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Clinical Research

A Prognostic Model for the Thirty-day Mortality Risk after Adult Heart Transplantation

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Objective: To develop a prognostic model for the thirty-day mortality risk after adult heart transplantation.
Methods: In this report we developed a prediction model for the 30-day mortality risk after adult heart transplantation. Logistic regression analysis was used to develop the model in 1,262 adult patients undergoing primary heart transplantation. We evaluated the accuracy of the prediction model; the agreement between the predicted probability and the observed mortality (calibration); and the ability of the model to correctly discriminate between the discordant survival pairs (discrimination). The internal validity of the prediction model was evaluated using the bootstrapping procedures.
Results: Recipients' age and sex, pre-transplant diagnosis, transplant status, waiting time, cardiopulmonary bypass time, donors' age and sex, donor-recipient mismatch for BMI and blood type were independent predictors for 30-day mortality risk after adult heart transplantation. The model showed a good calibration and reasonable discrimination (the corrected area under the receiver operating characteristic curve was 0.71). The internal validity of the prediction model was acceptable. For practical use, we converted the prediction model to score chart.
Conclusion: The accuracy and the validity of the prediction model were acceptable. This easy-to-use instrument for predicting the 30-day mortality risk after adult heart transplantation would benefit decision-making by classifying recipients according to their mortality risk and allowing optimal allocation of a donor to a recipient for heart transplantation.

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Keywords: heart transplant, mortality, risk, scoring system, prediction models

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Penelitian Klinis

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Model Prognostik Untuk Risiko Mortalitas Tiga Puluh Hari Pasca Transplantasi Jantung Dewasa

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Tujuan: Membuat model prognostik mortalitas 30-hari setelah transplantasi jantung.
Metode: Kami melaporkan pembuatan model prognostik mortalitas 30-hari setelah transplantasi jantung pada pasien dewasa. Analisis regresi logistik digunakan untuk membuat model menggunakan data 1,262 pasien dewasa yang menjalani transplantasi jantung. Akurasi model dinilai dari aspek kalibrasi (kesesuaian antara probabilitas yang diprediksi dengan mortalitas yang diobservasi) serta diskriminasi (kemapuan model untuk membedakan pasien dengan probabilitas kematian yang tinggi dan rendah dalam waktu 30 hari setelah transplantasi). Validitas internal dinilai menggunakan teknik *bootstrapping*.
Results: Usia dan jenis kelamin resipien, diagnosis pre-transplantasi, status transplantasi, waktu tunggu, durasi operasi *bypass* kardiopulmoner, usia dan jenis kelamin donor, serta ketidaksesuaian indeks masa tubuh dan golongan darah donor-resipien terpilih sebagai prediktor independen mortalitas 30-hari setelah transplantasi jantung. Model menunjukkan kalibrasi dan diskriminasi yang cukup baik (area di bawah *the receiver operating characteristic curve* adalah 0.71). Validitas internal model memadai. Untuk penggunaan dalam praktik sehari-hari, kami mentransformasi model logistik menjadi *score chart*.
Conclusion: Model prognostik mortalitas 30-hari setelah transplantasi jantung pada pasien dewasa ini memiliki akurasi dan validitas yang memadai. Model ini dapat membantu pengambilan keputusan melalui stratifikasi resipien berdasarkan probabilitas kematian setelah transplantasi dan memungkinkan alokasi donor transplantasi jantung secara lebih optimal.

(J Kardiol Indones. 2015;36:4-13)

Keywords: transplantasi jantung, mortalitas, risiko, *scoring system*, model prediksi

Introduction

Heart transplantation is the treatment of choice for patients with end-stage heart failure, in particular when it is severely impacting daily life (New York Heart Association class III or IV) despite maximal medical therapy, notably for those with left ventricular ejection fraction of 25% or less.[1-5] Several studies on

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risk factors of mortality in heart transplantation have been published.[2,6] Recently, we have shown the survival risk to be stable over 3 subsequent 5-year periods of heart transplantation.[7] Yet, a comprehensive prediction model for post-transplant survival is lacking.

