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A Clinical Model to Predict the Occurrence of Select High-risk Infections in the First Year Following Heart Transplantation

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Background. Invasive infection remains a dangerous complication of heart transplantation (HT). No objectively defined set of clinical risk factors has been established to reliably predict infection in HT. The aim of this study was to develop a clinical prediction model for use at 1 mo post-HT to predict serious infection by 1 y. **Methods.** A retrospective cohort study of HT recipients (2000–2018) was performed. The composite endpoint included cytomegalovirus (CMV), herpes simplex or varicella zoster virus infection, blood stream infection, invasive fungal, or nocardial infection occurring 1 mo to 1 y post-HT. A least absolute shrinkage and selection operator regression model was constructed using 10 candidate variables. A concordance statistic, calibration curve, and mean calibration error were calculated. A scoring system was derived for ease of clinical application. **Results.** Three hundred seventy-five patients were analyzed; 93 patients experienced an outcome event. All variables remained in the final model: aged 55 y or above, history of diabetes, need for renal replacement therapy in first month, CMV risk derived from donor and recipient serology, use of induction and/or early lymphodepleting therapy in the first month, use of trimethoprim-sulfamethoxazole prophylaxis at 1 mo, lymphocyte count under 0.75×10^3cells/μL at 1 mo, and inpatient status at 1 mo. Good discrimination (C-index 0.80) and calibration (mean absolute calibration error 3.6%) were demonstrated. **Conclusion.** This model synthesizes multiple highly relevant clinical parameters, available at 1 mo post-HT, into a unified, objective, and clinically useful prediction tool for occurrence of serious infection by 1 y post-HT.

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INTRODUCTION

Invasive infection is a dangerous complication of heart transplantation (HT). Some risk factors for infection are well-documented and widely accepted; others presumed based on clinical experience and biological plausibility. Included among these potential risk factors are comorbidities, immunosuppressive medications, individual infection and/or exposure history, episodes of rejection, and surgical complications. Transplant providers may instinctively synthesize some of these clinical factors to determine a general sense of infection likelihood. However, no objectively defined set of clinical factors has been demonstrated to reliably predict infection in this population.

Novel serum assays seek to quantify degree of immune suppression or predict the probability of specific infection, such

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as cytomegalovirus (CMV).[1-4] Although useful in certain clinical settings, such tests are still finding their role in everyday practice, as they require specialized laboratories, often have caveats in interpretation or generalizability, and are expensive. Moreover, the information they provide may lack important modifying clinical factors. A broadly applicable prediction tool integrating various clinical factors and simpler laboratory measures would be a valuable addition to the arsenal of heart transplant providers. Such a tool would give objective information that could sway decision-making regarding immunosuppression, screening, and surveillance strategy to better meet the needs of an individual patient.

Therefore, the aim of this retrospective cohort study was to develop an easily accessible and clinically useful model to be used at 1 mo post-HT for the prediction of high-risk opportunistic infection (CMV infection, herpesvirus I/II [HSV] or varicella zoster virus [VZV] infection, blood stream infection [BSI], invasive fungal infection [IFI], or nocardiosis) within the first year after heart transplant.

MATERIALS AND METHODS

Data and Participants

The study cohort included all patients who underwent heart transplant at a single center between January 2000 and October 2018, and subsequently had outpatient follow-up care at that same center for at least 1 y. The following exclusion criteria were applied: dual-organ transplant recipients, participants who died within 1 mo of heart transplant, and participants for whom a discharge summary was not available. This study was approved by the Tufts Medical Center Health Sciences Institutional Review Board.

Outcome

A composite outcome was used, which included CMV infection, HSV/VZV, BSI, IFI, and *Nocardia* infection. These infection types were chosen because they carry significant morbidity and mortality and could be objectively proven with microbiological data. In addition, prior studies have found independent associations between CMV and other opportunistic infections including BSI, IFI, and nocardiosis.[5-9] The immunomodulatory effects of CMV are thought to alter host response to these types of opportunistic infections, providing additional relevance of CMV beyond direct morbidity and mortality.[10] The follow-up period extended from 1 mo to 1 y posttransplantation. Infections occurring before 1 mo were not considered. The model was designed this way to capture critically important events that occur in the early posttransplant period that have potential for lasting impact on risk in the months that follow (eg, severe deconditioning or placement of long-term intravascular catheters related to prolonged hospitalization or need for renal replacement therapy, inability to tolerate routine posttransplant medications, such as trimethoprim-sulfamethoxazole [TMP-SMX]). By 1 mo postsurgery, many of these events have transpired, but it remains early enough in the posttransplant course to make meaningful adjustments based on risk assessment. The following definitions were used for the various components of the outcome. They are consistent with prior literature and require microbiological and/or histopathological evidence of pathogen.

