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The Ability of Comorbidity Indices to Predict Mortality After Heart Transplantation: A Validation of the Danish Comorbidity Index for Acute Myocardial Infarction, Charlson Comorbidity Index, and Elixhauser Comorbidity Index

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Background. Advanced heart failure patients often have comorbidities of prognostic importance. However, whether total pretransplantation comorbidity burden predicts mortality in patients treated with heart transplantation (HTx) is unknown. We used population-based hospital and prescription data to examine the ability of the Danish Comorbidity Index for Acute Myocardial Infarction (DANCAMI), DANCAMI restricted to noncardiovascular diseases, Charlson Comorbidity Index, and Elixhauser Comorbidity Index to predict 30-d, 1-y, 5-y, and 10-y all-cause and cardiovascular mortality after HTx. **Methods.** We identified all adult Danish patients with incident HTx from the Scandiatransplant Database between March 1, 1995, and December 31, 2018 (n = 563). We calculated Harrell's C-Statistics to examine discriminatory performance. **Results.** The C-Statistic for predicting 1-y all-cause mortality after HTx was 0.58 (95% confidence interval [CI], 0.50-0.65) for a baseline model including age and sex. Adding comorbidity score to the baseline model did not increase the C-Statistics for DANCAMI (0.58; 95% CI, 0.50-0.65), DANCAMI restricted to noncardiovascular diseases (0.57; 95% CI, 0.50-0.64), Charlson Comorbidity Index (0.59; 95% CI, 0.51-0.66), or Elixhauser Comorbidity Index (0.58; 95% CI, 0.51-0.65). The results for 30-d, 5-y, and 10-y all-cause and cardiovascular mortality were consistent. **Conclusions.** After accounting for patient age and sex, none of the commonly used comorbidity indices added predictive value to short- or long-term all-cause or cardiovascular mortality after HTx. (Transplantation Direct 2023;9: e1438; doi: 10.1097/TXD.0000000000001438.)

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Heart transplantation (HTx) is the recommended treatment for advanced heart failure patients refractory to drug or mechanical treatment.[1] Clinicians use prognostic scores like the Heart Failure Survival Score[2] and Seattle Heart Failure Model[3] to identify advanced heart failure patients with the highest mortality risk without HTx, which is essential because of scarce donor hearts. These scores use information on patient demographics, left ventricular ejection fraction, heart failure cause, drug use, and laboratory analyses to predict mortality in patients with advanced heart failure.[2,3]

A meta-analysis found 16 scores used to predict HTx survival.[4] These scores all incorporate some kind of clinical information—such as ischemic time, mechanical ventilation, or temporary circulatory support—limiting their use in population-based research.[4] Furthermore, all scores predicting HTx mortality incorporate little information on patient comorbidity.[4] For example, the Index for Mortality Prediction After Cardiac Transplantation (IMPACT), the most validated score to predict HTx mortality, only incorporates ischemic heart failure cause, serum bilirubin (as a marker of hepatic or biliary function), and creatinine clearance (as a marker of renal function).[5] Thus, the prognostic value of pretransplantation comorbidity burden after HTx is poorly understood.

Therefore, we examined the ability of commonly used comorbidity indices to predict short- and long-term mortality in adult HTx patients.

MATERIALS AND METHODS

Setting

The Danish National Health Service provides universal tax-supported health care, assuring free access for all Danish citizens and legal residents to general practitioners and hospitals in Denmark.[6] Danish citizens and legal residents receive a unique 10-digit Civil Personal Register number at birth or upon immigration, allowing linkage between Danish registries on an individual level.[7] In Denmark, advanced heart failure patients are referred to 1 of 2 national HTx centers when they, despite optimal medical treatment, still fulfill the criteria for end-stage heart failure and do not have any contraindications for HTx.[1]

Study Cohort

We used the Scandiatransplant Database[8] to identify all patients at least 18 y of age treated with first-time HTx (*International Classification of Diseases* 10th edition: DZ94.1) in Denmark between March 1, 1995, and December 31, 2018. The Scandiatransplant Database holds patient and donor information on all HTx in Denmark since 1994.[8] We also obtained information on donor age from the Scandiatransplant Database.