There are few previous studies which attempted to predict mortality risk,[8,9] but to our knowledge no comprehensive prediction model has been published yet. Some preoperative risk stratification models for heart transplantation have been developed,[9,10] but their predictive accuracy, i.e., calibration and discrimination have not been reported. This limits their generalizability and clinical applicability. Anyanwu and colleagues[8] attempted to derive a simple model for risk stratification after heart transplantation, but unfortunately their study population was too small to allow adequate statistical modelling.

Using a comprehensive database from a previous study including recipient, donor, pre- and peri-operative characteristics,[11] we developed a model for predicting the 30-day mortality risk after adult heart transplantation. The 30-day mortality was chosen as outcome for the model because it is a principal bench mark for successful surgical procedures. While the model should allow accurate identification of patients at high and low 30-day mortality risk it should be easily applicable. Besides providing important information to patients and their families, such model could support cardiac transplant team and surgeons to classify patients according to their mortality risk, and hence support decision on optimal allocation of the donor hearts to patients waiting for heart transplantation.

Methods

Study population

The study population consisted of 1,262 adult patients undergoing primary heart transplantation between March 1989 and December 2004 at the Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany. Donor and recipient were matched for ABO blood-type compatibility and body weight.

Ethics statement

Our institutional review board at the Heart & Diabetes Center North Rhine Westphalia in Bad Oeynhausen, Germany approved this clinical follow-up study. According to general institutional and national regulations of good epidemiological research practice a waiver for informed consent was given. This was because anonimised data were used.

Surgical techniques and immunosuppressive therapy

Donor heart procurement and preservation was achieved by combination of cold cardioplegic arrest, mainly using histidine–buffered tryptophane–ketoglutarate cardioplegia solution (Bretschneider-Custodiol; Kohler Chemie, Alsbach-Hahnlein, Germany) and topical hypothermia. All heart transplantations were performed orthotopically.[12]

Initial immunosuppressive regimen included cyclosporine A, azathioprine, and steroid. After early postoperative phase, double-drug therapy with cyclosporine A and azathioprine was preferred. In case of clinical- or biopsy-proven rejection, steroid-pulse therapy was initiated. Oral steroid maintenance was given only in case of recurrent rejection.

Follow-up and data collection

All survivors were regularly followed-up through our out-patient's service unit or by telephone interview with the patients, their relatives or family/ referring physician. All data of recipients and donors were collected prospectively and maintained on a computerized database. Follow-up was 100% complete. The main outcome was the 30-day mortality after heart transplantation, which was defined as death within 30 days after heart transplantation.

Predictors

Using reported findings on risk factors for early mortality after heart transplantation,[13] we selected the predictors for inclusion in the model. We selected 4 clusters of predictors relating to recipient characteristics, notably age, sex, body mass index (BMI), blood type, pretransplant diagnosis, previous sternotomy, transplant status, waiting time, and need of ventricular assist device; donor characteristics, notably age, sex, BMI, blood type, cause of death, need of cardiopulmonary resuscitation, and catecholamine; donor-recipient mismatch, notably sex, BMI, and blood type; and operative data, notably ischemic time and cardiopulmonary bypass time. All these variables were routinely recorded in our clinical database.

Statistical analysis

Modelling

First, we tested the univariable association of each predictor with 30-day mortality by using chi-square test for categorical variables, and the unpaired 2-tailed *t*-test or Mann-Whitney U test for continuous variables. Predictors with a *p*-value equal to or below 0.25 were selected for inclusion in the subsequent multivariable analysis. In building the final multivariable model we used a hierarchical approach that follows routine practice as close as possible. Our intention was to retain the most easily obtainable clinical predictors with the highest predictive value. For this, we applied a backward stepwise selection procedure and excluded predictors a *p*-value exceeded 0.25. We did not include interaction terms in any step of building the prediction model.[13] We used SPSS software, version 14.0 (SPSS Inc., Chicago, Illinois).

