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StenoSCORE: Predicting *Stenotrophomonas maltophilia* Bloodstream Infections in the Hematologic Malignancy Population

Sara M. Karaba,[a] Katherine E. Goodman,[b] Joe Amoah,[c] Sara E. Cosgrove,[d] Pranita D. Tamma[c]

[a]Johns Hopkins University School of Medicine, Department of Medicine, Division of Infectious Diseases, Baltimore, Maryland, USA
[b]University of Maryland School of Medicine, Department of Epidemiology and Public Health, Baltimore, Maryland, USA
[c]Johns Hopkins University School of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Baltimore, Maryland, USA
[d]Johns Hopkins University School of Medicine, Department of Medicine, Division of Infectious Diseases, Baltimore, Maryland, USA

ABSTRACT *Stenotrophomonas maltophilia* bloodstream infections (BSI) are associated with considerable mortality in the hematologic malignancy population. Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice; however, it is not routinely included in empirical treatment regimens, both because of its adverse event profile and the relative rarity of *S. maltophilia* infections. We developed a risk score to predict hematologic malignancy patients at increased risk for *S. maltophilia* BSI to guide early (TMP-SMX) therapy. Patients ≥12 years of age admitted to five hospitals between July 2016 and December 2019 were included. Two separate risk scores were developed, (i) a "knowledge-driven" risk score based upon previously identified risk factors in the literature in addition to variables identified by regression analysis using the current cohort, and (ii) a risk score based upon automatic variable selection. For both scores, discrimination (receiver operator characteristic [ROC] curves and *C* statistics) and calibration (Hosmer-Lemeshow goodness-of-fit test and graphical calibration plots) were assessed. Internal validation was assessed using leave-one-out cross-validation. In total, 337 unique patients were included; 21 (6.2%) had *S. maltophilia* BSI. The knowledge-driven risk score (acute leukemia, absolute neutrophil count category, mucositis, central line, and ≥3 days of carbapenem therapy) had superior performance (*C* statistic = 0.75; 0.71 after cross-validation) compared to that of the risk score utilizing automatic variable selection (*C* statistic = 0.63; 0.38 after cross-validation). A user-friendly risk score incorporating five variables easily accessible to clinicians performed moderately well to predict hematologic malignancy patients at increased risk for *S. maltophilia* BSI. External validation using a larger cohort is necessary to create a refined risk score before broad clinical application.

KEYWORDS *Stenotrophomonas maltophilia*, bloodstream infection, predictor, risk score

Stenotrophomonas maltophilia is a nonfermenting Gram-negative bacillus that causes a variety of infections—most notably, pulmonary infections and bloodstream infections (BSI). *S. maltophilia* infections are associated with mortality rates upwards of 40% in vulnerable populations (1–3). Timely treatment of *S. maltophilia* BSI with effective antibiotic agents is critical to reducing mortality (2, 4, 5). Owing to extensive health care exposures, high rates of broad-spectrum antibiotic use, and impaired immune systems, patients with hematologic malignancies are at particularly high risk for *S. maltophilia* BSI (4, 6, 7).

S. maltophilia is intrinsically resistant to most beta-lactam agents (including carbapenems) and aminoglycosides (4, 8, 9). Consequently, standard empirical antibiotic regimens for Gram-negative infections usually do not include coverage for *S. maltophilia*.

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Address correspondence to Sara M. Karaba, sara.karaba@jhmi.edu.

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Trimethoprim-sulfamethoxazole (TMP-SMX) is generally regarded as the treatment of choice for *S. maltophilia* infections (4, 10). However, the adverse event profile of TMP-SMX, which includes bone marrow suppression, hyperkalemia, and hypersensitivity syndromes, limits its routine use as empirical therapy (11). Prompt treatment of Gram-negative BSIs (GN-BSIs) in hematologic malignancy patients therefore poses a clinical challenge. On the one hand, with the increased risk and severity of *S. maltophilia* infections in this population, empirical initiation of TMP-SMX may be reasonable. On the other hand, *S. maltophilia* BSIs remain relatively rare compared to other GN-BSIs, and indiscriminate TMP-SMX therapy is associated with important side effects. Ideally, clinicians could determine, at the time a Gram stain identifies a GN-BSI in patients with a hematologic malignancy, for which patients the benefits of empirical TMP-SMX therapy for potential *S. maltophilia* BSI outweigh the risks.