Mortality Outcomes

We examined all-cause and cardiovascular mortality within 30 d, 1 y, 5 y, and 10 y after HTx. We used the Danish Civil Registration System to obtain information on all-cause mortality status.[7] The Danish Civil Registration System holds information on mortality and emigration status since 1968.[7] We used the Danish Register of Causes of Death to identify the cause of death.[9] We defined cause-specific mortality according to the main underlying cause of death.[9] Cardiovascular mortality was defined as death from congestive heart failure, myocardial infarction, stroke, or venous thromboembolism.

Comorbidity Indices

Comorbidity indices summarize a patient's comorbidity burden into a single score based on the number and severity (ie, weights reflecting their association with mortality) of the comorbidities.[10] The Danish Comorbidity Index for Acute Myocardial Infarction (DANCAMI) and DANCAMI restricted to noncardiovascular diseases (rDANCAMI) were developed to predict 1-y mortality after hospitalization for myocardial infarction,[11] the Charlson Comorbidity Index (CCI) was developed to predict 1-y mortality in a cohort of medical patients,[12] and the Elixhauser Comorbidity Index (ECI) was developed to predict in-hospital mortality in a cohort of diverse hospitalized patients.[13] Details regarding comorbidity selection and weighting are described elsewhere.[11,13,14]

We used the Danish National Patient Registry (DNPR) to identify all comorbidities in the 10 y before the date of transplantation.[15] The DNPR holds information on all nonpsychiatric inpatient contacts since 1977 and nonpsychiatric outpatient, psychiatric in and outpatient, and emergency contacts since 1995.[15]

Because diabetes, chronic pulmonary disease, schizophrenia, and affective disorder may be treated solely by a general practitioner, they may not have a record in the DNPR.[15] Therefore, we also defined these comorbidities if a relevant prescription had been redeemed in the 90 d before HTx. We used information from the Danish National Prescription Registry to define such prescription redemptions.[16] The Danish National Prescription Registry holds information on all redemptions of prescription drugs from Danish community pharmacies since 1995 but no information about in-hospital drug use.[16] **Table S1** (**SDC**, http://links.lww.com/TXD/A510) presents all comorbidities and their weights. **Table S2** (**SDC**, http://links.lww.com/TXD/A510) presents all *International Classification of Diseases* and *Anatomical Therapeutic Chemical Classification* codes used in the study.

Statistical Analyses

We followed patients from the date of HTx until the end of follow-up, death, emigration, or December 31, 2018, whichever occurred first. We used a Kaplan-Meier estimator to estimate all-cause mortality risk after HTx[17] and a log-rank test to compare all-cause mortality between categorized comorbidity burden.[18]

We focused on discrimination (and not calibration) because the indices are intended to be used for confounding adjustment rather than clinical prediction. We calculated the performance measure Harrel's C-Statistic for a baseline model including

TABLE 1.

Patient characteristics at the time of HTx

Characteristic	Number (%)
Total	563 (100)
Female sex	121 (22)
Patient age (y), median (interquartile range)	52 (43–59)
18–39	113 (20)
40–49	129 (23)
50–59	212 (38)
≥60	109 (19)
Donor age (y), median (interquartile range)	42 (31–51)
18–39	236 (42)
≥40	327 (58)
DANCAMI comorbidity burden	
No (score: 0)	211 (37)
Low (score: 1–3)	165 (29)
Moderate (score: 4–5)	100 (18)
Severe (score: ≥6)	87 (15)
rDANCAMI comorbidity burden	
No (score: 0)	353 (63)
Low (score: 1–3)	146 (26)
Moderate (score: 4–5)	31 (5.5)
Severe (score: ≥6)	33 (5.9)
CCI comorbidity burden	
No (score: 0)	384 (68)
Low (score: 1)	117 (21)
Moderate (score: 2)	46 (8.2)
Severe (score: ≥3)	16 (2.8)
ECI comorbidity burden	
No (score: 0)	403 (72)
Low (score: 1–5)	116 (21)
Moderate (score: 6–13)	41 (7.3)
Severe (score: ≥14)	3 (0.53)