The predictive accuracy

The predictive accuracy of the final model was quantified by using calibration and discrimination measures. Calibration, i.e., the agreement between the predicted probability and the observed death, was assessed graphically (generated in S-Plus Hmisc library "val.prob" function) and tested with the Hosmer–Lemeshow test, for which a *p*-value larger than or equal to 0.10 reflects good calibration.[14] The model's ability to discriminate between discordant survival pairs, i.e., one dies and one survives (discrimination) was determined with the area under the receiver operating characteristic curve area (AUC). AUC illustrates the relation between the false positive rate (1-specificity) and the true-positive rate (sensitivity) of death. It can range from 0.5 (no discrimination) to 1.0 (perfect discrimination).[15]

Validation

A bootstrapping technique was used to assess the internal validity of the model.[13,14] Bootstrap samples were drawn from the full data set with replacement and 100 replications. The backward selection of variables and model fitting was repeated within each bootstrap sample. This bootstrapping technique produced a corrected model's AUC and a correction factor (ranges from 0 to 1). The regression coefficients of the predictors in the model were multiplied by this correction factor to prevent optimism (i.e. too low or too high estimates) in similar future patients.[14,16] For these analyses we used S-plus 6.2 Professional (Insightful Corp., Seattle, WA, USA).

Score chart

To facilitate the application of the prediction model in practice, the final regression model was converted to a score chart. First, the model was first transformed into a nomogram (S-Plus *Hmisc* and *Design* library, function *nomogram*). A nomogram has a reference line for reading the score for each predictor in the model (default range 0-100). Based on this nomogram, we created a simple to use score chart. Once the reader manually totals the scores, the corresponding predicted probabilities of 30-day mortality risk of every individual can be eyeballed at bottom.

Results

Of 1,262 patients, 107 died within 30 days after heart transplantation (30-day mortality risk: 9%, 95%CI: 7% - 11%). The baseline characteristics and their univariable association with the outcome were presented in **Table 1**. We started the multivariable modelling with 14 variables with a univariable *p*-value ≤ 0.25.

Previous sternotomy, donor cause of death, donor-recipient mismatch for sex, and ischemic time subsequently showed a *p*-value > 0.25 for their multivariable association with the outcome, and thus were not included in the final model. Recipient age and sex, pretransplant diagnosis, transplant status, waiting time, donor age and sex, donor-recipient mismatch for BMI and blood type, and cardiopulmonary bypass time composed the final model (**Table 2**).

The prediction model's accuracy and validity

There was no significant difference between the predicted probability and actual death (Hosmer-Lemeshow test of the final model gave a *p*-value of 0.218). This was confirmed by the calibration plot of the model (**Figure 1**). Most of the plotted points were lying close to the diagonal line, demonstrating a good calibration. The final model had an AUC of 0.74 (95% CI: 0.69 – 0.79), which meant that given 100

Table 1 Baseline characteristics and univariable association with 30-day mortality risk after adult heart transplantation.