To address this challenge, we sought to identify the subgroup of hematologic malignancy patients at greatest risk for a *S. maltophilia* BSI. We sought to develop and validate a user-friendly clinical risk score to predict, among the subgroup of patients with GN-BSIs, when empirical TMP-SMX therapy for *S. maltophilia* may be warranted.

RESULTS

Study population. In total, 337 unique patients were identified as having a hematologic malignancy or hematopoietic stem cell transplant (HSCT) and GN-BSI, of whom 21 (6.2%) had *S. maltophilia* bacteremia (Table 1). Demographics, types of underlying malignancies, severity of illness, and median number of days of hospital exposure in the past 3 months were similar between the *S. maltophilia* and other GN-BSI groups. The median absolute neutrophil counts (ANC) on day 1 of bacteremia were not statistically different between the two groups, nor were the proportions of those with prolonged neutropenia ($\geq$7 days). There were, however, some significant differences between the two groups. Mucositis was present in 5 (23.8%) of the *S. maltophilia* patients compared to 24 (7.6%) of other GN-BSI patients (odds ratio [OR] = 3.80; 95% confidence interval [CI], 1.28 to 11.27; $P = 0.02$) (Table 2). Patients with *S. maltophilia* BSI were more likely to have received at least 3 days of carbapenem therapy in the past 3 months compared to patients with other GN-BSIs (8 [38.1%] versus 40 [12.7%]; OR = 4.25; 95% CI 1.66 to 10.88; $P < 0.01$).

Knowledge-driven risk score. Five variables were identified for inclusion in the multivariable logistic regression model that generated regression coefficients for the knowledge-driven risk score (Table 2). These included two variables with a *P* value of $<$0.05 in univariable and multivariable analysis (i.e., mucositis [adjusted odds ratio (aOR) = 4.05; 95% CI, 1.25 to 13.15; $P = 0.02$] and $\geq$3 days of carbapenem therapy in the previous 3 months [aOR = 4.06; 95% CI, 1.49 to 11.02; $P < 0.01$]) and three variables previously identified as risk factors for *S. maltophilia* BSI in the published literature (i.e., ANC, acute leukemia, and presence of a central venous catheter). Points were assigned as follows: acute myelogenous leukemia or acute lymphocytic leukemia (1 point); central venous catheter present (22 points); ANC level (3 points per each increasing level, up to a maximum of 12 points, with 0 to 99 as reference level with no points); mucositis (23 points); and $\geq$3 days of carbapenem use in the preceding 3 months (19 points).

Patient point scores ranged from -1 to 67, with a median score of 22 (interquartile range [IQR], 21 to 34) (Table 3). The *C* statistic was 0.75 for the multivariable logistic model and remained 0.75 after transformation to integer points. Following cross-validation, the *C* statistic for the risk score was 0.71. There was acceptable calibration (Hosmer-Lemeshow goodness-of-fit test $P = 0.22$) of the multivariable logistic model. Following transformation to a point scale, the knowledge-driven risk score underestimated the probability of *S. maltophilia* BSI along several points of the risk continuum (Hosmer-Lemeshow goodness-of-fit $P < 0.001$) (Fig. 1A).

Automatic variable selection risk score. Risk score 2, using the "automatic variable selection" approach, yielded two variables, mucositis and $\geq$3 days of carbapenem therapy in the preceding 3 months (Table 3). Patient point scores ranged from 0 to 2, with a median score of 0 (IQR, 0). The *C* statistic for the risk score was 0.63 (0.64 prior to coefficient-to-points transformation). Following cross-validation, the *C* statistic for

TABLE 1 Baseline characteristics of hematologic malignancy patients with *Stenotrophomonas maltophilia* bacteremia and with other GN-BSIs