CCI, Charlson Comorbidity Index; DANCAMI, Danish Comorbidity index for Acute Myocardial Infarction; ECI, Elixhausen Comorbidity Index; rDANCAMI, DANCAMI restricted to noncardiovascular comorbidities.

patient age (restricted cubic splines with knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles)[19,20] and sex and for models including the comorbidity indices plus patient age and sex. Harrell's C-Statistic is the probability that for a pair of random individuals, the model will assign a greater predicted risk to the individual dying first.[21] A C-Statistic of 0.5 indicates a chance prediction and 1 indicates perfect prediction.[21] We calculated 95% confidence intervals (CIs) for the C-Statistics using resampling methods (100 bootstrap replicates).

To test if categorized comorbidity burden performed similarly to the continuous comorbidity score, we categorized comorbidity burden based on the comorbidity score as no, low, moderate, and severe. To test whether the results differed within patient subgroups, we stratified the analyses by sex, patient age (18–39, 40–49, 50–59, and ≥60 y of age), and donor age (18–39 and ≥40 y of age). All statistical analyses were computed using STATA Version 16.1 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

We identified 563 adult patients with first-time HTx in Denmark. The median age was 52 y (interquartile range, 43–59) and 121 (20%) were females (Table 1). The most frequent comorbidities were cardiac arrhythmias (65%), peripheral vascular disorders (24%), and hypertension (20%; Table 2).

Mortality Prediction

Figure 1 displays the cumulative survival in the 10 y after HTx. The C-Statistic for 1-y mortality were comparable for the baseline model, including patient age and sex, and the continuous DANCAMI, rDANCAMI, CCI, and ECI models (Table 3). Thus, the C-Statistic was 0.58 for the baseline model, 0.58 for DANCAMI, 0.57 for rDANCAMI, 0.59 for CCI, and 0.59 for ECI. The categorical models performed comparably with the continuous models (Table 3). For all indices, categorical comorbidity burden performed compatible to continuous comorbidity score (**Table S3, SDC**, http://links.lww.com/TXD/A510). The results were consistent for 30-d, 5-y, and 10-y all-cause mortality (Table 3). The results were also consistent in strata of sex, patient age, and donor age (**Tables S4–S6, SDC**, http://links.lww.com/TXD/A510).

The C-Statistic when predicting 1-y cardiovascular mortality was similar for the baseline (0.68), DANCAMI (0.67), rDANCAMI (0.67), CCI (0.71), and ECI (0.71) models (Table 3). These results were consistent for 30-d, 5-y, and 10-y cardiovascular mortality (Table 3).

DISCUSSION

We found that after accounting for patient age and sex, neither DANCAMI, rDANCAMI, CCI, nor ECI increased the discriminative ability to predict short- or long-term all-cause or cardiovascular mortality after HTx.

TABLE 2.

Prevalence of the DANCAMI, CCI, and ECI comorbidities in adult HTx patients at the time of HTx