CMV infection: Evidence of CMV replication regardless of symptoms; defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen.[11,12]

CMV disease: Evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as a viral syndrome (ie, fever, malaise, leukopenia, and/or thrombocytopenia) or tissue invasive ("end organ") disease.[11]

HSV or VZV: Clinical signs and symptoms along with one of the following: (1) newly positive immunoglobulin M titer requiring antiviral treatment; (2) HSV or VZV isolated from viral culture; (3) presence of HSV DNA or VZV DNA in peripheral blood or cerebral spinal fluid; and (4) HSV or VZV viral antigen detection from a cutaneous lesion. Infections diagnosed purely on clinical appearance of cutaneous lesions were not counted.

BSI: Positive blood culture. Bacteremia caused by common skin contaminants was considered significant if the same organism was isolated from 2 blood cultures in the presence of clinical signs of infection and/or an intravascular device.[13]

IFI: Proven or probable infection by criteria of 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 Consensus Group.[14]

Nocardia infection: Isolation of *Nocardia* species from a suspected site.[15]

Occurrence of the outcome was based on objective microbiological criteria outlined earlier. Further characterization of the infection relied upon description by the treating transplant infectious disease physician.

Although death was a competing risk, the total number of deaths in this cohort was small relative to that of the composite outcome. Eight patients died after 1 mo and before reaching either the composite endpoint or 365 d. Median time to death among these patients was 172 d (mean 173 d). Therefore, it was felt that these patients contributed reasonable follow-up and they should remain in the analysis.

Candidate Variables

A total of 8 candidate variables were selected for potential inclusion in the model based on clinical judgment and existing literature predicting infectious outcomes. Variables with high likelihood for redundancy with other candidates were not included. The selected variables were the following (binary unless otherwise stated): age at time of transplant (dichotomized at age 55 y, which is the median of the cohort), history of diabetes mellitus, lymphopenia (absolute lymphocyte count below 0.75×10^3cells/μL) at 1 mo posttransplant, CMV serological risk group (categorical: high [donor seropositive, recipient seronegative; D+/R–], intermediate [recipient seropositive; R+], low [donor and recipient seronegative (D–/R–)]), use of induction therapy and/or lymphodepleting therapy as treatment for rejection in first month (agents used were basiliximab, antithymocyte globulin [ATG], or muromonab-CD3 [OKT3]), use of TMP-SMX at 1 mo posttransplant, need for renal replacement therapy in the first month, and inpatient status at the end of first month (continuation of index admission or readmission were both counted).[16-24]

Immunosuppression and Rejection

Patients did not typically receive induction immunosuppression except in cases of severe renal dysfunction. In such

cases, agents used for induction were ATG, OKT3, or basiliximab. Rarely, rituximab was given to highly sensitized patients.

Standard maintenance immunosuppression included an antimetabolite, a calcineurin inhibitor, and a prednisone. Over the period of study, there were 2 notable changes in practice. Around 2002, there was a shift from the use of azathioprine to mycophenolate; in 2008, a shift from cyclosporine to tacrolimus. For description of the cohort, the maintenance regimen was assessed at a single time-point: at time of index discharge or at 1 mo posttransplant, whichever came first.

Episodes of rejection were proven with endomyocardial biopsy and counted only if severe enough to be treated with corticosteroids, typically methylprednisolone 1 g daily for 3 d. ATG was used in cases of severe or steroid-refractory cell-mediated rejection. Those with antibody-mediated rejection were treated with rituximab, plasmapheresis, intravenous immunoglobulin, bortezomib, or, occasionally, photopheresis.

Antimicrobial Prophylaxis

Patients were stratified into CMV risk groups according to consensus guidelines (as described above under "Candidate Variables"); high- and intermediate-risk groups received 3 mo of antiviral prophylaxis with either valganciclovir or ganciclovir.[11] They received the equivalent of valganciclovir 900 mg daily, adjusted for renal function, for 3 mo post-transplantation.[25,26] The low-risk group instead received famciclovir 500 mg BID, adjusted for renal function. In 2008, antiviral prophylaxis in high-risk recipients was extended to a 6-mo duration. Until 2015, patients receiving a heart from a seropositive donor, also received prophylactic CMV immunoglobulin.