Patient characteristic[f]	Total (*N* = 337)	*S. maltophilia* BSI (*N* = 21)	Other GN-BSI (*N* = 316)	*P*
Demographics				
Age in yrs (median [IQR])	62 (49–70)	62 (44–70)	62 (49–70)	0.56
Sex, female (no. [%])	140 (41.54)	13 (61.90)	127 (40.19)	0.07
Type of malignancy or receipt of HSCT (no. [%])				
Acute myelogenous leukemia	109 (32.34)	8 (38.10)	101 (31.96)	0.52
Acute lymphocytic leukemia	35 (10.39)	3 (14.29)	32 (10.13)	0.52
T-cell lymphoma	7 (2.08)	1 (4.76)	6 (1.90)	0.52
Chronic lymphocytic lymphoma	12 (3.56)	0	12 (3.80)	0.52
Chronic myelomonocytic leukemia	2 (0.59)	0	2 (0.63)	0.52
Chronic myelogenous leukemia	3 (0.89)	0	3 (0.95)	0.52
Hodgkin lymphoma	7 (2.08)	1 (4.76)	6 (1.90)	0.52
Non-Hodgkin lymphoma	25 (7.42)	1 (4.76)	24 (7.59)	0.52
Multiple myeloma	42 (12.46)	0	42 (13.29)	0.52
Myelodysplastic syndrome	25 (7.72)	1 (4.76)	24 (7.59)	0.52
Diffuse large B-cell lymphoma	40 (11.87)	3 (14.29)	37 (11.71)	0.52
Other[a]	29 (8.61)	3 (14.29)	26 (8.23)	0.52
HSCT within preceding 12 mo	92 (27.30)	8 (38.10)	84 (26.58)	0.31
Degree of immunosuppression, potential risk factors				
ANC (cells/mm^3) (median [IQR])	49 (0–1,880)	180 (0–1,010)	30 (0–1,895)	0.87
Neutropenia[b] for ≥7 days (no. [%])	170 (51.36)	14 (66.67)	156 (50.32)	0.18
Mucositis present (no. [%])	29 (8.61)	5 (23.81)	24 (7.59)	0.03
Central venous catheter (no. [%])	260 (77.15)	20 (95.24)	240 (75.95)	0.06
Severity of illness				
Pitt bacteremia score (median [IQR])	1 (0–3)	1 (0–2)	1 (0–3)	0.48
ICU on day 1 of bacteremia (no. [%])	68 (20.18)	3 (14.29)	65 (20.57)	0.78
Prior colonization or infection in preceding 6 mo (no. [%])				
S. maltophilia	8 (2.37)	1 (4.76)	7 (2.22)	0.41
Other multidrug-resistant Gram-negative organisms[c]	48 (14.24)	2 (9.52)	46 (14.56)	0.75
Antibiotic history in preceding 3 mo (no. [%])				
Carbapenem[d] for ≥3 days	48 (14.24)	8 (38.1)	40 (12.7)	<0.01
Cefepime for ≥3 days	113 (33.53)	11 (52.38)	102 (32.28)	0.09
Piperacillin-tazobactam for ≥3 days	98 (29.08)	8 (38.10)	90 (28.48)	0.33
Prophylactic antibiotic[e]	230 (68.25)	17 (80.95)	213 (67.41)	0.23
Prior hospitalization in preceding 3 mo (median [IQR])				
No. of days hospitalized	11 (1–22)	15 (1–24)	11 (1–22)	0.83
No. of days in ICU	0 (0–0)	0 (0–0)	0 (0–0)	0.07

[a]Includes aplastic anemia (*n* = 4), myelofibrosis (2), central nervous system (CNS) lymphoma and B-cell lymphoma (1), mixed-phenotype (B-cell and myeloid/monocytic lineages) acute leukemia (1), chronic neutrophilic leukemia and myelofibrosis (1), bilineage acute leukemia (1), large granular lymphocytic leukemia (1), mucosa-associated lymphoid tissue (MALT) lymphoma (1), CNS lymphoma (1), multiple myeloma and myelodysplastic syndrome (1), hairy cell leukemia (1), Waldenstrom's macroglobulinemia versus lymphoproliferative disorder (1), acute promyelocytic leukemia (1), mantle cell lymphoma (1), monoclonal gammopathy and cardiac amyloid (1), follicular lymphoma (1), blastic plasmacytoid dendritic cell neoplasm (1), T-cell lymphoma (1), myeloproliferative neoplasm (1), high-grade B-cell lymphoma (1), primary plasma cell leukemia (1), prolymphocytic leukemia (1), cutaneous T-cell lymphoma (1), immunodeficiency (1), and sickle cell disease (1).

[b]Neutropenia with ANC of <1,500 cells/mm^3.

[c]Other multidrug-resistant Gram-negative organisms include presence of an extended-spectrum beta-lactamase, carbapenem resistant *Enterobacterales*, and multidrug-resistant *Enterobacterales*, *Pseudomonas*, *Acinetobacter*, or *Achromobacter* species defined as resistant to at least 1 drug in 3 drug categories (piperacillin-tazobactam, extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, or carbapenems (or ampicillin-sulbactam specifically for *Acinetobacter* spp.).

