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Development and validation of specific post-transplant risk scores according to the circulatory support status at transplant: A UNOS cohort analysis

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KEYWORDS:
heart transplantation;
mechanical circulatory support;
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BACKGROUND: The clinical use of post-transplant risk scores is limited by their poor statistical performance. We hypothesized that developing specific prognostic models for each type of circulatory support at transplant may improve risk stratification.

METHODS: We analyzed the UNOS database including contemporary, first, non-combined heart transplantations (2013-2018). The endpoint was death or retransplantation during the first year post-transplant. Three different circulatory support statuses at transplant were considered: no support, durable mechanical support and temporary support (inotropes, temporary mechanical support). We generated 1,000 bootstrap samples that we randomly split into derivation and test sets. In each sample, we derived an overall model and 3 specific models (1 for each type of circulatory support) using Cox regressions, and compared, in the test set, their statistical performance for each type of circulatory support.

RESULTS: A total of 13,729 patients were included; 1,220 patients (8.9%) met the composite endpoint. Circulatory support status at transplant was associated with important differences in baseline characteristics and distinct prognosis (p = 0.01), interacted significantly with important predictive variables included in the overall model, and had a major impact on post-transplant predictive models (type of variables included and their corresponding hazard ratios). However, specific models suffered from poor discriminative performance and significantly improved risk stratification (discrimination, reclassification indices, calibration) compared to overall models in a very limited proportion of bootstrap samples (<15%). These results were consistent across several sensitivity analyzes.

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HTx, heart transplantation; IABP, intra-aortic balloon pump; IDI, integrated discrimination improvement; ISHLT, International society for heart and lung transplantation; IQR, interquartile range; MCS, mechanical circulatory support; NRI, net reclassification improvement; UNOS, united network for organ sharing; VAD, ventricular assist device

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CONCLUSION: Circulatory support status at transplant reflected different disease states that influenced predictive models. However, developing specific models for each circulatory support status did not significantly improve risk stratification.

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In most countries, the allocation of heart allografts is based on a clinical stratification of the risk of poor pre-transplant outcomes, as assessed by the clinical condition and treatment received by the patient. Important limitations to this approach include the risk of influencing medical practice[1,2] and the lack of consideration of the risk of post-transplant mortality, thus neglecting the potential survival benefit of transplantation.[3] The development of a heart allocation score that would include the stratification of the risk of post-transplant outcomes has become the next priority following the recent revision of the United Network for Organ Sharing (UNOS) heart allocation system. However, all post-transplant risk scores suffer from poor statistical performance.[4,5] Particularly, their discrimination has been reported to be too low to allow an accurate and individual stratification of the risk of early post-transplant mortality.[6] By developing 1 score for all patients, these scores neglected heterogeneity between patients.

The increasing use of durable mechanical circulatory support (MCS) before HTx[7,8] and the recent increase in use of temporary MCS have dramatically contributed to this underlying heterogeneity.[2] Circulatory support status at transplant reflects different disease states that may influence post-transplant predictive models. As a reflection, the discrimination of risk scores has been shown to vary greatly according to the type of circulatory support at transplant.[6] We hypothesized that developing specific prognostic models for each support status may improve their statistical performance. We aimed to (1) identify independent risk factors for early post-transplant outcomes for each circulatory support status, (2) develop specific risk models for each status and (3) compare the statistical performance (discrimination, reclassification indices, calibration) of specific risk scores to a unique overall model for all patients.

Materials and methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. We followed the STROBE guidelines for data reporting of observational studies.

Definitions and selection of variables

We defined 3 circulatory support statuses at transplant: none, durable MCS (left ventricular assist device [VAD], right VAD, bi-VAD and total artificial heart) and temporary support (extracorporeal membrane oxygenator [ECMO], Impella, intra-aortic balloon pump [IABP], and inotropes). The clinical endpoint analyzed in this study was a composite endpoint of death and/or retransplantation during the first year post-HTx.

The severity of disease was assessed using the UNOS status at transplant and categorized as urgent (UNOS status 1A or 1-2-3 in the new allocation scheme) and nonurgent HTx (UNOS status 1B-2 or 4-5-6 in the new scheme).

We considered the predictive variables previously identified as independently associated with post-transplant outcomes in previously published risk models. We identified 16 independent risk scores.[6,9-23] The detailed search methodology has been published previously and is summarized in Supplementary Methods.[6] These models included a total of 70 different predictive variables. Among them, we selected a subset of 43 variables to avoid variables with ≥33% of missing values and redundant or obviously collinear variables (selection process detailed in Supplementary Table S1).

Patients and databases

We analyzed a contemporary UNOS cohort to take into account the rapidly evolving epidemiology of circulatory support status at transplant. All adult patients who underwent HTx between January 1, 2013 and December 31, 2018 were selected from the UNOS registry. Patients were excluded if they were 18 years or younger, underwent dual organ transplantation or redo-HTx, or if their vital status was not available. A flowchart is provided in Supplementary Figure S1. Studies using this dataset have been determined to be exempt from review by the Institutional Review Board of Cedars-Sinai Medical Center. We attest our strict compliance with the International Society for Heart and Lung Transplantation (ISHLT) ethics statement.