TMP-SMX, typically for 1 y, was given to all patients for prophylaxis against *Pneumocystis jirovecii* (and toxoplasmosis, if donor or recipient were seropositive). In cases of allergy or poor tolerance, dapsone or atovaquone was used instead.

Statistical Analysis

A least absolute shrinkage and selection operator (LASSO) regression model was fit using the 8 stated candidate variables to predict the composite outcome occurring between 1 mo and 1 y posttransplant. The LASSO method is a statistical method that provides both candidate selection and penalization per the number of candidates proposed—with the goal of a sparse model with good predictive ability that is not "overfit" to the cohort from which the model was derived.[27] The penalization step protects against excessive "optimism," a bias in which the performance of the model appears favorable in the derivation cohort but proves to be limited when applied to external cohorts. Lambda, the parameter that determines the amount of penalization (adjustment toward 0) of each variable, was set to the value that minimized the cross-validation prediction error rate.[27,28]

A concordance statistic (c-statistic) was calculated to assess discrimination. Internal validation was performed with 200 bootstrapped samples to quantify the optimism inherent in the raw c-statistic and produce an "optimism-corrected" c-statistic.[27] Calibration was assessed by visual inspection of a curve showing predicted versus observed outcomes. The mean absolute calibration error was quantified over bootstrapped samples. Additional measures of prediction error were calculated and are described further in the Appendix S1, SDC, http://links.lww.com/TXD/A590.

Based on the regression coefficients of the final model, a point system was derived to make the model clinically applicable at bedside. Each variable was assigned a number of points proportionate to the contribution made by its corresponding regression coefficient. To confirm the fidelity to the original model, each patient in the cohort was scored. Scores were plotted against predicted probability to evaluate alignment, and discrimination of the score was assessed with a c-index. Appropriate breakpoints were selected, which would enable a clinician to stratify a patient into low, standard, and high-risk groups based on their calculated risk score.

Because outcome events were skewed toward CMV infection within the composite outcome, additional analysis was performed to assess the performance of the model in predicting the other components of the composite outcome. This included calculation of a c-statistic for non-CMV events only and assessment of non-CMV infection incidence in all risk strata. Both attributable mortality and mortality risk ratio were calculated for the composite outcome and, separately, for non-CMV infection. R Studio version 3.6.1 was used for all statistical analysis.

RESULTS

A total of 375 participants met eligibility criteria and were included in the analysis (Figure 1). During the 11-mo follow-up period, 93 participants experienced at least 1 infection event; 18 of those participants experienced >1 infection. In total, there were 65 CMV infections, 3 HSV infections, 2 VZV infections, 28 BSI, 11 IFI, and 4 *Nocardia* infections. Table 1 compares patient characteristics of those who did and did not develop infection in the follow-up period.

Table 2 summarizes the types and frequencies of events observed. Sixty-five episodes of CMV occurred, on average, 218 d posttransplant (median 214 d). Although there were additional episodes of clinically diagnosed cutaneous HSV/VZV, a total of 5 microbiologically proven episodes occurred at an average of 185 d posttransplant (median 161 d). Twenty-two first episodes of BSI occurred an average of 119 d posttransplant (median 94 d); this does not include subsequent episodes of BSI in 6 patients who experienced >1 BSI. Eleven IFIs occurred an average of 83 d posttransplant (median 132 d). *Nocardia* infection occurred in 4 patients at a median of 172.5 d posttransplant.

There were no missing data for the 8 candidate variables. A penalized regression model was fit using the LASSO technique. All variables remained in the final model, indicating that each contributed significantly to the predictive ability of the final model even after penalization (Table 3).