[d]Prior carbapenem use includes prior meropenem and/or ertapenem; no patients received imipenem-cilastatin.

[e]Any antibiotic received as prophylaxis for ongoing neutropenia, as determined by chart review.

[f]IQR, interquartile range; HSCT, hematopoietic stem cell transplant; ANC, absolute neutrophil count; ICU, intensive care unit.

the risk score was 0.38. There was not acceptable calibration (Hosmer-Lemeshow goodness-of-fit test with $P < 0.01$) of the raw multivariable model or following point conversion ($P < 0.001$). The risk score overestimated the probability of *S. maltophilia* BSI at low and middle deciles and underestimated the probability at high deciles (Hosmer-Lemeshow goodness-of-fit $P < 0.001$) (Fig. 1B).

The sensitivity and specificity at different cutoff points for each risk score are described in Table 4. Both risk scores displayed high sensitivity at relatively low cutoff values, and higher specificity at higher values. In the risk score 1 group, >80% of observations were

TABLE 2 Logistic regression analyses for *Stenotrophomonas maltophilia* bloodstream infection (BSI) compared to other GN-BSIs among patients with hematologic malignancy or a hematopoietic stem cell transplant

Variable	Odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Acute leukemia (AML or ALL)	1.51 (0.62–3.67)	0.36	0.78 (0.30–2.04)	0.61
ANC (no. of cells/mm^3)	0.87 (0.70–1.08)	0.22	0.94 (0.77–1.15)	0.53
Mucositis present	3.80 (1.28–11.27)	0.02	4.05 (1.25–13.15)	0.02
Central venous catheter	6.33 (0.84–47.98)	0.07	4.89 (0.62–38.78)	0.13
Carbapenem receipt[a] for ≥3 days	4.25 (1.66–10.88)	<0.01	4.06 (1.49–11.02)	<0.01

[a]Prior carbapenem use includes prior meropenem and/or ertapenem as treatment in the preceding 3 months; no patients received imipenem-cilastatin.

correctly classified at ≥41 points (maximum of 67 points), while for risk score 2, >75% of observations were correctly classified at ≥1 point (maximum of 2 points).

DISCUSSION

We found that among patients with hematologic malignancy or HSCT in a multicenter observational cohort, a knowledge-driven risk score incorporating five variables readily available to treating clinicians performed better than a risk score purely based upon automatic variable selection to predict patients with hematologic malignancy or HSCT who are at greatest risk for *S. maltophilia* infection. The knowledge-driven risk score included the following variables: acute leukemia, absolute neutrophil count category, mucositis as determined by an oncologist, central venous catheter present, and ≥3 days of carbapenem therapy within the previous 3 months. A risk score is useful while awaiting organism identification in blood culture bottles, which are dependent on bacterial growth. Moreover, rapid diagnostic assays capable of identifying *S. maltophilia* are still not widely available in many clinical microbiology laboratories (12).

S. maltophilia BSI is associated with poor outcomes, with attributable mortality as high as 38%, making early identification of patients at highest risk for *S. maltophilia* critical to ensure they are placed on effective antibiotic therapy as early as possible (1). *S. maltophilia* can be challenging to treat with antibiotics due to its resistance to several antibiotic classes. *S. maltophilia* has a number of diverse mechanisms of antimicrobial resistance, including chromosomally encoded beta-lactamases (L1, a metallo-beta-lactamase, and L2, a serine beta-lactamase), multidrug efflux pumps, chromosomally encoded Sm*qnr* resistance genes, and aminoglycoside-modifying enzymes (4, 8–10). Given the antibiotic resistance associated with *S. maltophilia*, even once identified in clinical cultures, determining effective treatment can be challenging, as resistance to antibiotics expected to be active

TABLE 3 Regression models and corresponding point scoring system to predict *S. maltophilia* bloodstream infection among patients with hematologic malignancy or a hematopoietic stem cell transplant