Statistical analysis

Qualitative variables were described as their frequencies and compared with the chi-squared test. Quantitative variables were described as the mean values with the standard deviation and compared with the Student t-test or ANOVA. Cumulative survival curves for the time-to-event analyses were constructed according to the Kaplan-Meier method and compared with the log-rank test. Using univariate and then multivariate Cox models (candidate factors selected when the univariate likelihood ratio test p value was ≤0.10; backward elimination, complete-case analysis), we first built an overall predictive model and analyzed the interactions between significant predictive variables and circulatory support status at transplant (complete-case analysis). We then randomly generated 1,000 bootstrap samples (random sample with replacement, stratified by type of circulatory support at transplant). For each sample, we (1) randomly split the overall cohort in a derivation set (2/3) and a test set (1/3); (2) developed, in the derivation set, 4 distinct predictive models (complete-case analysis): an overall model including all patients and 3 specific models, 1 for each circulatory support status at transplant using multivariate Cox regression with automatic selection of variables and backward elimination; and (3) analyzed and compared, in the test set, the statistical performance (a- discrimination: concordance statistic compared using the STATA's "somersd" package, b- reclassification

indices: net reclassification improvement [NRI] and integrated discrimination improvement [IDI], c- calibration: graphical evaluation) of the specific and overall models for each type of circulatory support status. We analyzed the consistency of our results by performing several sensitivity analyses: analysis of continuous variables as categorical variables, analysis of a broader set of predictive variables and limitation of the sample size of the derivation set for the overall model (an overall model was derived in a subset of randomly selected patients, which equals the number of patients in the derivation set of each specific model). Statistical significance was set at $p \leq 0.05$. All tests were 2-sided. Statistical analyses were performed using STATA 15.1 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of patients

A total of 13,729 patients were included. Their main characteristics are summarized in Table 1. At transplant, 2,135 (15.5%), 6,695 (48.8%) and 4,899 (35.7%) patients were on no, durable and temporary circulatory support, respectively. We observed important differences in the main clinical characteristics between support status at transplant, including recipient gender, ethnicity, etiology of heart failure, diabetes and pre-transplant infection, and donor gender and cause of death.

During the first year post-transplant, a total of 1,220 patients (8.9%) met the composite endpoint of death or retransplantation (Supplementary Figure S2-A). Post-transplant survival significantly differed across circulatory support status at transplant (no support: reference; temporary support: HR = 0.92, 95%CI = 0.77-1.12; durable support: HR = 1.19, 95%CI = 1.01-1.41, $p = 0.01$) (Supplementary Figure S2-B).

Overall model and analysis of interaction

Among the 43 selected variables, 25 variables were associated with post-transplant outcomes in univariate Cox regression analysis ($p < 0.10$). After multivariate analysis,

Table 1 Characteristics of Patients

Recipient characteristics	N	Overall	No support	Durablesupport	Temporarysupport	*p* value
Age, years — mean (SD)	13,729	53.8 ± 12.6	53.9 ± 13.4	53.6 ± 12.2	54.1 ± 12.8	**0.05**
Female gender — no. (%)	13,729	3,646 (26.6)	777 (36.4)	1,339 (20.0)	1,530 (31.23)	**<0.001**
Ethnicity	13,729					
Caucasian		8,918 (65.0)	1,480 (69.3)	4,288 (64.1)	3,150 (64.3)	
African American		3,008 (21.9)	339 (15.9)	1,636 (24.4)	1,033 (21.1)	**<0.001**
Hispanic		1,146 (8.3)	193 (9.0)	510 (7.6)	443 (9.0)	
Others		657 (4.8)	123 (5.8)	261 (3.9)	273 (5.6)	
Body mass index, kg/m^2 — mean (SD)	13,723	27.6 ± 4.9	26.9 ± 4.8	28.7 ± 4.8	26.5 ± 4.7	**<0.001**
Etiology of heart failure — no. (%)	13,729					
Dilated / idiopathic		7,681 (55.9)	949 (44.5)	4,070 (60.8)	2,662 (54.3)	
Ischemic		4,510 (32.9)	650 (30.4)	2,384 (35.6)	1,476 (30.1)	**<0.001**
Congenital		407 (3.0)	140 (6.6)	52 (0.8)	215 (4.4)	
Other		1131 (8.2)	396 (18.5)	189 (2.8)	546 (11.2)	
Pre-transplant diabetes — no. (%)	13,722	3,851 (28.1)	473 (22.2)	2,048 (30.6)	1,330 (27.2)	**<0.001**
Mechanical ventilation at transplant — no. (%)	13,729	104 (0.8)	10 (0.5)	24 (0.4)	70 (1.4)	**<0.001**
eGFR at transplant, mL/min/1.73m^2 — mean (SD)	13,727	72.9 ± 33.5	72.7 ± 31.3	72.8 ± 29.7	73.1 ± 38.9	0.86
Dialysis after listing — no. (%)	13,727	243 (1.8)	19 (0,9)	150 (2.2)	74 (1.5)	**<0.001**
Total bilirubin at transplant, mg/dL — mean (SD)	13,715	0.94 ± 1.39	0.93 ± 1.64	0.88 ± 1.16	1.01 ± 1.55	**<0.001**
Pre-transplant infection — no. (%)	13,558	1,338 (9.9)	72 (3.4)	826 (12.5)	440 (9.1)	**<0.001**
Donor characteristics						
Age, years — mean (SD)	13,729	32.2 ± 11.2	32.7 ± 11.8	31.8 ± 10.7	32.6 ± 11.5	**<0.001**
Female gender — no. (%)	13,729	4,162 (30.3)	801 (37.5)	1,586 (23.7)	1,775 (36.2)	**<0.001**
Pre-transplant diabetes — no. (%)	13,662	519 (3.8)	97 (4.6)	238 (3.6)	184 (3.8)	0.11
Cause of death — no. (%)	13,460					
Traumatic		6,459 (48.0)	916 (43.8)	3,334 (50.7)	2.209 (46.1)	
Cerebrovascular		2,520 (18.7)	410 (19.6)	1,131 (17.2)	979 (20.4)	**<0.001**
Anoxia		2,875 (21.4)	468 (22.4)	1,399 (21.3)	1,008 (21.1)	
Other		1,606 (11.9)	297 (14.2)	714 (10.8)	595 (12.4)	
Transplant characteristics						
Ischemic time, hour — mean (SD)	13,729	3.11 ± 1.04	3.13 ± 1.11	3.10 ± 1.06	3.10 ± 0.98	0.41