Variable	Total (n = 1,262)	Death (n = 107)	Survivor (1,155)	P-value
Recipient				
Age (years)*	53.9 (11.1)	57 (10.8)	53.6 (11.1)	0.003
Sex, female	197 (16)	24 (22)	173 (15)	0.04
Body mass index (kg/m^2)*	23.5 (3)	23.2 (3)	23.5 (3)	0.33
Blood type				
A	558 (44)	51 (48)	507 (44)	0.45
B	138 (11)	8 (8)	30 (11)	
O	478 (38)	43 (40)	435 (38)	
AB	88 (7)	5 (5)	83 (7)	
Pretransplant diagnosis				
Dilated cardiomyopathy	631 (50)	40 (37)	591 (51)	0.01
Ischemic cardiomyopathy	543 (43)	55 (51)	488 (42)	
Other	88 (7)	12 (11)	76 (7)	
Previous sternotomy	411 (33)	44 (41)	367 (32)	0.05
Low-urgency status	1141 (90)	101 (94)	1041 (90)	0.15
Waiting time (months)†	3.3 (0.9 – 10.8)	6.4 (1.8 – 13.9)	3.1 (0.9 – 10.4))	0.002
Ventricular assist device	223 (18)	22 (21)	201 (17)	0.41
Donor				
Age (years)*	36.5 (13.6)	41.2 (12.6)	36.1 (13.6)	< 0.001
Sex, female	627 (50)	72 (67)	555 (48)	< 0.001
Body mass index (kg/m^2)*	23.9 (3.4)	24.1 (4.2)	23.9 (3.4)	0.45
Blood type				
A	539 (43)	47 (44)	492 (43)	0.41
B	137 (11)	10 (9)	127 (11)	
O	523 (42)	48 (45)	475 (41)	
AB	63 (5)	2 (2)	61 (5)	
Cause of death				
Trauma	478 (38)	28 (26)	450 (39)	0.002
Cerebrovascular accident	561 (44)	65 (61)	496 (43)	
Other	223 (18)	14 (13)	209 (18)	
Cardiopulmonary resuscitation	192 (15)	16 (15)	176 (15)	0.94
Catecholamine	772 (61)	64 (60)	708 (61)	0.76
Donor-recipient mismatch				
Sex				
Male donor to female recipient	55 (4)	5 (5)	50 (4)	0.04
Female donor to male recipient	485 (38)	53 (50)	432 (37)	
Body mass index ratio				
< 0.8 (undermatch)	79 (6)	8 (8)	71 (6)	0.1
> 1.2 (overmatch)	178 (14)	22 (21)	156 (14)	
Non-identical blood type	74 (6)	9 (8)	65 (6)	0.24
Operative data				
Ischemic time (minutes)*	194.5 (40.4)	206.6 (40.2)	193.4 (40.3)	0.001
Cardiopulmonary bypass time (minutes)*	114 (45.6)	139.6 (67)	111.6 (42.4)	< 0.001

Data presented as n (%) unless otherwise stated.
* Mean (± standard deviation)
† Median (interquartile range)

Table 2: Multivariable association of the predictors in the final prediction model for 30-day mortality risk after adult heart transplantation.

Variable	B	SE	OR	95% CI
Recipient's age (years)	0.015	0.012	1.02	0.99 – 1.04
Recipient sex (female)	0.604	0.276	1.83	1.07 -3.14
Pretransplant diagnosis				
Dilated cardiomyopathy			1	Reference
Ischemic cardiomyopathy	0.287	0.237	1.33	0.84 – 2.12
Others	0.574	0.370	1.78	0.86 – 3.66
Low-urgency status	0.867	0.484	2.38	0.92 – 6.15
Waiting time (months)	0.026	0.012	1.03	1.01 – 1.05
Donor's age (years)	0.018	0.009	1.02	1.01 – 1.04
Donor sex (female)	0.591	0.231	1.81	1.15 – 2.84
Donor-recipient body mass index ratio				
0.8 – 1.2 (match)			1	Reference
< 0.8 (undermatch)	0.189	0.424	1.21	0.53 – 2.77
> 1.2 (overmatch)	0.473	0.272	1.61	0.94 – 2.74
Donor-recipient blood group (non-identical)	0.678	0.408	1.97	0.89 – 4.38
Cardiopulmonary bypass time	0.010	< 0.001	1.010	1.007 – 1.014