Variable	β coefficient	Odds ratio (95% CI)	No. of points assigned[a]
Risk score 1 ("knowledge-driven" model risk score)			
Intercept	−5.14		
Acute leukemia	−0.08	0.92 (0.35–2.44)	1
Absolute neutrophil count level[b]	0.22	1.24 (0.93–1.67)	3/increasing group (max 12 points)
Mucositis	1.80	6.07 (1.70–21.71)	23
Central venous catheter present	1.77	5.84 (0.74–46.33)	22
Carbapenem receipt[c] for ≥3 days	1.48	4.41 (1.61–12.06)	19
Risk score 2 ("automatic variable selection" risk score)			
Intercept	−3.27		
Mucositis	1.41	4.10 (1.33–12.63)	1
Carbapenem receipt[c] for ≥3 days	1.50	4.46 (1.71–11.67)	1

[a]Points were created based upon the smallest model coefficient (1.41 for weeks of carbapenem in backwards selection model, 0.08 for acute leukemia in full selection model). Points were then calculated based upon scaling of these. For example, in the full model, acute leukemia received 1 point, by dividing by 0.08. All other coefficients were then also divided by 0.08 and rounded to the nearest integer.
[b]ANC level defined by groups of 0 to 99, 100 to 499, 500 to 999, 1,000 to 1,499, and ≥1,500 cells/mm^3.
[c]Prior carbapenem use includes prior meropenem and/or ertapenem as treatment in the preceding 3 months; no patients received imipenem-cilastatin.

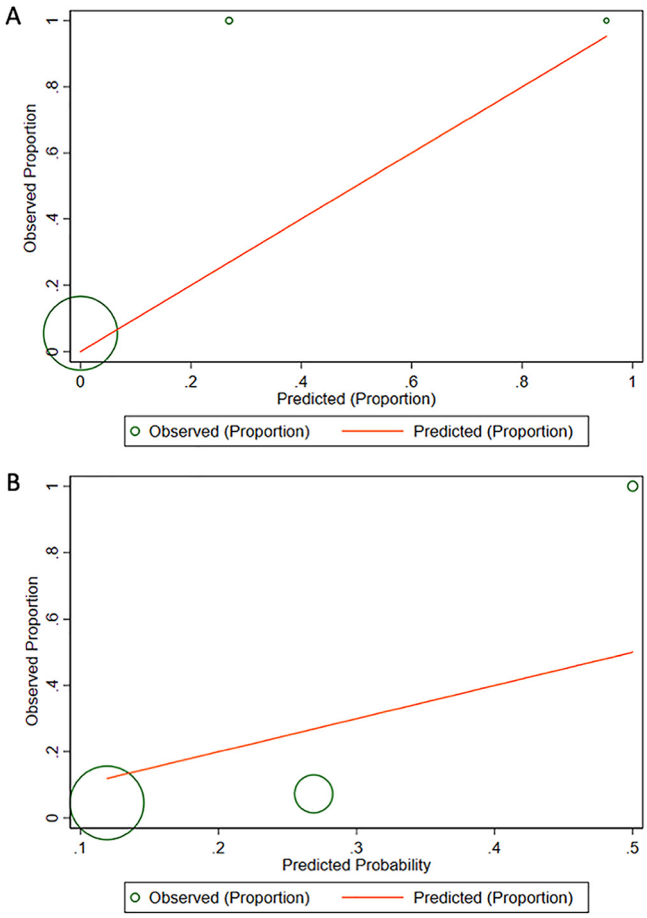

FIG 1 Calibration plots for the risk score models, after conversion to points. (A) Calibration plot of observed proportion versus *Stenotrophomonas maltophilia* BSI predicted by risk score 1 ("knowledge-driven" risk score model), by decile groups. (B) Calibration plot of observed proportion versus *S. maltophilia* BSI predicted by risk score 2 ("automatic variable selection" risk score model), by decile groups.

against wild-type *S. maltophilia* is also increasing (8). In addition, robust comparative effectiveness treatment studies for *S. maltophilia* are lacking (13–17).

Similar to what others have shown, recent carbapenem use was associated with increased *S. maltophilia* BSI in our cohort, potentially because carbapenem therapy can reduce intestinal colonization of a broad range of aerobic and anaerobic Gram-positive and Gram-negative bacteria, but not that of *S. maltophilia*, due to its intrinsic carbapenem resistance (7, 18). Mucositis has also been described as a risk factor for *S. maltophilia* BSI (19, 20), although not consistently. Mucositis represents toxicity of chemotherapy regimens/immunosuppression and a decreased epithelial barrier, which may explain its role in translocation of *S. maltophilia* resulting in invasive infections. Aitken and colleagues demonstrated that for each 1% increase in relative abundance of *S. maltophilia* in the oral microbiome, there is an associated 3% increase in the hazard of *S. maltophilia* infection in patients with acute myelogenous leukemia receiving chemotherapy (18). Variables such as neutropenia, the presence of a central venous catheter, and leukemia, in addition to mucositis and prior carbapenem use, have been previously associated with an increased risk of *S. maltophilia* infections (3, 6, 7, 18).

