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ORIGINAL ARTICLE

Donor–recipient risk assessment tools in heart transplant recipients: the Bad Oeynhausen experience

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Abstract

Aims Some risk assessment tools have been developed to categorize mortality risk in heart transplant recipients, but it is unclear whether these tools can be used interchangeable in different transplant regions.

Methods and results We performed a retrospective single-centre study in 1049 adult German heart transplant recipients under jurisdiction of Eurotransplant. Univariable and multivariable Cox regression analysis was used to generate a risk scoring system. C-statistics were used to compare our score with a US score and a French score regarding their ability to discriminate between 1 year survivors and non-survivors within our study cohort. Of 38 parameters assessed, seven recipient-specific parameters [age, height, dilated cardiomyopathy (DCM), ischaemic cardiomyopathy (ICM), total bilirubin, extracorporeal membrane oxygenation (ECMO), and biventricular assist device/total artificial heart (BVAD/TAH) implant], one donor-specific parameter (cold ischaemic time), and one recipient-independent and donor-independent other parameter (late transplant era) were statistically significant in predicting 1 year mortality. The initial score was generated by using the regression coefficients from the multivariable analysis as follows: 1.70 * ln age − 4.0 * ln height − 0.9 * diagnosis (= 1 if diagnosis = DCM) − 0.67 * diagnosis (= 1 if diagnosis = ICM) + 0.33 * ln total bilirubin + 1.74 * ln cold ischaemic time + 0.98 * mechanical circulatory support (MCS) implant (= 1 if MCS implant = ECMO) + 0.47 * MCS implant (= 1 of MCS implant = BVAD/TAH) − 0.66 * transplant era (= 1 if transplant era = 2017–2018). The initial score was converted into the Bad Oeynhausen (BO) score as a positive integer variable by means of the following formula: BO score = (initial score + 8) * 3. In patients scoring 2 to <7 points (n = 112), 7 to <11 points (n = 580), 11 to <15 points (n = 339), and 15 to 20 points (n = 18), 1 year survival was 93.1%, 84.2%, 66.9%, and 27.8%, respectively. The c-index of our score was 0.73 [95% confidence interval (CI): 0.69–0.77]. Values were in our cohort for the US and French scores 0.66 (95% CI: 0.62–0.70) and 0.63 (95% CI: 0.59–0.67), respectively.

Conclusions Data indicate that our score, but also risk assessment tools from other transplant regions, may be used as a reliable support for risk-adjusted organ allocation and potentially help to improve outcomes in heart transplantation. Further developments will have to include as yet unaccounted risk factors for even more reliable predictions.

Keywords Heart transplantation; Mortality; Survival; Risk adjustment; c-statistics

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Introduction

Since the first successful human heart transplant in 1967, this therapy has become the gold standard treatment for advanced heart failure (HF) refractory to other therapies. Even the implantation of a durable mechanical circulatory support (MCS) device has not outperformed the transplantation of a donor heart. Cardiac transplantation (HTx) has a far better prognosis in the long term. MCS is an alternative in HF patients not eligible for transplantation or when the scarcity of donor organs does not permit timely transplantation.

The results after heart transplantation were improved through refinements of procurement and preservation techniques.[1] Individualized immunosuppressive strategies and thorough post-transplant surveillance have further added to the currently good outcomes.[2,3] Next to these measures, however, beneficial outcome after heart transplantation crucially depends on proper matching of recipient and donor characteristics. Obvious matching criteria include blood group, gender, age, and body height and weight, but experienced clinicians have to thoroughly consider many other features beyond these basics. For example, recipient-specific risk factors include concomitant pulmonary hypertension, sensitization, inotrope dependency, urgency, anatomical features, or previous surgical interventions.[4–6] Among the donor-specific risk factors, higher age, concomitant cardiovascular disease, status post-resuscitation, or gender mismatch have to be discussed. Finally, the distance from the donor hospital to the transplant centre determinates the prospective ischaemic times. The current donor organ shortage encourages physicians to compromise on both recipient and donor-derived risk factors.

Recently, a risk assessment tool has been published by Joyce *et al*.[7] using the United Network for Organ Sharing (UNOS) database. The US transplant score could show that the outcome after heart transplantation correlates to a sum of donor-derived and recipient-derived risk factors. Likewise, a French transplant score has been published,[4] also demonstrating that preoperative donor and recipient parameters can be used to calculate post-operative mortality in heart transplant recipients. However, the UNOS and French regions may be quite different to the Eurotransplant (ET) legislational area and Germany in view of different allocation policies, donation rates, donor organ qualities, and thereby affected waiting times. Such differences may potentially influence the predictive value of single recipient-specific and donor-specific risk factors.