		Comorbidity index			
DANCAMI		**CCI**		**ECI**	
Comorbidity	**Number (%)**	**Comorbidity**	**Number (%)**	**Comorbidity**	**Number (%)**
Intermittent arterial claudication	11 (2.0)	Any malignancy, including lymphoma and leukemia, except malignant neoplasm of the skin	23 (4.1)	Cardiac arrhythmias	365 (65)
Aortic disease	7 (1.2)	Metastatic solid tumor	≤5	Valvular disease	98 (17)
Valvular heart disease	89 (16)	AIDS/HIV	≤5	Pulmonary circulation disorders	35 (6.2)
Stroke	37 (6.6)	Diabetes, with chronic complication	17 (3.0)	Peripheral vascular disorders	137 (24)
Hypertension	112 (20)	Dementia	≤5	Lymphoma	≤5
High-risk cancer (5-y mortality>70%)	6 (1.1)	Hemiplegia or paraplegia	≤5	Metastatic cancer	≤5
Low-risk cancer (5-y mortality≤70%)	22 (3.9)	Renal disease	74 (13)	Solid tumor without metastasis	18 (3.2)
Coagulopathy	37 (6.6)	Chronic pulmonary disease	80 (14)	Coagulopathy	10 (1.8)
Diabetes, uncomplicated	82 (15)	Mild liver disease	14 (2.5)	Blood loss anemia	≤5
Diabetes, with end organ damage	39 (6.9)	Moderate or severe liver disease	≤5	Deficiency anemia	≤5
Dementia	≤5	Rheumatic disease	7 (1.2)	Obesity	23 (4.1)
Hemiplegia	≤5			Weight loss	≤5
Neurodegenerative disorder	≤5			Fluid and electrolyte disorders	19 (3.4)
Epilepsy	11 (2.0)			Paralysis	≤5
Alcohol and drug abuse	≤5			Other neurological disorders	15 (2.7)
Schizophrenia or antipsychotic drug	7 (1.2)			Drug abuse	≤5
Affective disorder or antidepressant drug	46 (8.2)			Depression	47 (8.4)
Chronic kidney disease	71 (13)			Renal failure	74 (13)
Chronic pulmonary disease	75 (13)			Chronic pulmonary disease	80 (14)
Ulcer disease	18 (3.2)			Liver disease	16 (2.8)
Mild liver disease	≤5				
Moderate to severe liver disease	≤5				
Chronic pancreatitis	≤5				
Obesity	23 (4.1)				
Connective tissue disease	16 (2.8)				

AIDS, auto immunodeficiency syndrome; CCI, Charlson Comorbidity Index; DANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction; ECI, Elixhauser Comorbidity Index; HIV, human immunodeficiency virus; HTx, heart transplantation.