SE: standard error; CI: confidence interval; OR: odds ratio

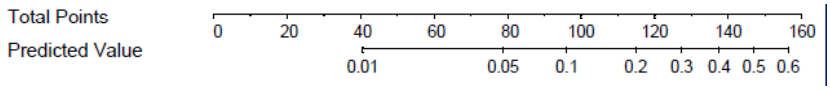

Table 3: Score chart for 30-day mortality risk after adult heart transplantation

RECIPIENT				***DONOR***			
Predictors	***Value***	Score if present	Answer	Predictors	Value	Score if present	Answer
Age	0-15 years > 15 years	0 (age recipient -15) / 3		Age	0-5 years > 5 years	0 (age donor -5) / 2.5	
Sex	Male Female	0 13		Sex	Male Female	0 13	
Ischemic cardiomyopathy	No Yes	0 6		Blood type	Identical Non-identical	0 20	
Other than ischemic and dilated cardiomyopathy	No Yes	0 12		Donor-recipient body mass index ratio	Match Undermatch Overmatch	0 5 11	
Urgency status	High Low	0 18					
Waiting time	None In months	0 waiting time * 0.6					
Cardiopulmonary bypass time (CBP)*	In minutes	CBP time / 4.5					
Recipient total scores				Donor total scores			
Total scores (Recipient + Donor)							

* Estimated by the skill of the surgeon at the facility

The calibration plot illustrates the observed mortality versus the predicted probability of the 30-day mortality after adult heart transplantation. The solid line is a smoothed curve that represents a non-parametric estimate of the relation between the predicted probability and the observed mortality. Ideally, this line fits the diagonal dotted line that represents perfect calibration. The triangles indicate the observed mortality risk per equal-size-deciles of the predicted probability of the 30-day mortality. Distribution of the predicted probabilities is indicated with vertical lines at the bottom.

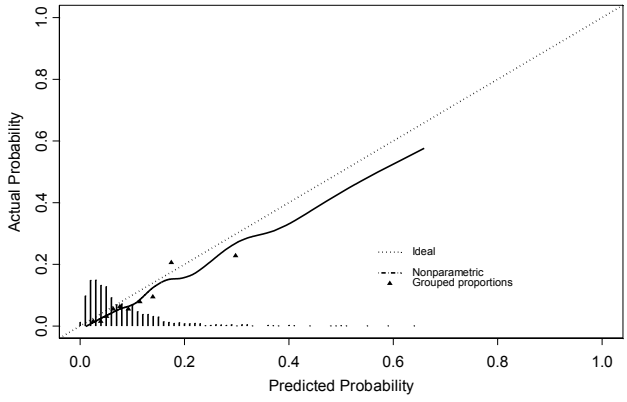

Figure 1. Calibration plot showing the observed mortality versus the predicted probability of the 30-day mortality after adult heart transplantation.

discordant survival pairs, i.e., one dies and one survives, the model could correctly discriminate 74% of them. From the bootstrapping procedure, a correction factor of 0.81 was obtained; showing an acceptable internal validity. The corrected AUC was 0.71. When a predicted probability of 12% was chosen as the cut-off point for stratifying high and low risk of 30-day mortality after the transplantation, the sensitivity was 57% and the specificity was 80% (**Figure 2**).

The score chart and its application

To enhance clinical usefulness of the model we transformed the final regression model into a score chart (**Table 3**). A physician could easily calculate the total points given donor's and recipient's characteristics and afterwards determine the corresponding predicted probability of the 30-day mortality after heart transplantation, which increased steeply for total points of 100 or higher

For example, a 50 year old male patient was diagnosed with dilated cardiomyopathy. The transplantation was not urgent and he had been on the waiting list for 10 months. There was a new donor candidate, a 40 year old female, who had a different blood type from the recipient, and a BMI ratio 0.75 over the recipient. Unfortunately, there was no skilled surgeon at the facility and the estimated CBP time would be around 240 minutes. For this case, the recipient's characteristics scored 89 ((50-15)/3+0+0+0+18+(10*0.6)+(240/4.5)), while the donor's characteristics scored 52 ((40-5)/2.5+13+20+5), with a total score of 141. The corresponding predicted probability of 30-days mortality after heart transplantation was about 44%. If only there was a skilled surgeon who could shorten CBP time to 120 minutes, the recipient's characteristics would score 62.3 ((50-15)/3+0+0+0+18+(10*0.6)+(120/4.5)), while the donor's characteristics remained 52, with a total score of 114.3 and the corresponding predicted probability of 30-days mortality of about 20%.