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 2 Overall Predictive Model (Multivariable Cox Model)

Variables	Label	Number of patients	Number of events	HR	95%CI	p
RECIPIENT CHARACTERISTICS						
Age	per 10-year increment	13,169	1,164	1.18	[1.11-1.24]	<0.001
Prior history of	No	6,348	443	1	-	
cardiac surgery	Yes	6,821	721	1.40	[1.23-1.58]	<0.001
Diabetes mellitus	No	9,461	770	1	-	
	Yes	3,708	394	1.16	[1.02-1.32]	0.02
Etiology of	Dilated	7,357	584	1	-	
Heart Failure	Ischemic	4,328	425	0.99	[0.87-1.14]	
	Congenital	392	59	2.30	[1.73-3.07]	<0.001
	Other	1,092	96	1.16	[0.94-1.45]	
Body Mass Index	≤18.5 kg/m2	291	29	1.38	[0.94-2.02]	
	18.5-25 kg/m2	4,053	306	1	-	
	25-30 kg/m2	4,834	411	1.12	[0.96-1.30]	<0.001
	≥30 kg/m2	3,991	418	1.37	[1.18-1.59]	
Dialysis after listing	No	12,938	1,115	1	-	
	Yes	231	49	2.20	[1.65-2.95]	<0.001
Transfusion after	No	10,087	811	1	-	
Listing	Yes	3,082	353	1.25	[1.10-1.43]	0.001
Mechanical	No	13,071	1,140	1	-	
ventilation	Yes	98	24	2.77	[1.84-4.17]	<0.001
Total bilirubin	per 1-mg/dL increment	13,169	1,164	1.085	[1.07-1.10]	<0.001
DONOR CHARACTERISTICS						
Age	per 10-year increment	13,169	1,164	1.075	[1.02-1.14]	0.011
Cause of death	Traumatic	6,330	529	1	-	
	Cerebrovascular	2,477	280	1.26	[1.08-1.48]	
	Anoxia	2,802	228	0.96	[0.82-1.12]	0.005
	Other	1,560	127	0.92	[0.76-1.12]	
TRANSPLANT CHARACTERISTICS						
Ischemic time	per 1-hour increment	13,169	1,164	1.18	[1.12-1.24]	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

12 predictive variables were independently associated with the occurrence of the primary endpoint (Table 2, concordance statistic = 0.676), including 9 recipient-related variables (age, body mass index, etiology of heart failure, prior history of cardiac surgery, diabetes, total bilirubin, dialysis after listing, transfusion after listing, and mechanical ventilation at transplant), 2 donor-related variables (age and cause of death) and 1 transplant-related variable (ischemic time).

We found significant interaction between the circulatory support status at transplant and 5 out of 12 predictive variables selected in the multivariate model (Supplementary Figure S3), including donor age ($p = 0.01$), transfusion after listing ($p = 0.01$), dialysis after listing ($p = 0.04$), body mass index ($p = 0.05$), and total bilirubin ($p = 0.06$).

Development of specific predictive models

First, we developed specific predictive models for each circulatory support status at transplant on the overall cohort. We found important differences between models in terms of both the predictive variables included and their respective weight in the multivariate model (Table 3, concordance statistic = 0.696, 0.641 and 0.660 for no support, durable support and temporary support models, respectively).

Then, we developed an overall model and 3 specific models (no support, durable support and temporary support models) in the derivation set of each one of the 1,000 bootstrap samples generated. As described in Figure 1, we observed important differences in the set of variables independently associated with post-transplant outcomes between models. However, the overall models represented a mix ~~average~~ of specific models. Most variables among the 10 most selected variables for each specific model were also among the 10 most selected variables in the overall models (no support model: $n = 7/10$; durable support model: $n = 7/10$; and temporary support model: $n = 6/10$).

Comparison of overall and specific models: discrimination, reclassification indices and calibration

In the test set of the 1,000 bootstrap samples, the median concordance statistic of the specific models was 0.613 (IQR = 0.573-0.653), 0.615 (IQR = 0.595-0.634) and 0.600 (IQR = 0.574-0.621) compared to 0.67 (IQR = 0.597-0.708), 0.630 (IQR = 0.586-0.652) and 0.630 (IQR = 0.606-0.652) for the overall models in patients with no, durable and temporary support, respectively (Figure 2). The specific model significantly outperformed the discrimination of the

Table 3 Multivariable Predictive Model for Each Circulatory Support Status at Transplant