The model's discrimination was assessed by calculation of the c-index, which was 0.80. After correction for optimism, the c-index was 0.78. A calibration curve is displayed in Figure 2 showing generally good agreement with predicted and observed outcomes over the full range of predicted probabilities. The average absolute calibration error over bootstrapped samples was 3.6% (Appendix S1, SDC, http://links.lww.com/TXD/A590).[30]

Table 3 also displays points assigned to each variable based upon the magnitude of the regression coefficient in the final model. Further details about the derivation of the

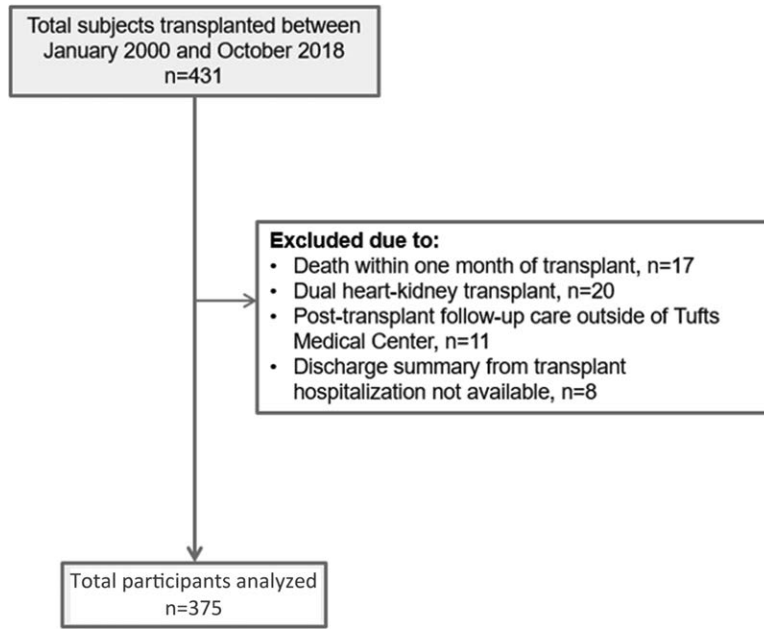

FIGURE 1. Cohort selection and application of eligibility criteria.

scoring system are provided in the Appendix S1, SDC, http://links.lww.com/TXD/A590. The range of possible scores for a given patient is –2 to 29, with 29 corresponding to the highest risk. The median and mean score within our cohort was 9 (interquartile range 4–13). Those who score 8 or less, have <20% predicted probability of infection. Those scoring 9–15 have about a 20%–50% predicted probability of infection. A score of ≥16 suggests a probability of infection in the range of 50% or higher. These breakpoints, based on clinical interpretation of calculated risk produced from the model, allow for stratification into low-, standard-, and high-risk categories. For example, a 50-y-old patient who received a CMV mismatched heart (D+/R–), with low lymphocyte count and continued hospitalization at 1 mo posttransplant, receiving routine TMP-SMX prophylaxis, with no other risk factors specified in Table 3, would score 18; this correlates with a high risk of infection (>50% probability) in the first year. The frequency of scores in our cohort is displayed in Figure 3A. The alignment of numeric score with associated probability of infection is displayed in Figure 3B. We confirmed that discrimination based on the scoring system was unchanged from discrimination using the regression model (Appendix S1, SDC, http://links.lww.com/TXD/A590).

The separately calculated discrimination for non-CMV events was very similar to that of the composite outcome with a c-statistic of 0.77 (SE 0.04). The mean risk score among this subgroup was 14.4 (median 14). In the low-risk group (score <8), the cumulative incidence of non-CMV infection in the first posttransplant year was 3/172 (2%); in the intermediate-risk group (score 9–15), it was 20/152 (13%); in the high-risk group (score>15), it was 13/51 (25%). The attributable mortality related to the composite outcome was 3.6% (95% confidence interval [CI], –1.7 to 9.0) and mortality risk ratio 2.3 (95% CI, 0.81-6.4). The attributable mortality related to non-CMV infection was 13.8% (95% CI, 1.5-26.1) and mortality risk ratio 5.9 (95% CI, 2.2-16.0).

DISCUSSION

The final prediction model consists of 8 variables, which, in combination, provided the strongest ability to stratify patients according to their risk for infection by 1 y (Table 3). Selection of appropriate candidate variables was a key step in the development of this prediction tool. As mentioned, candidates were chosen a priori based on prior literature and clinical judgment, with attention to avoidance of redundancy between candidates. We focused on a few broad categories that meaningfully influence clinical assessment of infection risk: patient characteristics, such as age and pertinent comorbid conditions, use of specific highly immunosuppressive medications (ATG, OKT3, basiliximab), indirect indicators of immune function (low absolute lymphocyte count, occurrence of early high-grade rejection, CMV risk group status based on serology), and markers of posttransplant complication (need for posttransplant renal replacement therapy, hospitalization at 1 mo posttransplant). Inpatient admission status at 1 mo was felt to be a global marker of illness severity and postoperative complication that concisely carried valuable information about a diverse set of longer-term risk factors for infection even after eventual discharge (deconditioning, long-term indwelling catheters, colonization with resistant nosocomial pathogens).