Existing studies that have explored risk factors for *S. maltophilia* infections have been informative but also have limitations that include their mostly single-center nature; heterogeneous study populations (i.e., not limited to hematologic malignancy or HSCT), which make extrapolation of findings to specific high-risk patient populations more challenging; and their inclusion of diverse *S. maltophilia* specimen types that capture multiple sources of infection as well as potential colonization. Moreover, no

TABLE 4 Sensitivity, specificity, and classification accuracy for each risk score at various cutoff points for predicting *S. maltophilia* bloodstream infection[a]

	Risk score[c]					
	1			2		
Risk score cutoff point[b]	Sensitivity (%)	Specificity (%)	Correctly classified (%)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
≥0	100.0	2.3	8.5	100.0	0.0	6.2
≥1				42.9	79.8	77.5
≥2				19.1	100.0	95.0
≥3	100.0	5.8	11.9			
≥5	100.0	10.1	15.8			
≥6	100.0	10.4	16.1			
≥8	100.0	11.4	17.0			
≥11	100.0	12.0	17.3			
≥12	100.0	12.0	17.6			
≥18	100.0	20.8	25.8			
≥21	100.0	21.1	26.1			
≥22	95.2	38.6	42.3			
≥23	85.7	55.8	57.8			
≥24	85.7	56.8	58.7			
≥25	81.0	58.2	59.6			
≥27	81.0	61.0	62.3			
≥28	76.2	62.0	62.6			
≥30	71.4	63.6	64.1			
≥31	66.8	64.9	65.1			
≥33	66.8	66.6	66.6			
≥34	61.9	72.4	71.7			
≥40	42.9	82.1	79.6			
≥41	38.1	87.3	84.2			
≥43	28.6	89.3	85.4			
≥44	19.1	89.9	85.4			
≥45	19.1	94.8	90.0			
≥46	14.3	96.4	91.2			
≥49	14.3	97.1	91.8			
≥50	14.3	97.7	92.4			
≥52	14.3	98.1	92.7			
≥53	14.3	98.7	93.3			
≥63	14.3	100.0	94.5			
≥67	4.8	100.0	93.9			

[a]From a cohort of patients with hematologic malignancy or hematopoietic stem cell transplant and Gram-negative bloodstream infections.
[b]Cutoff points of <0 are not shown, as sensitivity remained 100% and specificity was 0% (for the risk score based on the "full" model of variables). For simplicity, whole numbers of integers are shown.
[c]Risk score 1, knowledge-driven; risk score 2, automatic variable selection.

previous studies investigating *S. maltophilia* risk factors have attempted to construct risk scores to simplify end user application and to predict which patients have *S. maltophilia* infections. To explain further, although traditional risk factor analyses are useful for understanding etiologic causes of disease (and thus potential prevention targets), such causal risk factors may not necessarily be effective at distinguishing between those who do or do not have the outcome of interest, depending upon their distribution in a cohort. In contrast, sufficiently discriminative risk scores can help answer prediction questions, e.g., "Who may benefit the most from empirical TMP-SMX therapy to target *S. maltophilia* in addition to usual empirical antimicrobial regimens?"

We built two risk scores to identify patients with *S. maltophilia* BSI, a knowledge-driven approach that included variables selected based upon the prior literature or significance in univariable analysis (risk score 1), and an automatic variable selection approach that included only those variables that were retained following stepwise variable selection procedures (risk score 2). Risk score 1 performed well (area under the curve [AUC] = 0.75 and 0.71 following cross-validation). In comparison, risk score 2 had

inferior discrimination compared to that of risk score 1 (AUC = 0.63 and 0.38 following cross-validation). The knowledge-driven risk score model was only marginally more complex, at five variables, and had superior performance despite including some variables that did not achieve statistical significance.