Variables	Label	No support	Durable support	Temporary support
RECIPIENT CHARACTERISTICS				
Age	per 10-year increment	1.21 [1.02-1.42]	1.23 [1.14-1.34]	1.10 [1.001-1.22]
Ethnicity	Caucasian			1 -
	Af. American			1.56 [1.11-2.19]
	Hispanic			0.88 [0.65-1.20]
	Other			0.86 [0.51-1.43]
Blood group	A		1 -	
	B		1.13 [0.87-1.46]	
	0		0.91 [0.75-1.11]	
	AB		0.42 [0.21-0.82]	
Prior cardiac surgery				1.53 [1.22-1.92]
Diabetes mellitus				1.30 [1.03-1.66]
Steroids use			0.40 [0.22-0.68]	
Etiology of	Dilated	1 -		
Heart Failure	Ischemic	1.14 [0.73-1.77]		
	Congenital	3.97 [2.07-7.61]		
	Other	1.68 [1.05-2.67]		
Time on the	≤31			1 -
waitlist, days	32-109			0.80 [0.61-1.06]
	110-306			0.96 [0.71-1.31]
	≥307			1.34 [0.96-1.86]
Body Mass Index	≤18.5 kg/m2	4.61 [2.08-10.18]	1.34 [0.59-3.06]	
	18.5-25 kg/m2	1 -	1 -	
	25-30 kg/m2	1.28 [0.82-1.99]	1.13 [0.88-1.45]	
	≥30 kg/m2	1.42 [0.89-2.27]	1.45 [1.14-1.85]	
Mean pulmonary	≤19		1 -	
artery pressure,	19-25		1.01 [0.79-1.28]	
mmHg	25-33		1.11 [0.87-1.42]	
	>33		1.44 [1.12-1.85]	

(*continued on next page*)

Table 3 (*Continued*)

Variables	Label	No support	Durable support	Temporary support
Dialysis after listing		5.91 [2.45-14.24]	1.97 [1.25-3.09]	2.39 [1.32-4.31]
Transfusion				1.67 [1.21-2.30]
Mech. ventilation		5.22 [1.27-21.51]	2.78 [1.15-6.74]	2.08 [1.11-3.91]
Total bilirubin	per 1-mg/dL increment	1.12 [1.08-1.17]	1.12 [1.09-1.15]	1.06 [1.03-1.10]
DONOR CHARACTERISTICS				
Age	per 10-year increment	1.29 [1.12-1.50]		1.17 [1.06-1.28]
Cause of death	Traumatic		1 -	
	Cerebrovasc		1.28 [1.02-1.61]	
	Anoxia		0.82 [0.64-1.05]	
	Other		0.98 [0.72-1.31]	
TRANSPLANT CHARACTERISTICS				
Ischemic time	per 1-hour increment	1.22 [1.05-1.41]	1.21 [1.12-1.30]	

Abbreviations: Af American, African American; CI, confidence interval; HR, hazard ratio; Mech. Ventilation, mechanical ventilation.

overall model in only 0.9%, 3% and 1.6% of the bootstrap samples in patients with no, durable and temporary support, respectively. The discrimination of specific models was mostly driven by variables already included in the overall model. The addition of variables exclusively present in specific models resulted in a marginal improvement in discrimination (Figure 3).

The NRI (event, no event and global) and IDI of specific models compared to the overall models are presented in Figure 4A and B. Compared to the overall models, specific models significantly improved risk stratification in a limited number of samples (NRI: 11.1, 13.4 and 13.4%; IDI: 9.6, 4.9 and 6.7% of samples for no support, durable support and temporary support models, respectively).

A graphical evaluation of calibration of the specific and overall models is provided in Figure 5. We observed a trend towards an overestimation of the risk of event in high-risk patients which was more important in specific models, particularly for the no support model.

Sensitivity analyses

First, we analyzed continuous variables as categorical variables (categorized into quartiles or validated classifications). The specific models significantly outperformed the discrimination of overall models in less than 2% of samples. Similarly, specific models improved risk reclassification in a very limited number of samples (Supplementary Table S2).

Second, we considered a broader set of variables of interest by including all variables included in the 16 prognosis scores. The improvement in discrimination and risk reclassification with specific models compared to overall models remained marginal (Supplementary Table S2).

Third, when limiting the sample size of the derivation set for the overall model, the specific models had a significantly greater discrimination than the overall model in less than 10% of the samples (Supplementary Figure S4) and improved reclassification in less than 20% of samples (Supplementary Table S2).

Finally, when taking into account the severity of disease as assessed by the UNOS status at transplant, specific models significantly outperformed overall models in a minority of cases (Supplementary Table S2).

Discussion

In our analysis of a contemporary UNOS cohort of adult first non-combined HTx, we found that circulatory support status at transplant was associated with major differences in baseline characteristics and distinct prognosis, presented significant interactions with important predictive variables included in an overall predictive model, and had a major influence on post-transplant predictive models (type of variables and their associated hazard ratios). However, the development of specific predictive models for each type of circulatory support had limited impact on the statistical performance of predictive models. Our results do not support the development and the use of a specific post-transplant prognostic model for each circulatory support status at transplant.

While the development of a heart allocation score has become the next priority following the recent revision of