Other candidate variables were considered. For example, several other characterizations of renal function were available (history of chronic kidney disease, pretransplant glomerular filtration rate [GFR], GFR at 1 mo, GFR <60 at 1 mo); however, the occurrence of posttransplant renal impairment severe enough to require renal replacement therapy was thought to be the most impactful measure. It likely also carries with it some correlation with other posttransplant complications. In addition, antiviral prophylaxis was also considered for candidacy (use of valganciclovir, ganciclovir, CMV immune globulin) but was felt to be adequately represented by CMV serostatus risk group given the protocolized nature of our prophylaxis strategy. Other white blood

TABLE 1.

Demographic and clinical characteristics of those who did and did not experience infection between 1 mo and 1 y posttransplant

	No outcome (n = 282)	Outcome (n = 93)
Age at time of transplant, mean (SD)	52 (12)	56 (10)
Race, n (%)		
White	236 (84)	81 (87)
Black	18 (6.4)	3 (3.2)
Hispanic	25 (8.9)	6 (6.5)
Asian	3 (1.1)	3 (3.2)
Male sex, n (%)	205 (72.7)	66 (71.0)
Body mass index at time of transplant, mean (SD)	27.3 (5.1)	28.8 (5.5)
Comorbidities, n (%)		
History of ischemic cardiomyopathy	105 (37.2)	41 (44.1)
History of diabetes mellitus	88 (31.2)	39 (41.9)
History of chronic kidney disease	76 (27.0)	31 (33.3)
History of autoimmune disease	12 (4.3)	7 (7.5)
CMV risk status based on donor and recipient serology, n (%)		
Low risk (D–/R–)	84 (29.8)	7 (7.5)
Intermediate risk (R+)	134 (47.5)	39 (41.9)
High risk (D+/R–)	64 (22.7)	47 (50.5)
Use of basiliximab in first month posttransplant, n (%)	11 (3.9)	15 (16.1)
Use of ATG in first month posttransplant, n (%)	8 (2.8)	4 (4.3)
Use of OKT3 in first month posttransplant, n (%)	5 (1.8)	2 (2.2)
Use of rituximab in first month posttransplant, n (%)	4 (1.4)	0 (0)
Maintenance immunosuppression[a]		
Mycophenolate+tacrolimus+prednisone, n (%)[b]	188 (66.7)	70 (75.3)
Antimicrobial prophylaxis, n (%)[a]		
Bactrim	253 (89.7)	75 (80.6)
Valganciclovir or ganciclovir	195 (69.1)	84 (90.3)
CMV immunoglobulin	93 (33)	37 (39.8)
Treatment for rejection event within 1 mo of transplant, n (%)	37 (13.1)	5 (5.4)
Inpatient status at 1 mo posttransplant, n (%)	40 (14.2)	37 (39.8)
Labs at 1 mo posttransplant, mean (SD)		
White blood cell count	7.5 (2.9)	8.4 (3.9)
Absolute neutrophil count	5.9 (2.6)	6.9 (3.3)
Absolute lymphocyte count	0.97 (0.7)	0.75 (0.7)
GFR[c]	68.8 (27.4)	58.8 (33.3)
Lymphopenia[d] at 1 mo posttransplant, n (%)	135 (47.9)	66 (71.0)
Need for renal replacement therapy in first month posttransplant, n (%)	17 (6)	21 (22.6)

[a]Assessed at time of hospital discharge following transplant or at 1 mo, whichever came first.
[b]Other regimens included combinations with cyclosporine, sirolimus, everolimus, azathioprine.
[c]Estimated GFR based on CKD-EPI (*Chronic Kidney Disease* Epidemiology Collaboration) equation using serum creatinine.[29]
[d]Lymphopenia defined as absolute lymphocyte count $\leq 0.75 \times 10^3$ cells/μL.
ATG, antithymocyte globulin; CKD, chronic kidney disease; CMV, cytomegalovirus; GFR, glomerular filtration rate; OKT3, muromonab.

TABLE 2.