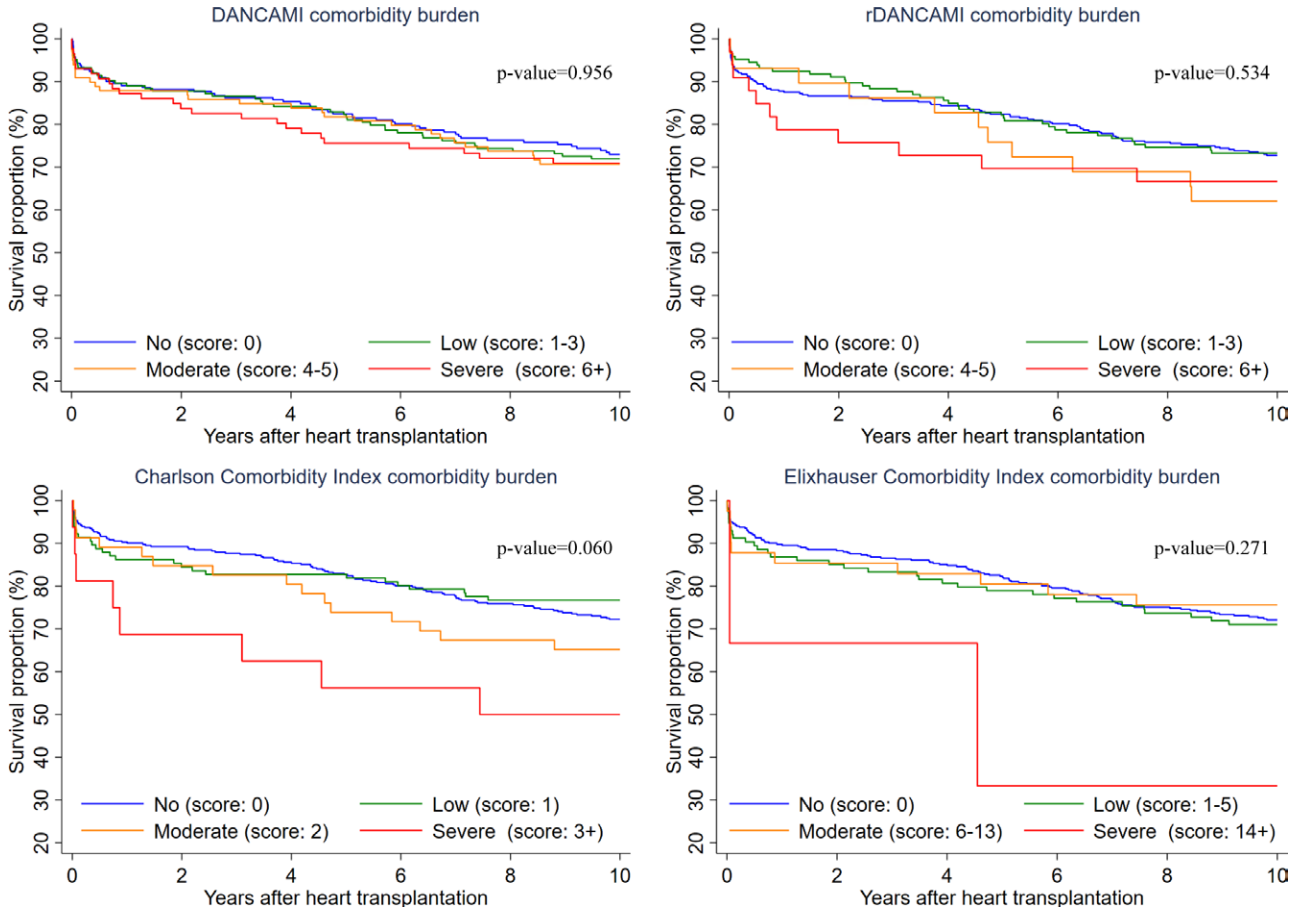

FIGURE 1. Ten-y survival after first-time HTx, by comorbidity index. CCI, Charlson Comorbidity Index; DANCAMI, Danish Comorbidity index for Acute Myocardial Infarction; ECI, Elixhauser Comorbidity Index; HTx, heart transplantation; rDANCAMI, DANCAMI restricted to noncardiovascular diseases.

Previous Literature

Prognostic Scores

Of 16 existing scores predicting HTx mortality, 7 have been externally validated.[4] IMPACT is the most validated score and was developed to predict 1-y mortality in adult US HTx patients from 1997 to 2008.[5] Both IMPACT and other prognostic scores have shown predictive performance similar to that of the comorbidity scores examined in this study when examining 1-y mortality but higher predictive performance when examining 3-mo and overall mortality.[4] Contrary to the comorbidity scores, previous prognostic scores include clinical information on, for example, laboratory analyses and treatments.[4,5] The fact that clinical information is highly associated with HTx mortality[5] likely explains the low discriminatory performance of the comorbidity scores not incorporating such information and, thereby, the difference in performance between the comorbidity scores and other prognostic scores.

Comorbidity Scores

Comorbidity scores are often used instead of individual comorbidities to adjust for confounding by comorbidity burden because of simplified analysis and a higher statistical efficiency when the sample size is limited.[22] The ability of a comorbidity score to reduce confounding depends both on its association with the exposure and outcome under study. It has been shown in many settings that a model including patient age and sex predicts outcomes equivalent to a model including patient age, sex, and a comorbidity score.[22] This lack of increased predictive ability when incorporating a comorbidity score has been attributed to an oversimplistic estimation of comorbidity burden when using registry data.[22] Thus, the fact that neither comorbidity score examined in this study predicted HTx mortality suggests that after controlling for patient age and sex, further controlling for any comorbidity score (when estimated using registry data) likely does not reduce confounding further, despite a strong association with the exposure of interest. Therefore, researchers should strive to obtain clinical information and not depend on registry-based information on comorbidities for confounding adjustment.

All comorbidity scores examined in this study have been validated in patients with several cardiovascular diseases, including myocardial infarction, ischemic stroke, and venous thromboembolism.[11,23–28] In these patients, the comorbidity scores have generally been able to predict mortality (C-Statistic >0.70).[11,23–28] Only the CCI and ECI have been validated in heart failure patients. In these patients, the CCI accurately predicted in-hospital (C-Statistic = 0.78)[29] and 2-y (C-Statistic = 0.72)[30] but not 6-mo mortality (C-Statistic = 0.65),[31] and the ECI accurately predicted in-hospital (C-Statistic = 0.78)[29] but not 6-mo mortality (C-Statistic = 0.65).[31] Because many comorbidities are contraindications to HTx,[1] patients referred to and treated with HTx constitute a selective group with limited comorbidity burden and severity. This selection likely leads to large differences between HTx and all heart failure patients, thereby explaining the dissimilarity between the results in this study and the results above.