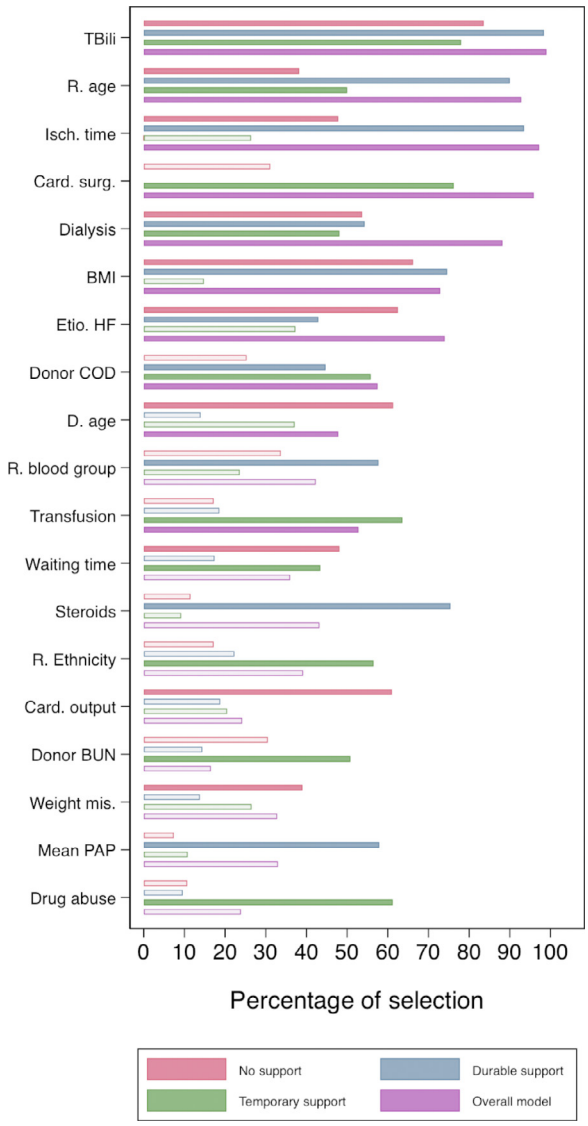

Figure 1 Most selected predictive variables according to the circulatory support status at transplant. This figure represents the percentage of bootstrap samples (n = 1,000) in which the variable of interest was found to be independently associated with post-transplant outcomes (the 10 most selected variables in all models are presented). Important differences in the set of selected variables were observed between models. Opaque bars: variable among the 10 most selected for this model. Transparent bars: variable not among the 10 most selected for this model. BMI, body mass index; BUN, blood urea nitrogen; Card. Surg, prior history of cardiac surgery; Card. output, cardiac output; COD, cause of death; D, donor; eGFR, estimated glomerular filtration rate; Etio. HF, etiology of heart failure; HF, heart failure; Isch. Time, ischemic time; PAP, pulmonary artery pressure; R, recipient; TBili, total bilirubin.

the UNOS heart allocation system, it has become necessary to counterbalance the prioritization of patients based on the assessment of the risk of death on the waitlist by accurate stratification of the risk of death after HTx in order to avoid futile transplantations. We recently reported the poor statistical performance of 16 post-transplant risk scores, particularly concerning their discrimination abilities.[6] These models do not allow a precise and individual stratification of the risk of early post-transplant mortality or retransplantation, thus limiting the evaluation of the individual transplant benefit. Developing more accurate models is an essential step before considering using these scores in clinical practice. Taking into account part of the heterogeneity between patients by developing risk models for specific populations may be an interesting approach.

Several prognostic models have been specifically developed in patients on durable MCS at transplant. The bridge to transplant risk score was developed in patients on left VAD at transplant (UNOS database, transplantation from 2008 to 2014).[11] The transplantation Risk Index in Patients with MCS was developed in patients on any type of MCS excluding ECMO (UNOS database, transplantation from 2000-2013).[14] Both multivariate predictive model included common predictive variables previously identified as independent risk factors for post-transplant mortality in patients without MCS at transplant. In line with our results, these 2 models were less discriminant than several models developed on non-VAD patients to predict outcomes in patients on durable MCS.[6]

We found that the specific models included different combinations of predictive variables. While total bilirubin and eGFR were similarly selected in all specific models, several variables were clearly imbalanced between models. Ischemic time, recipient age and mean pulmonary artery pressure were much more selected in durable support models that in the other specific models. On the other hand, donor cause of death, transfusion after listing and prior history of cardiac surgery were more often selected in the temporary support models, while donor age and etiology of heart failure were more frequently included in the no support model. These important differences between models may reflect (1) a different donor/recipient matching process according to the circulatory support at transplant, (2) differences in baseline characteristics and sample size and (3) different impacts of predictive variables on outcomes according to the circulatory support status.

As observed and discussed previously for all previously published predictive models, the overall discrimination of specific and overall models in our study was limited.[6,24] Additionally, the development of specific models for each circulatory support status did not result in improved statistical performance compared to that in overall models. First, the relatively limited number of variables taken into account for our primary analysis may limit statistical discrimination. However, this set of variables gathered all variables already included in previous prognostic models and ISHLT annual reports. The consideration of additional variables in the development of the model resulted in marginal improvement in discrimination. The lack of granularity of data in the UNOS registry may be the underlying explanation. The UNOS Thoracic Committee recently decided to expand the collection of data to capture more prognostic markers in order to improve risk stratification. Second, the overall models were an average of all specific models and included their most discriminant predictive variables. The addition of variables that were specific of a particular circulatory support model did not improve discrimination. Third,