Identification and frequencies of pathogens comprising the composite outcome

	Total
No event	**282**
CMV type	**65**
Asymptomatic infection	7
Viral syndrome	16
Tissue invasive GI	42
Non-GI site	0
HSV	**3**
VZV	**2**
BSI	**28**
Gram negative	**14**
Enterobacter spp.	1
Escheria coli	1
Klebsiella spp.	6
Pseudomonas aeruginosa	4
Salmonella, nontyphi	1
Serratia marescens	1
Gram positive	**14**
Coagulase-negative *Staphylococcus*	1
Enterococcus spp.	7
Listeria monocytogenes	2
Streptococcus group B/C/G	1
Viridans group streptococci	1
Staphylococcus capitus	1
Weissella confuse	1
IFI	**11**
Candida spp.	1
Cryptococcus neoformans	2
Fusarium solani	1
Aspergillus fumigatus	3
Zygomycetes	2
Trichophyton rubrum	1
Other[a]	1
Nocardia or invasive mycobacterial infection	**4**
Nocardia spp.	4

This table tabulates all infections occurring in the follow-up period. There were 18 patients who had >1 infection. For the purposes of building the prediction model, a patient who had >1 infection was counted only once.
[a]Probable IFI (*Pneumocystis jirovecii*) based on persistently elevated beta-D-glucan, radiographic pulmonary lesions, and response to antifungal therapy in an appropriate host.
BSI, blood stream infection; CMV, cytomegalovirus; HSV, herpes simplex virus I or II; IFI, invasive fungal infection.

cell measures were available but likely less important than low lymphocyte count, which has repeatedly demonstrated association with CMV and other infection outcomes.[5,21,31-33] Use of rituximab would also have been of significant interest as a candidate, but the number of participants who received rituximab in our cohort (in their first posttransplant month) was exceedingly low.

Measures of model performance including c-statistic, calibration curve, and Harrell's E and E_{90} (Appendix S1, SDC, http://links.lww.com/TXD/A590) are all favorable, suggesting acceptable discrimination and calibration. The methodology used in this analysis (LASSO) to select the variable combination with greatest predictive ability is a novel technique specifically designed to create sparse, generalizable models, with inherent protection against over-fitting to the derivation cohort.

In our cohort, the number of CMV events was notably larger than the number of non-CMV events (such as BSI or IFI), which raised concern that the model would perform less well in predicting non-CMV events as compared with predicting the composite outcome. To evaluate this concern, we calculated a c-statistic for the model's ability to predict non-CMV events only, which remained strong at 0.77 (SE 0.04). We also examined what the occurrence of non-CMV infection was in the 3 different risk strata and appropriately found escalating cumulative incidence

TABLE 3.
Model variables

Variable	Regression coefficient	Odds ratio[a]	Points
Aged 55 y or above at transplant	0.35	1.41	2
History of diabetes mellitus	0.13	1.14	1
CMV risk status[b]			
D–/R–	–	–	–
R+	1.29	3.63	6
D+/R–	2.26	9.58	11
Use of induction and/or early lymphodepleting therapy[c]	0.91	2.48	5
Use of TMP-SMX prophylaxis at 1 mo posttransplant	–0.46	0.63	–2
Renal replacement therapy in the first posttransplant month	0.69	1.99	3
Inpatient status at 1 mo posttransplant	0.74	2.10	4
Lymphopenia at 1 mo posttransplant[d]	0.58	1.79	3

All candidate variables remained in the final prediction model. The table displays each variable with corresponding regression coefficient, odds ratio for developing infection, and number of points assigned when risk factor present.
[a]The LASSO statistical method does not produce odds ratios or CIs for individual variables. To provide a more intuitive quantification of the relationship between variable and outcome regression coefficients were exponentiated to give the odds ratios shown here; however, the focus should remain on the relationship of the overall prediction tool to outcome.
[b]D–/R– group treated as reference group.
[c]Agents included basiliximab, ATG or OKT3.
[d]Lymphopenia defined as absolute lymphocyte count $\leq 0.75 \times 10^3$ cells/μL.
ATG, antithymocyte globulin; CI, confidence interval; CMV, cytomegalovirus; LASSO, least absolute shrinkage and selection operator; OKT3, muromonab; TMP-SMX, trimethoprim-sulfamethoxazole.

