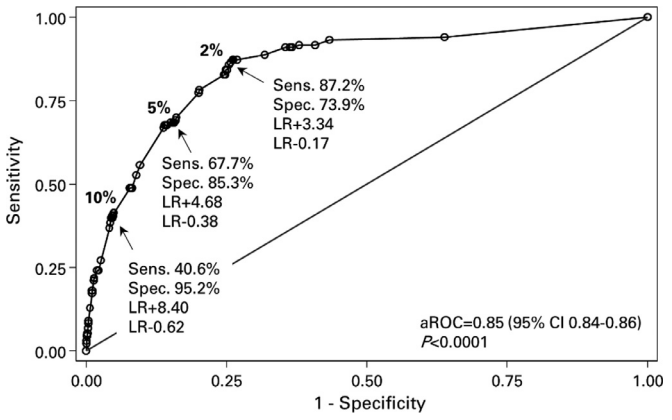

Fig. 2. Risk model discrimination and diagnostic characteristics at 2, 5 and 10% risk. An area under the receiver operator curve (aROC) analysis was performed with model-predicted probabilities for 60-day EORTC/MSG defined proven or probable invasive mould disease. Sens., sensitivity, Spec., specificity, LR+, positive likelihood ratio, LR-, negative likelihood ratio, 95% CI, 95% confidence interval.

illustrate how the nomogram is used to calculate risk with a patient from our original dataset. A 57-year-old female with diffuse B-cell lymphoma was admitted to our institute with relapsed lymphoma (4 points) for treatment with high-dose chemotherapy followed by autologous HSCT. She had a history of extensive corticosteroid treatment in the last month (5 points). She was also found to have CMV reactivation of 5000 IU/mL in blood that required ganciclovir treatment (7 points). Her total score on admission was 16 (baseline risk approximately 6%-similar to an AML/MDS induction chemotherapy patient). On day 22 following her admission while receiving fluconazole prophylaxis, she developed persistent fever associated with nodular opacities on chest CT exam. A serum galactomannan test was positive at an index of 0.7. Although not predicted at the time of admission, the patient subsequently developed a fourth risk factor of prolonged neutropenia (PMN $<$ 100 cells/mm^3 $>$ 10 days; an additional 9.5 points, total 25.5 or 22% risk) because of delayed engraftment associated with ganciclovir therapy.

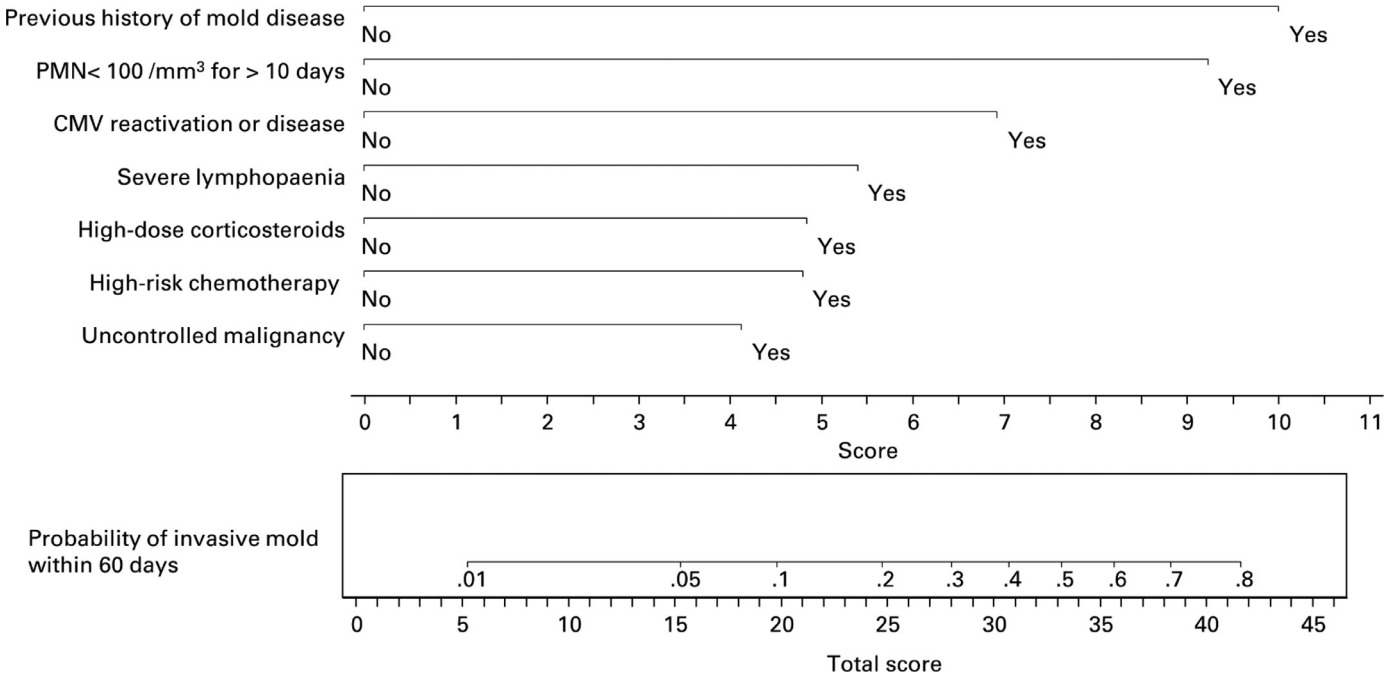

Fig. 3. Nomogram for estimating patient 60-day risk of invasive mould disease. Patients are screened for seven risk factors listed above. The user assigns a score to each risk factor (to the nearest 0.5 points) by drawing a line directly down from the end of the line (at "yes") for each risk factor to the scale labelled "score." The scores for risk factors present are then summed to calculate a total score, which is used to estimate 60-day estimated probability of invasive mould disease from the scale inside the lower box. See text for sample patient calculation.