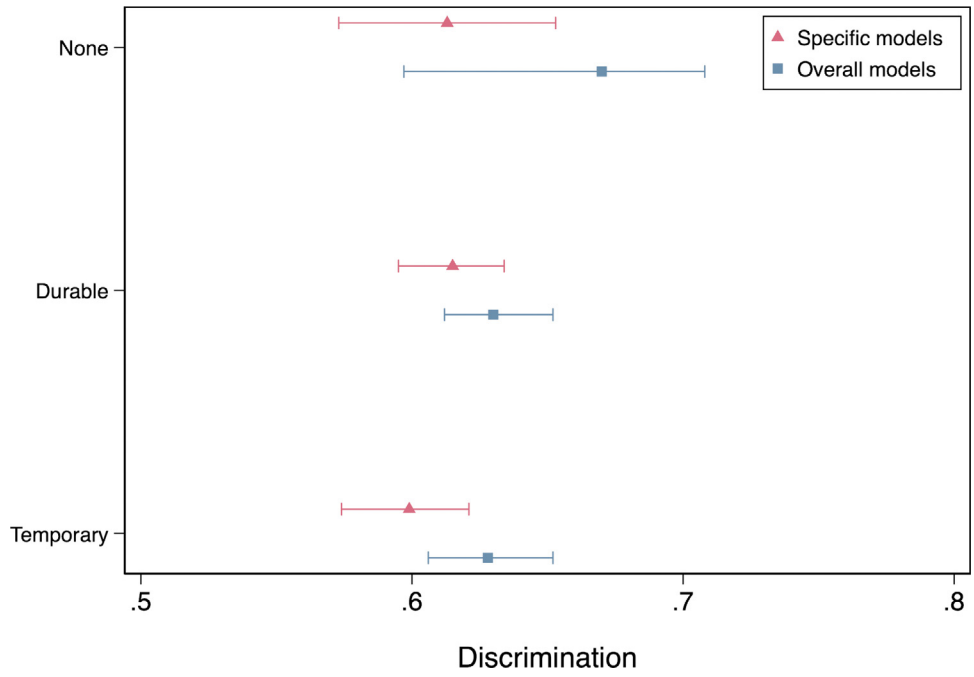

Figure 2 Discrimination of the overall and specific models for each circulatory support status. This figure represents the median and interquartile range of the concordance index observed in the test set of each bootstrap sample (n = 1,000). For each type of circulatory support at transplant, the discrimination of the specific model and of the overall model are given.

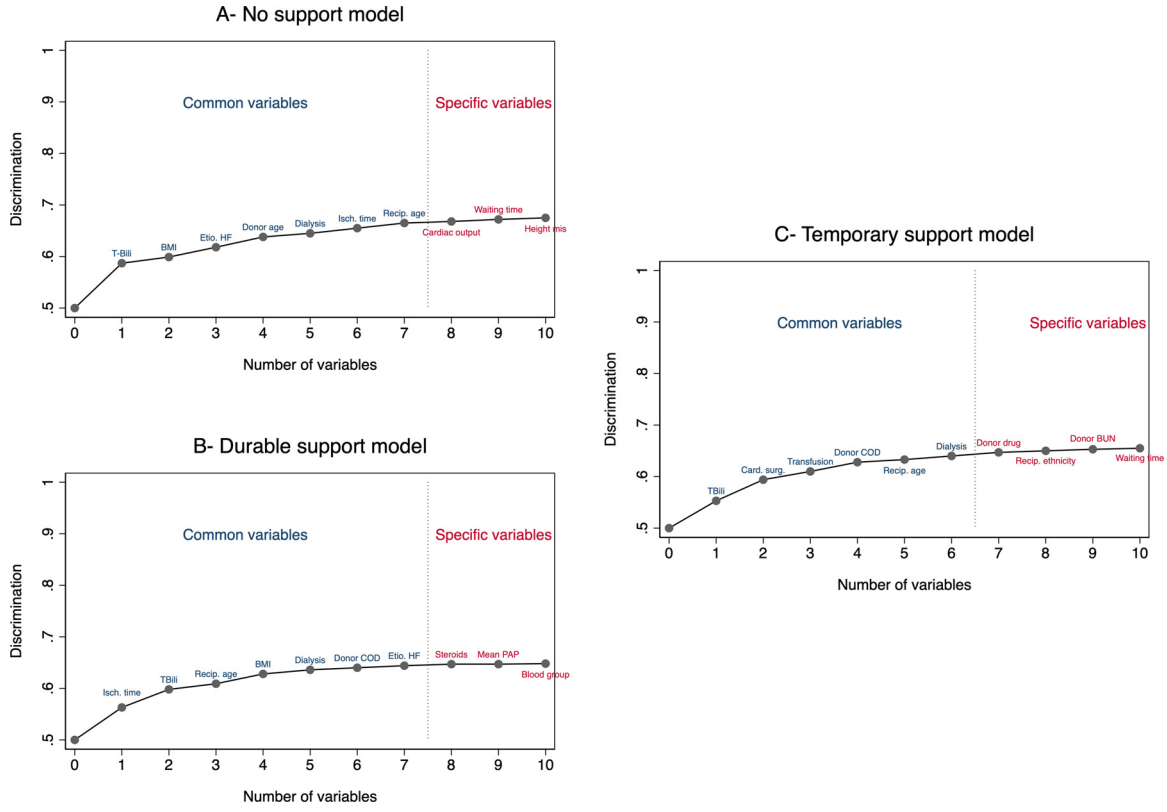

Figure 3 Evolution of discrimination according to the number and type of variables included in the specific models. The evolution of discrimination is described after progressive inclusion of the most selected variables in specific models. (A) No support model. (B) Durable support model. (C) Temporary support model. "Common variables" designs variables among the 10 most selected in the specific model and in the overall model. "Specific variables" designs variables among the 10 most selected in the specific models but not in the overall model. BMI, body mass index; BUN, blood urea nitrogen; Card. surg, prior history of cardiac surgery; Donor COD, donor cause of death; Etio. HF, etiology of heart failure; Isch. Time, ischemic time; PAP, pulmonary artery pressure; Recip, Recipient, T-Bili, total bilirubin.