Our study therefore aimed at investigating whether these two earlier risk scores can reliably be used to asses mortality in the largest German heart transplant programme under jurisdiction of ET. Moreover, we aimed to study whether or not the creation of a risk scoring system using our own database would reflect the status of our patients more precisely.

Methods

Patients

All adult heart transplantation procedures (recipient age at transplant $>$ 18 years) performed at the Heart and Diabetes Center North Rhine Westphalia, Ruhr-University Bochum, Bad Oeynhausen, Germany, between January 2000 and August 2018 were analysed. Data were retrieved retrospectively from our prospectively maintained patient database. Informed consent for the scientific use of clinical data is routinely obtained from all patients prior to listing. An ethics committee approval was waived by the local authorities based on the retrospective design of the study. The study was performed according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[8]

Study design

All performed heart transplantation files were screened for specific risk-score relevant data. Briefly, we assessed recipient-specific risk factors that were used by the US and/or French scores such as age, gender, cardiac diagnosis, previous cardiac surgery, pre-transplant waiting times, permanent MCS with a left ventricular assist device (LVAD), extracorporeal membrane oxygenation (ECMO), mechanical ventilation at transplant, renal function, hepatic function, and diabetes mellitus at listing. Moreover, we assessed donor-specific risk factors, such as age and ischaemic times, as well as the combined risk factor gender mismatch. In addition, we assessed the recipient-specific risk factors weight, height, blood group, urgency of transplantation, and transplantation era and the donor-specific risk factors weight, height, cause of death, and resuscitation. Mortality was assessed up to 1 year after heart transplantation. Completeness of mortality data was 100%.

Statistics

We summarized categorical variables as percentages and number of observations. Continuous variables are presented as median with interquartile range (IQR), because all data were non-normally distributed, as checked by the Kolmogorov–Smirnov test. We used the Kruskal–Wallis and χ^2 tests to assess group differences in continuous and categorical variables where appropriate. *P*-values $<$ 0.05 were considered statistically significant.

For the creation of our own risk score, we used univariable and multivariable Cox regression analysis. Every univariate variable showing significant association with 1 year mortality was then tested in a multivariable logistic regression model and removed stepwise if no significant influence was proved. Only those variables that were significantly associated with 1 year mortality remained in the multivariable model. For this purpose, in a first step, *P*-values $<$ 0.05 were considered statistically significant. In a second step, the Benjamini and Hochberg false discovery rate method was applied to account for multiple testing.[9] The false recovery rate was set at 10%. Continuous

parameters were logarithmically transformed before analysis. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazard assumption of the Cox regression model was tested for each predictive variable by testing the significance of the interaction terms between the variable and follow-up time in the Cox regression model predicting 1 year mortality. The Bad Oeynhausen (BO) transplant risk score was then generated by summing the products of the recipient and donor variables included in the final model and their β estimations. The BO score was validated using bootstrapping by resampling the prediction population 1000 times with replacement. To generate low-risk to high-risk groupings, we divided the BO score into four strata according to patients' scoring points. We generated the Kaplan–Meier curves by risk strata for the frequency of 1 year survival as a function of time since transplantation. The log-rank test was used to test for differences in survival rates between subgroups. Receiver operating characteristic (ROC) curves and the c-statistics were used to assess the ability of the BO score and the two other scores to predict 1 year mortality of our study cohort. We also assessed the ability of the three scores to predict 30 day mortality.

We applied the statistical software package IBM SPSS, Version 27 (IBM Corp, Armonk, NY, USA) to perform the analyses.

Results

Characteristics of the study cohort

A total of 1386 heart transplant procedures were performed between January 2000 and August 2018. Of these, 1049 procedures were ultimately analysed (Supporting Information, *Figure S1*). The other 337 procedures were excluded because they either involved paediatric cases (recipient age $<$ 18 years) or had incomplete datasets for calculation of the scores. Characteristics of the study cohort are shown in *Table 1*.