Discriminative ability of the final prediction model of the 30-day mortality risk after adult heart transplantation. The corrected area under the receiver operator characteristic curve was 0.71, which reflects a good discrimination. Given 5% predicted probability of 30-days mortality, the specificity is 43% and sensitivity is 85% (▲); at 10% predicted probability, the specificity is 75% and sensitivity is 62% (■); and at 12% predicted probability, the specificity is 80% and sensitivity is 57% (●).

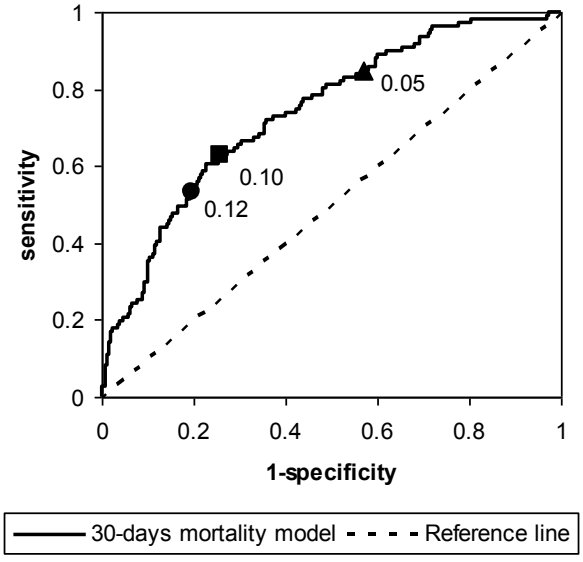

Figure 2. Discriminative ability of the final model for prediction of the 30-day mortality risk after adult heart transplantation.

Discussion

The present analysis based on data from a large cohort of heart transplant patients resulted in a novel simple model that may be used to adequately predict the 30-day mortality risk after adult heart transplantation. We show that recipients' age and sex, pretransplant diagnosis, transplant status, waiting time, donor age and sex, donor-recipient mismatch for BMI and blood type, and cardiopulmonary bypass time are independent predictors for the 30-day mortality risk after adult heart transplantation.

The effect of donor and recipient's sex on the outcome after heart transplantation is a complex issue and remains uncertain. Reed and colleagues[17] suggested that female recipients had decreased survival compared to male recipients. Female recipients have been known to have a higher frequency of rejection and more likely requires inotropic support before surgery. [1,18] Female donors have been also identified as risk factor in many studies. [4,19] It has been suggested that heart from male donors improves results for recipient with pulmonary hypertension due to a greater right ventricular mass in larger male heart as compared with female one. The International Society for Heart & Lung Transplantation registry[5] consistently confirmed that female recipient or donor was a significant risk factor of mortality after heart transplantation. Donor-recipient sex mismatch has been reported to increase the number of rejection episodes and reduce creatinine clearance, survival, and censored survival in the first year after heart transplantation.[20] However, De Santo and colleagues[21] found that recipient or donor sex as well as donor-recipient sex mismatch did not significantly modify the short and mid-term survival, functional recovery and freedom from rejection. They attributed these results to a correct donor-recipient size matching. One may speculate that female donor heart is simply unable to support the circulation of male recipient due to its small size or poor ventricular function. In our study, we found that either recipient or donor sex was an independent predictor of poor outcome, but donor-recipient sex mismatch was not.

We also found that individual BMI of either recipient or donor was not an independent predictor for the 30-day mortality after adult heart transplantation. However, donor-recipient BMI mismatch was an independent predictor for decreased survival. A donor-recipient BMI mismatch can occur in two directions: overmatch and undermatch. An overmatch donor heart should not be transplanted to a recipient whose native heart disease does not result in cardiomegaly or when there has been previous cardiac surgery resulted in rigidity of the mediastinum.[22] Severe overmatch can produce serious restricted physiology (and potentially graft failure) if the donor heart can not be accommodated by maneuvers such as incising the pericardium which allows the donor heart to protrude into the left pleural space. This results the inability to close the chest without cardiac compression. Severe undermatch is important due to concerns that the donor heart will be unable to support the circulation. Besides, there are potential reduced reserves for the load imposed by primary graft dysfunction associated with reperfusion injury or hemodynamically significant rejection.