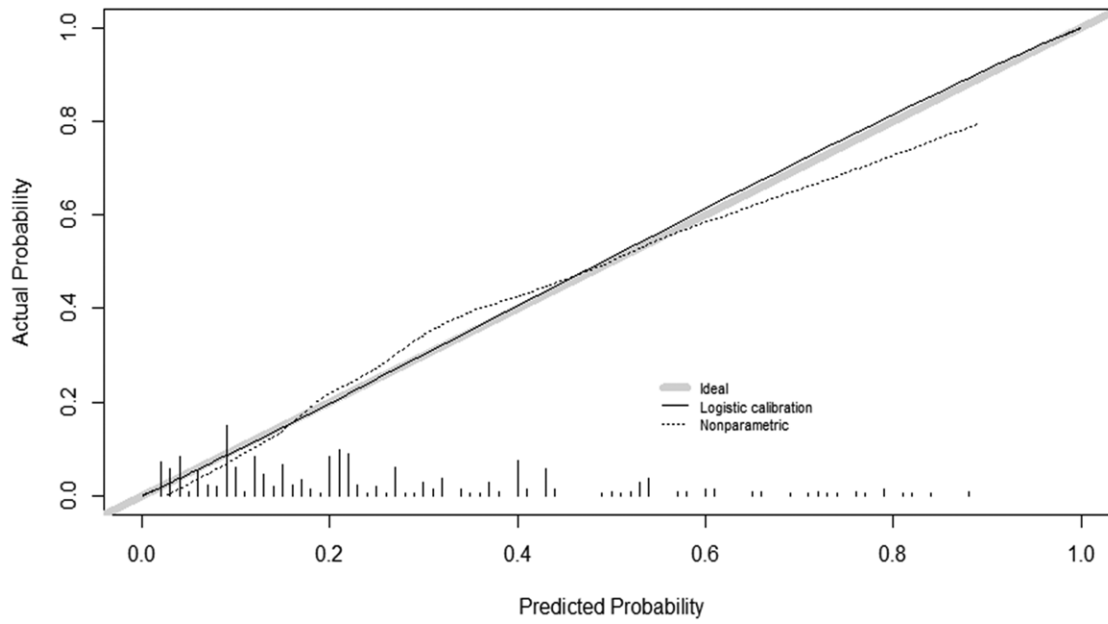

FIGURE 2. Calibration plot. Actual vs predicted probability of infection by 1 y. Gray line = ideal (line of identity). Dotted line = smoothed nonparametric calibration curve. Relative frequency distribution of calibrated probabilities displayed at bottom.

within each successive stratum, ultimately with non-CMV infection occurring in 2% of patients in the lowest risk group and in a quarter of patients in the highest-risk group.

In addition to the novelty of the method used to derive the model, clinical prediction models, in general, are relatively novel in transplant infectious disease. Such models exist for other important complications of heart transplant, such as chronic allograft vasculopathy.[34] Notably, we are aware of one other model in the HT population designed to predict infection in the first 3 mos based on laboratory immune markers. Sarmiento et al[35] designed an immunological risk score taking into account the presence of low immunoglobulin G, complement C3, natural killer cell count, and CD4 lymphocyte count. Although these parameters remain of interest, they are not routinely checked in our center and could not be incorporated into this assessment. The clinical factors considered in the immunological risk score (ultimately not included in that model) were different from those used in ours and likely had more influence on early posttransplant infection. Our model proposes a more clinically oriented approach with prediction out to 1 y, allowing for opportunity to make adjustments in clinical management based on the score at 1 mo. This tool provides objective assessment of risk, which can be used to weigh difficult decisions regarding infection, surveillance, prophylaxis, and management of immunosuppressive medications.

Although various strategies are in place to specifically predict CMV infection in the solid organ transplant population,