Table 1 Selected patient characteristics in the entire study cohort and in subgroups with different Bad Oeynhausen score points

	Entire cohort n = 1049	BO score 2 to <7 points n = 112	BO score 7 to <11 points n = 580	BO score 11 to <15 points n = 339	BO score 15 to 20 points n = 18	*P*-value
Age (years)[a]	54 (44;61)	31 (22;38)	53 (45;54)	59 (51;64)	59 (52;64)	<0.001
Male recipients[b]	831 79.2	90 (80.4)	473 (81.6)	257 (75.8)	11 (61.1)	0.043
Height (cm)[a]	176 (170;182)	180 (173;186)	177 (172;182)	174 (168;180)	170 (166;176)	<0.001
Weight (kg)[a]	75 (65;85)	73 (61;91)	76 (66;86)	73 (65;84)	70 (65;80)	0.06
Diagnosis						
Dilated cardiomyopathy[b]	579 (55.2)	103 (92.0)	365 (63.0)	108 (31.9)	3 (16.7)	<0.001
Ischaemic cardiomyopathy[b]	388 (37.0)	9 (8.0)	199 (34.3)	175 (51.6)	5 (27.8)	<0.001
Other diagnoses[b]	82 (7.8)	0 (0.0)	16 (2.8)	56 (16.5)	10 (55.6)	<0.001
Diabetes mellitus[b]	110 (10.5)	3 (2.7)	62 (10.7)	42 (12.4)	3 (16.7)	0.025
GFR (mL/min/1.73 m^2)[a]	58.3 (41.6;77.3)	77.7 (58.7;104.0)	58.2 (41.6;74.5)	55.4 (39.7;72.5)	62.1 (26.5;75.7)	<0.001
Bilirubin (μmol/L)[a]	10.8 (7.2;17.0)	8.4 (6.5;13.0)	9.6 (6.7;14.9)	13.7 (9.2;20.4)	38.1 (14.0;89.5)	<0.001
Warm ischaemic time (min)[a]	44 (36;55)	40 (31;50)	43 (36;52)	48 (40;61)	63 (41;74)	<0.001
Cold ischaemic time (min)[a]	218 (187;247)	187 (161;228)	206 (180;233)	239 (216;270)	270 (232;292)	<0.001
Previous cardiac surgery[b]	533 (50.8)	37 (33.0)	253 (43.6)	230 (67.8)	13 (72.2)	0.001
Mechanical ventilation[b]	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.6)	0.0	0.24
MCS implant						
ECMO[b]	13 (1.2)	0 (0.0)	3 (0.5)	5 (1.5)	5 (27.8)	<0.001
LVAD[b]	276 (26.3)	32 (28.7)	153 (26.4)	90 (26.6)	1 (5.6)	0.22
BVAD/TAH[b]	108 (10.3)	3 (2.7)	30 (5.2)	66 (19.4)	9 (50.0)	<0.001
High-urgency listing	874 (83.3)	109 (97.3)	497 (85.7)	252 (74.3)	16 (88.9)	<0.001
Donor age (years)[a]	44 (31;51)	30 (21;42)	44 (32;51)	46 (36;53)	50 (41;53)	<0.001
Male donors[b]	499 (47.6)	62 (55.4)	281 (48.5)	150 (44.2)	6 (33.3)	0.13
Donor height (cm)[a]	172 (167;180)	175 (170;182)	174 (168;180)	170 (165;178)	170 (167;174)	<0.001
Donor weight (kg)[a]	75 (68;85)	75 (67;85)	75 (68;85)	75 (65;85)	75 (68;85)	0.30
Transplant era						
2000–2004[b]	192 (18.3)	22 (19.6)	110 (19.0)	59 (17.4)	1 (5.5)	0.49
2005–2008[b]	185 (17.6)	23 (20.5)	103 (17.8)	54 (15.9)	5 (27.8)	0.46
2009–2012[b]	263 (25.1)	17 (15.2)	137 (23.6)	100 (29.5)	9 (50.0)	0.001
2013–2016[b]	292 (27.8)	23 (20.5)	148 (25.5)	118 (34.8)	3 (16.7)	0.003
2017–2018[b]	117 (11.2)	27 (24.1)	82 (14.1)	8 (2.4)	0 (0.0)	<0.001

BO, Bad Oeynhausen; BVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; LVAD, left ventricular assist device; MCS, mechanical circulatory support; TAH, total artificial heart.
[a]Median with 25th and 75th percentiles.
[b]Number and per cent.

Score generation

Results of the univariable and multivariable Cox regression analysis are presented in *Table 2*. Even after applying the false discovery rate method by Benjamini and Hochberg to account for the issue of multiple testing, all results with *P*-values < 0.05 in the univariable and multivariable Cox regression analysis remained significant.