Discussion

This study has shown that it is possible to predict with reasonable accuracy the future risk of developing IMD in patients admitted for treatment of a haematological malignancy. Although risk scores for invasive candidiasis have been extensively studied and applied in clinical studies for non-neutropenic ICU patients,[22–24] similar prognostic risk models for mould disease in patients with haematological malignancies are scarce.[13] Nevertheless, mould infections share several characteristics with other diseases where prognostic models have proven to be clinically useful, including: (1) complex, multivariate, and dynamic risk factors for disease development; (2) Multiple challenges and uncertainty surrounding the diagnosis; and (3) Availability of evidence-based interventions with proven survival benefit in a select populations.[25] Moreover, multivariable prognostic risk models could also aid the interpretation of current and future genetic risk factors for IMD, by allowing the comparison prognostic estimates derived from established clinical risk factors alone and with the addition of candidate genetic SNPs to better define the incremental prognostic information gained by genetic testing.

Individualized risk assessment for IMD is also fundamental to diagnostic and antifungal stewardship in haematology wards. Accurate identification of patients for whom the pre-test probability of IMD supports serum galactomannan and/or other biomarker testing is critical (e.g., >5% pre-test probability), as 80% of patients admitted to our institution did not meet this threshold. Current diagnostic tests for mould disease are also prone to false positive results, which is more problematic in patients with lower pre-test probability of disease.[26] Prognostic-model supported risk assessment could also allow for fine- tuning of prophylaxis strategies while reducing empirical antifungal use by applying different interventions based on graded risk (i.e. > 5%, > 10%, > 20%).

Our prognostic model has several limitations. It was developed from adult patient admission data in a single centre in Northern Italy. Therefore, IMD risk was likely affected by our population mix, clinical protocols, and possibly environmental factors. Although risk factors retained in the final multivariable model used to develop the nomogram are widely cited and consistent with general risk assessments proposed in current clinical guidelines,[4] the calibration of the model may be affected when applied to other centres with different patient mix. This phenomenon was evident in a recent comparison of *Candida* risk scores for non-neutropenic ICU patients derived from different centres with heterogeneous ICU populations.[23] Our main outcome measure was restricted to EORTC/MSG defined probable or proven fungal infections, therefore additional risk factors that are more frequent in patients with less diagnostic certainty (i.e. possible cases) may have been underrepresented in our analysis. The risk model was also internally validated using bootstrap resampling following recommended practices[18,27]; however external validation studies would increase confidence in the model performance and generalizability to other centres.

It could also be argued that multiple hospital admissions for the same patient should not be used to develop a risk score and may result in unintended bias. However, most patients follow a continuum of treatment from initial (induction) chemotherapy, consolidation or remission maintenance, then possibly transplantation. In many cases, IMD develops with subsequent admissions or during malignancy relapse. It is during these subsequent admissions when decisions regarding management of IMD are less certain and a clinical risk score is more helpful. Therefore, we opted to use all patient data to develop a model that more closely reflects clinical practice rather than a clinical trial.

The nomogram was designed to be applied to patients with all haematological diseases. Development of more targeted prognostic risk models for IMD in specific patient groups (e.g., AML/MDS induction vs. consolidation, acute lymphoblastic leukaemia, lymphoma, allogeneic HSCT) would likely change the weighting of variables and might reveal a greater effect of antifungal prophylaxis. These models could also help clarify the excess risks for IMD associated with new chemotherapies (e.g., ibrutinib in lymphoma patients). Development of more specific population risk models is an ongoing focus of research in our centre.

We also acknowledge that several other plausible risk factors for IMD disease were not analysed in this study. Variables that were not easily assessed or available at the time of admission were not considered in our analysis. Nevertheless, our model was able to accurately differentiate high-risk patients irrespective of underlying malignancy and treatment phase who are most likely to benefit from a proactive (non-empirical) management strategy for IMD.[25]

Ultimately, the development of a prognostic risk model or nomogram for IMD is a work in progress that requires continuous refinement and revalidation. We also emphasize that our nomogram is intended to support, not replace, sound clinical judgement and careful diagnostic workup in patients suspected to be at risk for IMD. However, as accurate risk assessment is fundamental to the effective management of mould infections and stewardship of diagnostic and treatment resources, we believe validated prognostic risk models are a supportive of optimal management of mould infections in patients with haematological malignancies and should be further explored and refined in future studies.

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Supplementary materials

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