TABLE 3.

C-Statistics[a] of the continuous comorbidity indices for predicting mortality after HTx

	Follow-up			
Mortality	**30 d**	**1 y**	**5 y**	**10 y**
All-cause				
Baseline[b]	0.55 (0.47-0.63)	0.58 (0.50-0.65)	0.57 (0.52-0.63)	0.58 (0.53-0.62)
DANCAMI[c]	0.58 (0.50-0.67)	0.58 (0.50-0.65)	0.57 (0.52-0.63)	0.58 (0.53-0.63)
rDANCAMI[c]	0.56 (0.48-0.65)	0.57 (0.50-0.64)	0.58 (0.52-0.63)	0.58 (0.54-0.63)
CCI[c]	0.60 (0.51-0.69)	0.59 (0.51-0.66)	0.58 (0.53-0.64)	0.59 (0.54-0.63)
ECI[c]	0.59 (0.50-0.67)	0.59 (0.52-0.66)	0.57 (0.51-0.62)	0.58 (0.53-0.62)
Cardiovascular[d]				
Baseline[c]	0.77 (0.54-1.00)	0.68 (0.53-0.83)	0.64 (0.54-0.75)	0.62 (0.53-0.71)
DANCAMI[c]	0.80 (0.65-0.96)	0.67 (0.50-0.83)	0.68 (0.59-0.77)	0.63 (0.55-0.71)
rDANCAMI[c]	0.77 (0.52-1.00)	0.67 (0.55-0.79)	0.69 (0.59-0.80)	0.65 (0.57-0.74)
CCI[c]	0.79 (0.57-1.00)	0.71 (0.58-0.83)	0.66 (0.57-0.75)	0.62 (0.54-0.71)
ECI[c]	0.77 (0.54-1.00)	0.71 (0.56-0.87)	0.67 (0.57-0.77)	0.65 (0.56-0.73)

The results are presented as C-Statistic (95% CI).

[a]The probability that for a pair of random individuals the model will assign a greater predicted risk to the individual dying first. C-Statistic of 0.5 indicates chance prediction and 1 indicates perfect prediction.

[b]Cox model including patient age and sex.

[c]Baseline model plus the individual comorbidity score.

[d]Main underlying cause of death congestive heart failure, myocardial infarction, stroke, or venous thromboembolism.

CCI, Charlson Comorbidity Index; CI, confidence interval; DANCAMI, Danish Comorbidity index for Acute Myocardial Infarction; ECI, Elixhausen Comorbidity Index; HTx, heart transplantation; rDANCAMI, DANCAMI restricted to noncardiovascular comorbidities.

Limitations

The low number of deaths after HTx limited precision. We had no missing data on the information used in the predictive models (age, sex, and individual comorbidities). We did not use information on place or surgery, blood group compatibility between donor and recipient, and donor age and sex from the Scandiatransplant Database because we aimed to examine whether population-based data on patient comorbidity burden could predict HTx mortality. Many of the used comorbidities have been validated within the DNPR, with high positive predictive values found for several cardiovascular[32] and CCI comorbidities.[33] We mitigated the issue of some comorbidities potentially being treated solely by a general practitioner and, therefore, not registered in the DNPR, by also using information on redemptions of relevant prescription drugs to define these diseases.[34] We chose not to use information on antihypertensive drugs to define hypertension because of the overlap with anticongestive drugs (eg, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, diuretics, and beta-blockers) and inherent risk of misclassification. Furthermore, obesity may be underestimated because its completeness is only 11% within the DNPR.[35]

CONCLUSION

Pretransplantation comorbidity burden, as measured by 4 commonly used comorbidity indices, did not add discriminative value in predicting short- or long-term mortality after HTx after accounting for age and sex. Researchers studying HTx prognosis should strive to obtain detailed clinical information known to be associated with HTx prognosis and not depend solely on comorbidity indices for confounding adjustment.

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