Recipient age and height, bilirubin, diagnoses such as dilated cardiomyopathy (DCM) and ischaemic cardiomyopathy (ICM), and MCS implants such as ECMO and biventricular assist device/total artificial heart (BVAD/TAH) were significant predictors of 1 year mortality. Cold ischaemic time was the only donor-specific predictor. Late transplant era was a recipient-independent and donor-independent predictor. The initial score was generated by using the regression coefficients from the multivariable analysis as follows: 1.70 * ln age − 4.0 * ln height − 0.9 * diagnosis (= 1 if diagnosis = DCM) − 0.67 * diagnosis (= 1 if diagnosis = ICM) + 0.33 * ln total bilirubin + 1.74 * ln cold ischaemic time + 0.98 * MCS implant (= 1 if MCS implant = ECMO) + 0.47 * MCS implant (= 1 of MCS implant = BVAD/TAH) − 0.66 * transplant era (= 1 if transplant era = 2017–2018). The proportionality of hazard assumption was satisfied for all predictor variables ($P > 0.05$) (continuous parameters were categorized by quartiles). Bootstrapping did not change results of the multivariable analysis substantially, the only exception being that ECMO implant became borderline significant (Supporting Information, *Table S1*). It is however noteworthy that only 1.2% of the study cohort received ECMO implants.

Table 2 Univariable and multivariable correlates for 1 year survival after heart transplantation

	Univariable		Multivariable		
	P-value	HR (95% CI)	*P*-value	HR (95% CI)	β estimation
Ln age	<0.001	3.78 (2.10–6.78)	<0.001	5.46 (2.94–10.16)	1.70
Male recipients	0.18	0.81 (0.59–1.10)			
Ln height	<0.001	0.02 (0.003–0.19)	<0.001	0.02 (0.00–0.14)	−4.00
Ln weight	0.49	1.27 (0.65–2.48)			
Diagnosis (reference: other diagnoses)					
Dilated cardiomyopathy	<0.001	0.33 (0.2–0.49)	<0.001	0.41 (0.27–0.62)	−0.90
Ischaemic cardiomyopathy	0.001	0.44 (0.47–0.71)	0.003	0.51 (0.33–0.79)	−0.67
Diabetes mellitus	0.89	0.97 (0.62–1.51)			
Ln GFR	0.016	0.72 (0.55–0.94)			
Ln bilirubin	<0.001	1.59 (1.30–1.95)	0.003	1.39 (1.12–1.73)	0.33
Ln warm ischaemic time	<0.001	2.17 (1.43–3.30)			
Ln cold ischaemic time	<0.001	5.80 (2.96–11.36)	<0.001	5.67 (2.77–11.62)	1.74
Previous cardiac surgery	<0.001	1.83 (1.40–2.42)			
Mechanical ventilation	0.003	8.04 (1.99–32.46)			
ECMO	<0.001	4.53 (2.24–9.19)	0.020	2.67 (1.17–6.10)	0.98
LVAD	0.40	1.14 (0.85–1.53)			
BVAD/TAH	<0.001	1.95 (1.37–2.77)	0.014	1.61 (1.10–2.34)	0.47
Urgency of transplantation	0.11	0.77 (0.55–1.06)			
Blood Group A	0.18	1.20 (0.92–1.56)			
Blood Group B	0.59	0.89 (0.58–1.36)			
Blood Group AB	0.43	1.21 (0.75–1.97)			
Blood Group 0	0.14	0.81 (0.60–1.08)			
Ln waiting time	0.69	1.02 (0.94–1.11)			
Ln donor age	<0.001	1.02 (0.94–1.11)			
Male donors	0.38	0.89 (0.68–1.16)			
Ln donor height	0.35	0.32 (0.03–3.50)			
Ln donor weight	0.24	0.66 (0.33–1.33)			
Donor resuscitation	0.68	0.94 (0.68–1.29)			
Donor diagnosis					
Cerebral trauma	0.34	0.86 (0.64–1.16)			
Cerebral bleeding	0.08	1.27 (0.97–1.65)			
Cerebral ischaemia	0.33	0.84 (0.58–1.21)			
Others	0.77	0.92 (0.54–1.59)			
Recipient/donor mismatch	0.40	0.90 (0.70–1.16)			
Transplant era					
2000–2004	0.30	0.83 (0.58–1.18)			
2005–2008	0.85	1.03 (0.74–1.45)			
2009–2012	0.026	1.38 (1.04–1.83)			
2013–2016	0.94	0.99 (0.74–1.33)			
2017–2018	0.040	0.53 (0.29–0.97)	0.034	0.52 (0.28–0.95)	−0.66

BVAD, biventricular assist device; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; HR, hazard ratio; Ln, natural logarithm; LVAD, left ventricular assist device; TAH, total artificial heart.