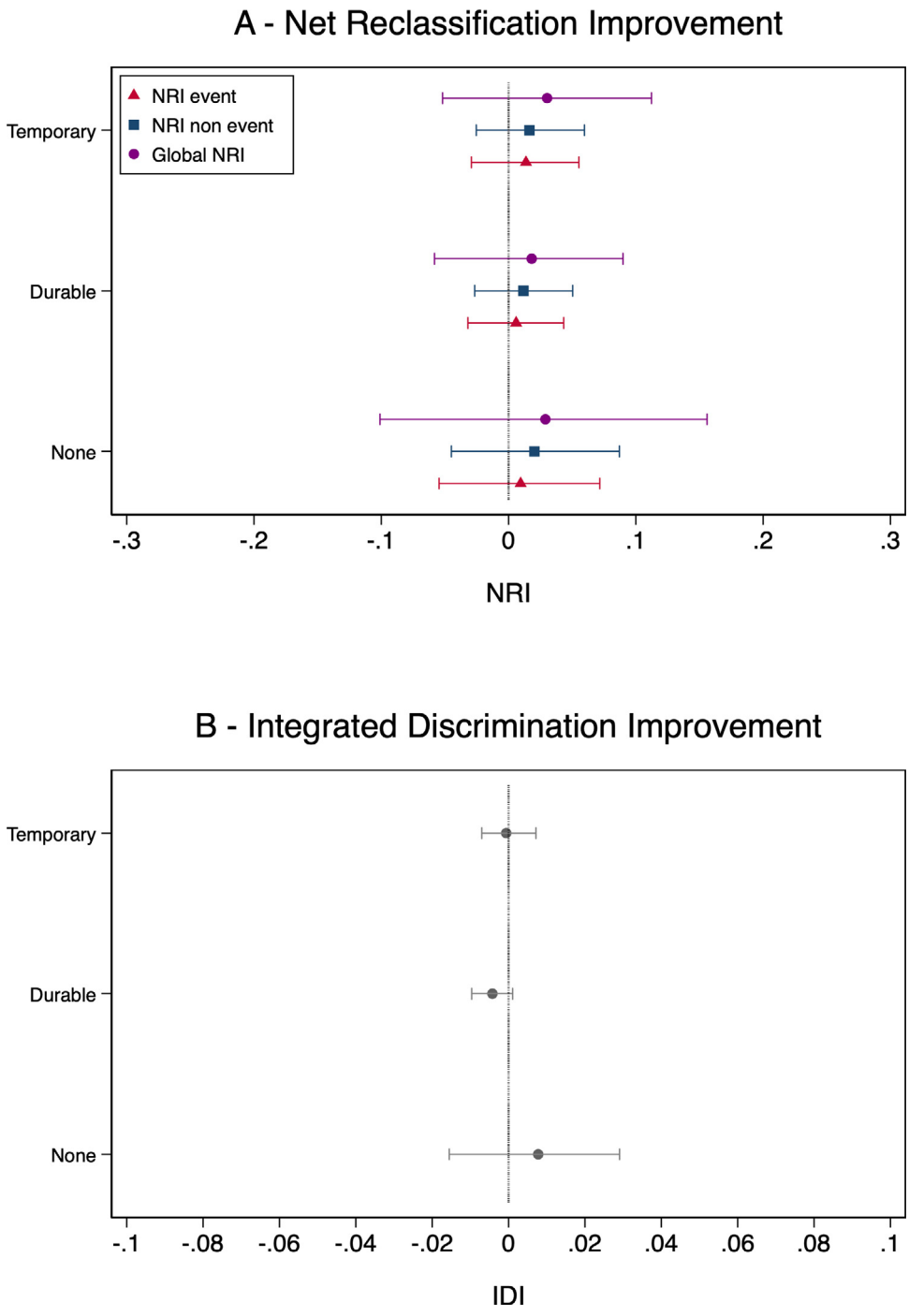

Figure 4 Net reclassification improvement and integrated discrimination improvement. Comparison of specific and overall models for each type of circulatory support. This figure represents the median and interquartile range of the Net reclassification improvement (A) and integrated discrimination improvement (B) observed in the test set of each bootstrap sample (n = 1,000).

each circulatory support subpopulation included less patients and events than those in the overall population, thus limiting the number of independent predictive variables selected in the specific models compared to those in the overall model. However, developing specific predictive models in similar derivation set sample sizes than those in the overall model resulted in marginal improvement of discrimination with specific models. Finally, circulatory support subgroups at transplant may include a wide heterogeneity of illness intensity. However, taking into account disease severity as assessed by the UNOS status at transplant did not modify our results.

Our results show that current predictive models do not allow a precise and individual stratification of the risk of early post-transplant mortality. However, we believe that considering post-transplant outcomes remains crucial in an allocation scheme based on the "sickest first" principle to avoid futile procedures. Pending the development of more accurate predictive models, we believe that post-transplant mortality risk scores should only be seen as a way to avoid