Heart transplant status and waiting time to heart transplantation remains a crucial issue. We found that heart transplantation with a high-urgency status and shorter waiting time may improve outcome. We believe that heart transplantation should be performed as soon as possible before other end-organ failure in the recipient develops. Cardiopulmonary bypass time may compromise results. Longer cardiopulmonary bypass time leads to severe depletion of clotting factors, and thereby increases mortality through the postoperative complication such as massive bleeding. In a situation where a long cardiopulmonary bypass time due to previous cardiac surgery with expected scar tissue is estimated, the decision on who will perform the heart transplantation should be carefully considered.

Our prediction model is easily applicable in clinical practice since it comprises predictors which are commonly available and easily obtainable pre- or perioperatively for most heart transplant patients. When this model is used pre-operatively, we can estimate CBP time based on history of previous surgery or the presence of skilled surgeon in the facility. This model could also be used to predict the 30-days mortality given complete data of recipient, donor, and the operation. In building our model we followed routine clinical practice as much as possible. For this, we used data obtained from a large heart center with a large study population with a complete follow-up of adult patients undergoing heart transplantation from about 16 subsequent years.

Our prediction model could predict 30-day mortality after adult heart transplantation with acceptable accuracy. The calibration plot shows that

the predicted probability categories are close to the ideal line. Hence, in general our model is rather well calibrated over the complete range of predicted probabilities. After correction for optimism, the AUC changed from 0.74 to 0.71, which shows that AUC of 0.71 is the figure that we could expect from the application of this model in a new population. As always there are opportunities to improve prediction models. In general, including more (important) predictors into the model will improve model's discrimination. Our data was derived from a database which was initially not prepared for research purposes. Therefore, one of our study limitations is that we unfortunately lost information on parameters known to be predictive for outcome after heart transplantation (e.g., recipient renal function, pulmonary function, vascular disease, etc; donor left ventricular hypertrophy, etc.). These presumed predictors may likely causally influence outcome but their additive predictive value are yet unknown. Perhaps, it is possible to include them and other data in an updated model or a further prospective study.

What is more important is determining the optimal cut-off point of the predicted probability for risk stratification because it will influence the amount of misclassification. When we considered 5% predicted probability of 30-days mortality as the cut-off and consequently performing heart transplantation among cases with lower probability, the sensitivity is 85%. **Figure 2** clearly demonstrated that the higher the cut-off point, the higher the specificity, at the cost of lower sensitivity, and vice versa.

Small number of events relative to the high number of potential predictors is a common limitation in many studies. For developing a reliable prediction model, the rule of thumb is that per candidate predictor there should be at least 10 events (1 to 10 ratio).[23] In our cohort, we had 14 potential predictors with 107 events (1 to 7.6). Nevertheless, the bootstrapping procedures showed that the internal validity of the model was acceptable.[13,14] Still, external validation or perhaps even update of our model in a new population, i.e. in USA or other countries, should ideally follow to apply our prediction model to other populations with confidence.

In conclusion, we have developed and validated a prediction model for the 30-day mortality risk after adult heart transplantation by using simple predictors which are generally available in the clinical setting. Our model may serve clinicians in predicting the outcome after adult heart transplantation, who will then provide this information to patients and their family for their consideration. Moreover, the score chart may assist the heart transplant team and surgeon in risk stratification. Thereby, our prediction model can be used for matching donor to recipient and to assist decision on optimal allocation of a donor heart to a patient waiting for heart transplantation.