While automatic variable selection is commonly employed in the literature in the risk score-building process, our results illustrate some of its potential pitfalls. As stated previously, independent causal risk factors do not necessarily make ideal predictors (21, 22). For example, the identification of an independent risk factor assists in understanding what is contributing to *S. maltophilia* BSI, and thus illuminates a target where one may be able to intervene (i.e., by limiting use of carbapenem therapy). However, a risk score (in our example) focuses on predicting which patients have *S. maltophilia* BSI while awaiting confirmatory testing; the goal is not necessarily to identify intervention targets, but rather to understand what variables best discriminate between those who do and do not have *S. maltophilia* BSI.

Importantly, risk scores also exhibit end user flexibility, where the cutoff point can be varied to tailor the desired sensitivity and specificity. For example, increasing the sensitivity of the cutoff value (i.e., lower point values) increases the proportion of patients receiving TMP-SMX and increases the likelihood of providing adequate empirical coverage for a patient with *S. maltophilia* BSI; however, this decision would come with more "false-positive patients" receiving empirical TMP-SMX. Alternatively, prioritizing specificity by raising the cutoff point value would reduce the number of patients unnecessarily exposed to TMP-SMX but could lead to "missed" cases of *S. maltophilia* BSI. Even with a relatively low prevalence of *S. maltophilia* BSI of 6% in our cohort, our opinion would be that prioritizing sensitivity may be preferred, given the high morbidity and mortality associated with delayed treatment for *S. maltophilia* BSIs in this vulnerable population. For example, by choosing a threshold cutoff of $\geq$27 points in our knowledge-driven risk score, a clinician would identify 17 *S. maltophilia* BSI patients for early appropriate treatment, who would otherwise have received empirical therapy ineffective against *S. maltophilia*, and miss 4 cases, while 123 or 39% of patients would be false positives who would unnecessarily receive empirical TMP-SMX therapy. On the other hand, by selecting a threshold of $\geq$40 points, a clinician would identify 9 *S. maltophilia* BSI patients for early appropriate therapy and miss 12 cases, with 57 (or 18%) false-positive patients receiving unnecessary TMP-SMX empirical therapy.

Our study has several limitations. First, while this is a multicenter study, it was from a single region. There may be regional differences in chemotherapy regimens and their associated degree of immunosuppression that might change observed associations in cohorts from other regions and cancer centers. Additionally, prior studies have suggested that microbiome domination may precede infection in hematologic malignancy patients. In the hospitals included in our cohort, hematologic malignancy and HSCT patients undergo weekly rectal surveillance cultures for Gram-negative organisms with resistance to third-generation cephalosporins. However, *S. maltophilia* growth on surveillance cultures is not routinely reported in the electronic medical record. Therefore, we were unable to rigorously investigate if antecedent colonization status would be an important predictor for *S. maltophilia* BSI in our study population. Given the importance of mucositis in our models, this would be an important target for future research. Additionally, our study had a small number of *S. maltophilia* BSI events, making the development of a risk score challenging. The small sample size likely contributed to poor calibration after conversion to point scales. Nevertheless, the discrimination of our knowledge-driven risk score remained acceptable even after cross-validation, suggesting that despite small sample sizes, this model was not overfitted to the data. External validation of our risk score in a larger, geographically diverse data set, and possibly with more events, would be essential prior to broad clinical implementation.

In conclusion, given the high mortality associated with *S. maltophilia* BSI and the lack of therapeutic efficacy with antibiotics traditionally prescribed for patients with hematologic malignancies/HSCT, a risk score that can be utilized easily by clinicians to predict which patients may benefit from early, effective therapy for *S. maltophilia* (e.g., TMP-SMX),

despite the known toxicities, is of value. We developed and internally validated a risk score that performed moderately well to identify such patients. External validation in a larger cohort is necessary to create a refined risk score that can be broadly applied.

MATERIALS AND METHODS

Setting and participants. This was an observational cohort study of unique patients 12 years of age and older admitted between 1 July 2016 and 1 December 2019 to one of five hospitals within the Johns Hopkins Health System, which serves the greater Maryland region. Patients met eligibility criteria if they had at least one blood culture with an *Enterobacterales* or a nonfermenting Gram-negative bacillus and were actively receiving chemotherapy for a hematologic malignancy and/or received a hematopoietic stem cell transplant (HSCT) within the preceding 12 months. Only the first episode of GN-BSI (including polymicrobial episodes) during the study period for each eligible patient was included. This study was approved by the institutional review board of the Johns Hopkins University School of Medicine, with a waiver of informed consent. Informed consent was not obtained from patients because this work was retrospective and did not modify care received.