The initial score was then converted into the BO score as a positive integer variable by means of the following formula: BO score = (initial score + 8) * 3. The BO score ranged from 2.3 to 19.7, with a median value of 10 (*Figure 1*). The c-index of the BO score was 0.73 (95% CI: 0.69–0.77). *Table 1* and *Figure 2* present baseline characteristics and 1 year survival rates, respectively, by BO score strata. Data demonstrate significant differences between BO score strata in several preoperative characteristics. The estimated 1 year overall survival after transplantation using the Kaplan–Meier curves

Figure 1 Bad Oeynhausen risk score distribution in the study cohort (n = 1049).

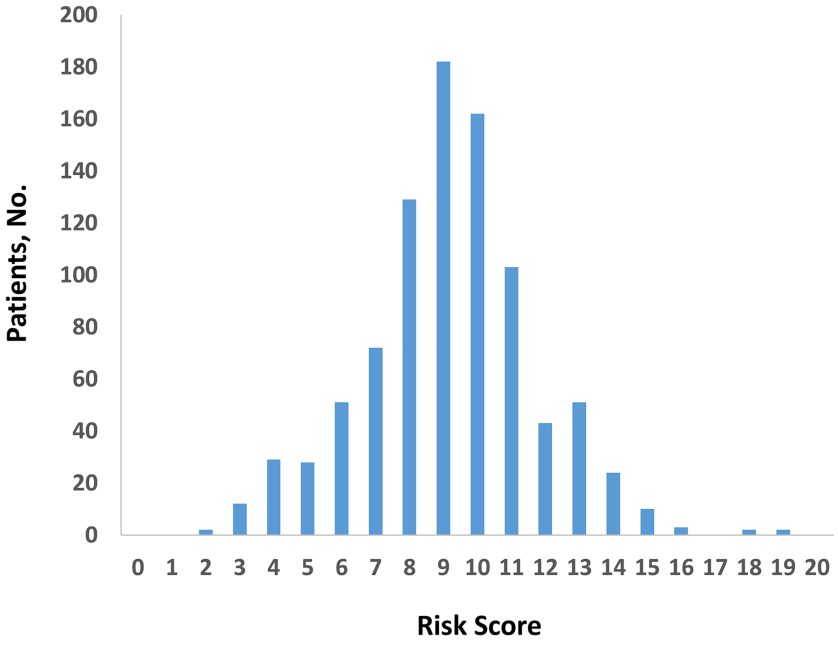
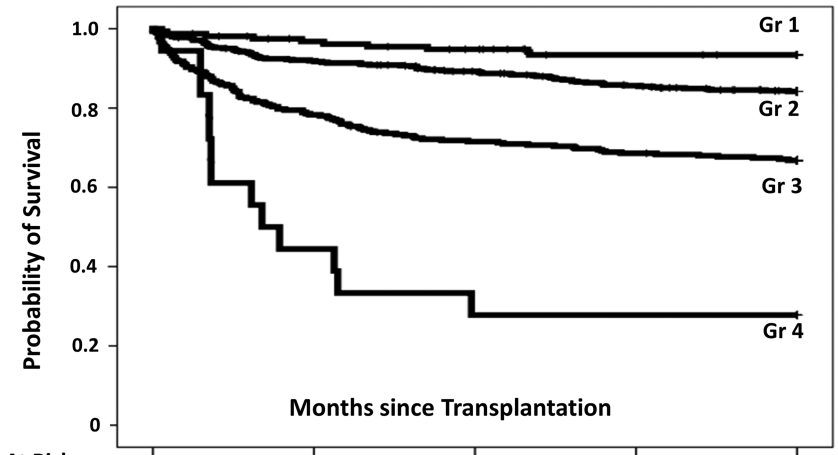


Figure 2 One-year overall survival in heart transplant recipients according to Bad Oeynhausen risk score strata; Groups 1–4: patients scoring 2 to <7 points, 7 to <11 points, 11 to <15 points, and 15 to 20 points (log-rank test: $P < 0.001$).