References

1. Nohria A, Lewis E, Stevenson LW (2002) Medical management of advanced heart failure. JAMA 287: 628-640.
2. Bonet LA (2005) Predictors of mortality following heart transplantation: Spanish Registry of Heart Transplantation 1984-2003. TransplantProc 37: 4006-4010.
3. Drakos SG, Kfoury AG, Gilbert EM, Long JW, Stringham JC, et al. (2007) Multivariate predictors of heart transplantation outcomes in the era of chronic mechanical circulatory support. AnnThoracSurg 83: 62-67.
4. John R, Rajasinghe H, Chen JM, Weinberg AD, Sinha P, et al. (2000) Impact of current management practices on early and late death in more than 500 consecutive cardiac transplant recipients. AnnSurg 232: 302-311.
5. McCarthy JF, McCarthy PM, Massad MG, Cook DJ, Smedira NG, et al. (1998) Risk factors for death after heart transplantation: does a single-center experience correlate with multicenter registries? AnnThoracSurg 65: 1574-1578.
6. Taylor DO, Edwards LB, Boucek MM, Trulock EP, Aurora P, et al. (2007) Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report--2007. JHeart Lung Transplant 26: 769-781.
7. Tjang YS, van der Heijden GJ, Tenderich G, Grobbee DE, Korfer R (2008) Survival analysis in heart transplantation: results from an analysis of 1290 cases in a single center. EurJ-CardiothoracSurg 33: 856-861.
8. Anyanwu AC, Rogers CA, Murday AJ (1999) A simple approach to risk stratification in adult heart transplantation. EurJCardiothoracSurg 16: 424-428.
9. Bourge RC, Naftel DC, Costanzo-Nordin MR, Kirklin JK, Young JB, et al. (1993) Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. JHeart Lung Transplant 12: 549-562.
10. Bourge RC, Kirklin JK, Naftel DC, McGiffin DC (1997) Predicting outcome after cardiac transplantations: lessons from the Cardiac Transplant Research Database. CurrOpinCardiol 12: 136-145.
11. Omoto T, Minami K, Bothig D, Schutt U, Tenderich G, et al.

(2003) Risk factor analysis of orthotopic heart transplantation. Asian CardiovascThoracAnn 11: 33-36.
12. Lower RR, Shumway NE (1960) Studies on orthotopic homotransplantation of the canine heart. SurgForum 11: 18-19.
13. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD (2001) Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. MedDecisMaking 21: 45-56.
14. Harrell FE, Jr., Lee KL, Mark DB (1996) Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. StatMed 15: 361-387.
15. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143: 29-36.
16. Efron B, Tibshirani R (2010) An introduction to the bootstrap. New York, NY Chapman and Hall. .
17. Reed E, Cohen DJ, Barr ML, Ho E, Reemtsma K, et al. (1992) Effect of recipient gender and race on heart and kidney allograft survival. TransplantProc 24: 2670-2671.
18. Crandall BG, Renlund DG, O'Connell JB, Burton NA, Jones KW, et al. (1988) Increased cardiac allograft rejection in female heart transplant recipients. JHeart Transplant 7: 419-423.
19. Del Rizzo DF, Menkis AH, Pflugfelder PW, Novick RJ, McKenzie FN, et al. (1999) The role of donor age and ischemic time on survival following orthotopic heart transplantation. JHeart Lung Transplant 18: 310-319.
20. Prendergast TW, Furukawa S, Beyer AJ, III, Browne BJ, Eisen HJ, et al. (1998) The role of gender in heart transplantation. AnnThoracSurg 65: 88-94.
21. De Santo LS, Marra C, De FM, Amarelli C, Romano G, et al. (2002) The impact of gender on heart transplantation outcomes: a single center experience. ItalHeart J 3: 419-423.
22. Ott GY, Norman DJ, Hosenpud JD, Hershberger RE, Ratkovec RM, et al. (1994) Heart transplantation in patients with previous cardiac operations. Excellent clinical results. JThoracCardiovascSurg 107: 203-209.
23. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. JClinEpidemiol 49: 1373-1379.