Data extraction. Demographics, type of malignancy and degree of immunosuppression, severity of illness, prior antibiotic use within the previous 3 months, health care exposure within the previous 3 months, and previous microbiologic results within the previous 6 months (including both *S. maltophilia* and other multidrug-resistant Gram-negative organisms [MDRGN]), were collected by manual review of electronic medical records and entered into a secure REDCap database. Degree of immunosuppression was determined by the absolute neutrophil count (ANC), neutropenia ($<$1,500 neutrophils/mm^3) for 7 or more preceding days, or the presence of mucositis (based on significant oral pain or ulcers as documented by the oncology team), all on day 1 (defined as the day of blood culture collection). Severity of illness was evaluated by admission to an intensive care unit (ICU) and by the Pitt bacteremia score, both on day 1 (23). Prior antibiotic use consisted of inpatient and outpatient days of antibiotic therapy with Gram-negative activity, including antibiotic prophylaxis, within the 3 months prior to day 1. Other MDRGNs that were included were as follows: extended-spectrum beta-lactamase-producers (confirmed by phenotypic or molecular testing); carbapenem-resistant *Enterobacterales*; or *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Achromobacter* species, or *Enterobacterales* that were resistant to at least 1 drug in 3 or more of the following antibiotic categories (piperacillin-tazobactam, extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, or carbapenems, or specifically for *Acinetobacter baumannii*, ampicillin-sulbactam) (5).

Knowledge-driven risk score. Two risk scores were developed. The first was a knowledge-driven risk score (risk score 1). The knowledge-driven risk score includes both (i) risk factors for *S. maltophilia* infections in hematologic malignancy patients described in the limited published literature (18, 19, 24–27); and (ii) any additional variables that were statistically significant in our cohort based on univariable logistic regression analysis at a significance level of 0.05. The reference group was patients with GN-BSIs other than *S. maltophilia*, including both *Enterobacterales* and glucose-nonfermenting Gram-negative bacilli. In order to develop a risk score that is user friendly for manual bedside calculation, continuous variables were converted to ordinal categories. As an example, ANC values were recategorized into the following ordinal levels: 0 to 99, 100 to 499, 500 to 999, 1,000 to 1,499, and $\geq$1,500 cells/mm^3. Fisher's exact test compared categorical variables, and the Wilcoxon rank sum test was used for continuous variables. Univariable regression analysis evaluated the association between each variable and the outcome of *S. maltophilia* BSI. Variables that were statistically significant in univariable regression at a significance level of 0.05 were included in a multivariable model. Additionally, risk factors described in the published literature (18, 19, 24–27) were "forced" into the model. The regression coefficients derived from the multivariable model were rescaled by dividing by the smallest final model coefficient and rounding to the nearest integer to create risk score "points." Patient scores were calculated by summing their respective points.

Automatic variable selection risk score. Additionally, we constructed an automatic variable selection risk score (risk score 2). Automatic variable selection is a common, although debated approach, in the literature for building risk scores (21, 28, 29). The same procedures were used as for risk score 1, but the multivariable logistic regression model was fitted using stepwise backward variable selection at an alpha value of 0.05 across all variables (28, 29). *A priori* identified risk factors in the literature were not included in risk score 2. Using the same procedures as for risk score 1, risk score "points" and patient scores were calculated.

Risk score discrimination, calibration, and validation. Discrimination evaluates the ability of a model to distinguish between those who do and do not have the outcome of interest. In the present application, it represents the probability that the risk score will predict that a patient (later confirmed to have a *S. maltophilia* BSI) has a higher probability of being infected with *S. maltophilia* compared to that of a randomly selected hematologic malignancy patient with a GN-BSI caused by an organism other than *S. maltophilia*. For both risk scores, discrimination was assessed via receiver operator characteristic (ROC) curves and accompanying *C* statistics (area under the curve [AUC]). Calibration evaluates agreement between observed and predicted outcomes and was assessed using the Hosmer-Lemeshow goodness-of-fit test and graphical calibration plots. Both risk scores were internally validated using leave-one-out cross-validation. All statistical tests were two-sided, and a *P* value of $<$0.05 was considered statistically significant. Statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX).

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