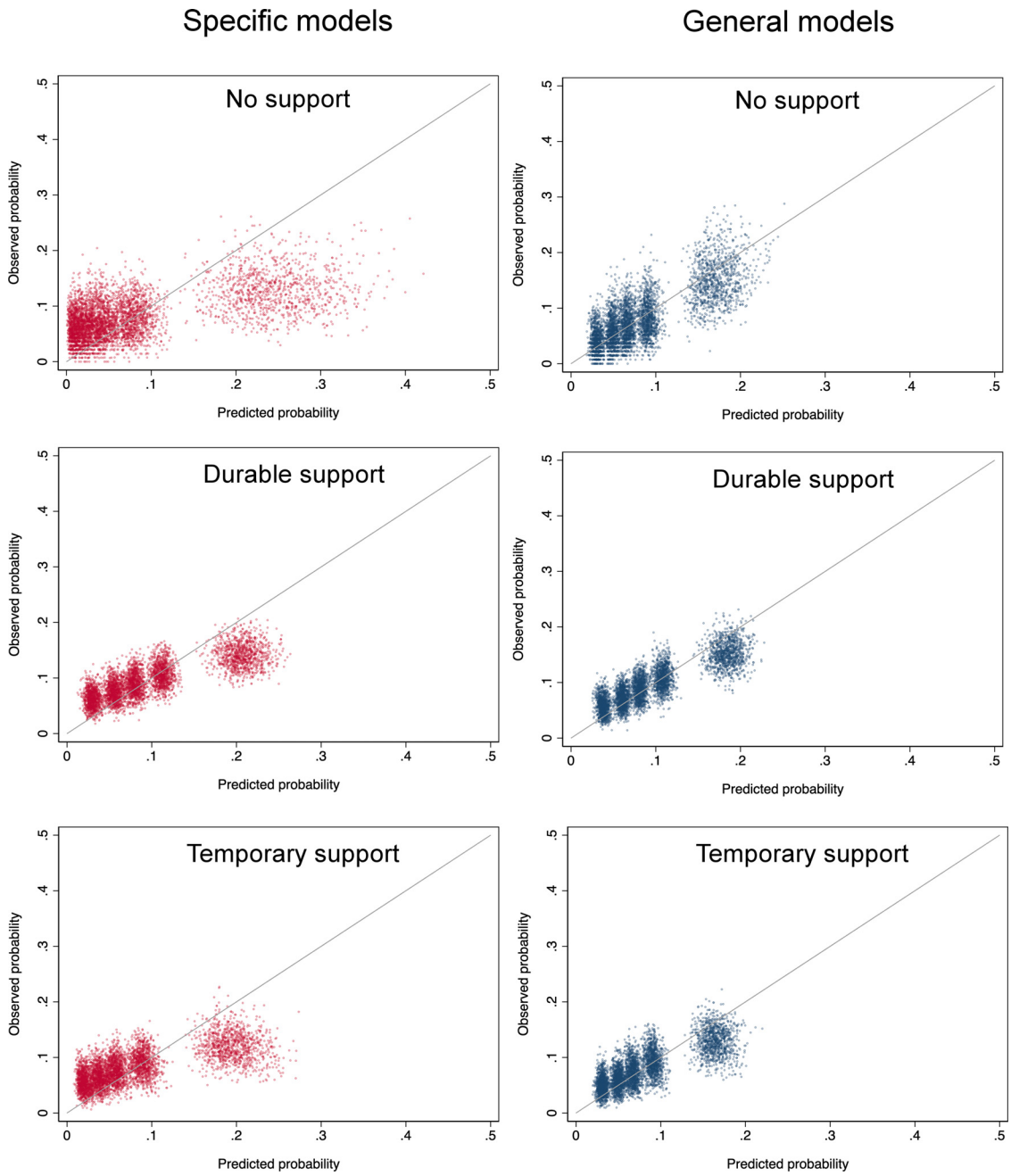

Figure 5 Calibration of the specific and overall models for each type of circulatory support at transplant. Test set: graphical evaluation of the calibration of each model by plotting predicted and observed probability of events (quintiles of predicted probability). Each circle represents 1 bootstrap sample (n = 1,000).

very high-risk procedures associated with unacceptable outcomes and not as a continuous score aimed at evaluating precisely and individually the transplant benefit.

Our study should be interpreted in the context of its limitations. First, we analyzed a very limited number of patients transplanted with the 2018 allocation scheme, thus representing an important limitation to the clinical applicability of our results. Important changes in the frequencies of mechanical support at transplant have followed the implementation of the new scheme, particularly concerning a dramatic increase in temporary MCS at transplant.[2,25,26] The limited number of patients on ECMO and IABP in the 2013-2018 UNOS cohort did not allow for the development of specific models for this subpopulation. However, recent data suggest that the profile of risk of patients transplanted with the new allocation scheme do not differ significantly compared to that in patients transplanted earlier, thus making it unlikely to improve discrimination by developing new specific models for these subgroups of patients.[2] Second, the use of the c-statistic as a measure of discrimination has been criticized for its low sensitivity in comparing models from different datasets and for the arbitrary selection of acceptable thresholds. However, the

concordance index is a commonly accepted way to assess the discrimination of a model, and we applied it to analyze the discrimination ability of multiple risk scores on the same set of data. Third, an important limitation of all of the scores included in the analysis is that only the outcomes of patients that were actually transplanted were assessed and wait-list mortality was not accounted for.

Conclusion

Circulatory support status at transplant reflects different disease state of heart failure and had a major influence on post-transplant predictive models, concerning both the type of variables and their associated hazard ratios. However, developing specific models for each type of circulatory support did not result in improved statistical performance.

Author contributions (ICJME)

GC contributed to the design and analysis, drafted the work, approved the final version and agreed to be accountable for all aspects of the work.

GB contributed to the acquisition and analysis, drafted the work, approved the final version and agreed to be accountable for all aspects of the work.

EK contributed to the design, drafted the work, approved the final version and agreed to be accountable for all aspects of the work.

AL contributed to the conception and interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

JM contributed to the interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

PL contributed to the conception, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

JAK contributed to the design and interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

JKP contributed to the conception and interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

Disclosure statement

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.06.010.

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