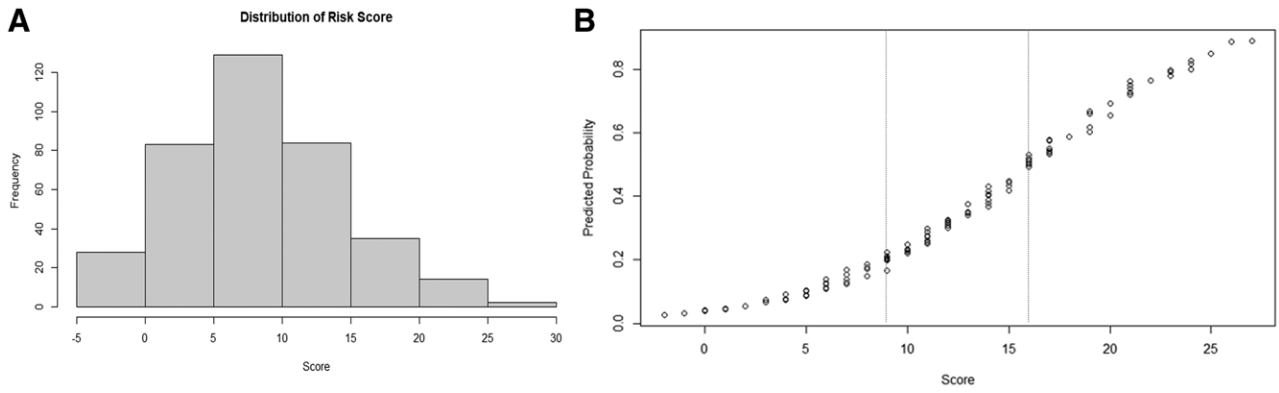

FIGURE 3. Display of score alignment within the cohort. (A) Frequency of calculated risk scores among the cohort. (B) Risk score vs predicted probability of infection. Dashed lines are displayed at scores correlating with roughly 20% (numeric score 9) and 50% (numeric score 16) predicted probability of infection, the proposed cutoffs to categorize patients into low-, intermediate-, and high-risk strata. Each integer in the risk score correlates with a small range of predicted probability, as displayed.

the added value of this model is the ability to gauge risk for a broader range of serious infections. CMV infection is independently associated with the other infection types grouped in the composite outcome, possibly because of immunomodulatory changes that it triggers in the host.[5-10] This was, in large part, the reasoning for grouping these infections together as a single outcome. However, as one way to quantify the value of anticipating specifically non-CMV infections, we calculated a mortality risk ratio and identified a 6-fold difference in those who developed non-CMV infection versus those who developed no infection. These estimates are striking and further demonstrate the potential impact of the ability to predict and ideally mitigate the risk for such an infection. Short of mortality, there is also a significant impact of morbidity that could be measured in attributable hospitalization. All patients in this cohort who developed IFI, nocardiosis, or BSI were hospitalized; however, data on the overall hospitalization rate for any reason among the full cohort are not available and, therefore, the calculation is not possible.

This study had a few notable limitations. Given the retrospective nature of the study, we had only routine clinical laboratory data and could not test other, more nuanced, immune markers (immunoglobulin G, C3, $CD4^+$, natural killer cells, ImmuKnow, and CMV ELISPOT) as candidate variables. However, as it stands with clinical information and basic laboratory measures only, the model performs very well. Another limitation was the span of the study period, which needed to be prolonged to accumulate sufficient events for the statistical analysis to generate sound conclusions, but opens the possibility of practice changes causing variability in incidence of infection over time. In particular, CMV care has had significant advancements during the study period, such as the implementation of prolonged prophylaxis, post-prophylaxis monitoring, and, in some clinical settings, the use of CMV T-cell assays and valganciclovir alternatives. Despite this, however, the majority of variables that comprise the model are generally features that are expected to have been stable over the period. Although the LASSO technique provides strong internal validation, a separate validation cohort from the current era and perhaps from 1 or more other centers would be ideal in solidifying the generalizability necessary for use at other centers. Finally, the model needs to be carefully applied and interpreted in clinical practice, as it does not carry the ability to predict infection outside of those specifically included in the composite outcome and it cannot be used to predict infection in the first posttransplant month (as multiple variables are determined by events occurring in the first month).

Strengths of this study include the large size and completeness of the database. The model includes risk factors that are easy to access, and the time-point of 1 mo posttransplant is specifically designed for greatest clinical utility—a period typically with highest vulnerability to infection, where clinical management can be adjusted to meet the needs of the individual patient to mitigate risk. Although risk assessment and mitigation strategies for CMV infection are in place, this broadens the ability to quantify infection risk. When weighed carefully against risk of rejection, the model could be used to make more personalized adjustments to broadly applied immunosuppression weaning protocols. It may also be helpful in evaluating level-of-care decisions for patients who call or present with nonspecific symptoms or low-grade fever, where a patient with a very high–risk score may be appropriate for admission and work-up, 1 with a low score may be relatively safe with close outpatient work-up.

In summary, this study proposes a clinical prediction model for use in heart transplant recipients for the assessment of risk of serious infection. The selected variables create a model, which is able to predict infections in the highest-risk period with reliable discrimination and calibration. It is designed for use at 1 mo posttransplant to anticipate potential events in the coming year. If appropriately weighed against risk of rejection, it can inform decision-making about intensity of maintenance immunosuppression and screening protocols.

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