At Risk:	0	3	6	9	12
Gr 1:	112	101	96	87	85
Gr 2:	580	516	489	463	441
Gr 3:	339	266	241	231	224
Gr 4:	18	5	5	5	5

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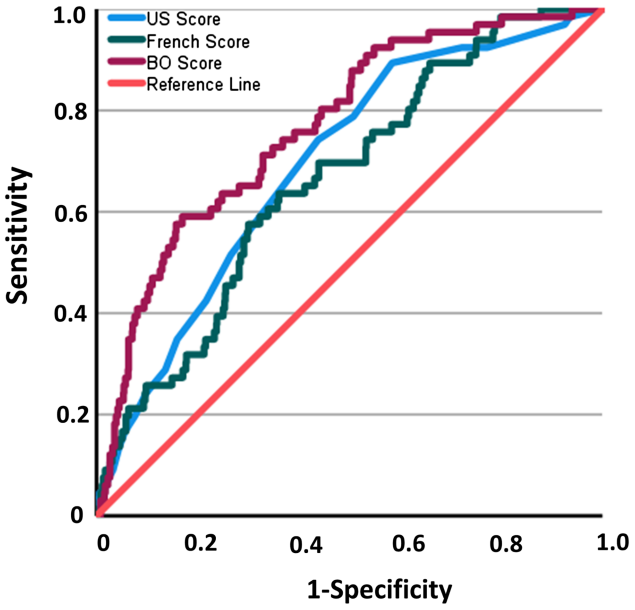
Table 3 Mean values, standard deviation, and c-statistics of the Bad Oeynhausen score, the US score, and the French score

Risk score	BO cohort Mean (SD)	BO cohort c-index	Prediction cohort[a] c-index	Validation cohort[a] c-index
BO score	10.0 (2.4)	0.73 (95% CI: 0.69–0.77)	—	—
US score	6.6 (4.6)	0.66 (95% CI: 0.62–0.70)	0.64 (95% CI: no data)	0.62 (95% CI: no data)
French score	13.5 (5.6)	0.63 (95% CI: 0.59–0.67)	0.67 (95% CI: 0.64–0.69)	0.64 (95% CI: 0.59–0.69)

BO, Bad Oeynhausen; CI, confidence interval; SD, standard deviation.
[a]indicates results obtained in the original prediction and validation cohorts.

Figure 3 Receiver operating characteristics curve for the BO score, the US score, and the French score to predict 1 year mortality of our study cohort of heart transplant recipients (n = 1049). BO, Bad Oeynhausen.



was 78.4% (95% CI: 77.7–79.1%). In patients scoring 2 to <7 points, 7 to <11 points, 11 to <15 points, and 15 to 20 points, 1 year survival was 93.1%, 84.2%, 66.9%, and 27.8%, respectively, indicating that the BO score could reliably discriminate between high and low post-operative 1 year mortality risk.

Comparison of the Bad Oeynhausen score with the US and French scores

The ability of the BO score to predict 1 year mortality is presented in *Table 3*. According to the c-statistics, the BO score indicates a good model of predicting 1 year mortality [0.73 (95% CI: 0.69–0.77)]. In our study cohort, the US and French scores resulted in c-indices of 0.66 (95% CI: 0.62–0.70) and 0.63 (95% CI: 0.59–0.67), respectively, which are similar to the indices in their validation cohorts (*Table 3*). *Figure 3* illustrates graphically in our study cohort the area under the ROC curve obtained with the three scores. The BO score resulted in a smaller standard deviation than the US and French scores (*Table 3*), indicating that few parameters have a substantial impact on the BO score. Because the majority of our patients had a body height within the normal range, suffered from DCM or ICM, did not receive ECMO or BVAD/TAH implants, and had normal hepatic function, we also performed an analysis where we restricted the predictor variables to recipient age and cold ischaemic time (simplified BO score: 1.46 * ln age + 1.96 * ln cold ischaemic time). This resulted in a c-index of 0.67 (95% CI: 0.60–0.74). Categorization of age and cold ischaemic time did not improve study results substantially (data not shown).

Thirty-day mortality was 6.3% (n = 66). The c-index regarding 30 day mortality was in our study cohort for the BO score, the US score, and the French score 0.77 (95% CI: 0.71–0.82), 0.69 (95% CI: 0.63–0.75), and 0.66 (95% CI: 0.60–0.73), respectively.

Discussion

The present study has several major findings. First, the BO score indicated a good model for predicting 30 day and 1 year mortality in our study cohort. Second, the ability to predict mortality primarily depended on recipient risk factors rather than on donor risk factors, with the exception of cold ischaemic time. Third, the US and French scores resulted in a similar discrimination of survivors and non-survivors in our study cohort as in their respective validation cohorts.

Donor heart allocation in Germany follows the jurisdiction of the ET foundation and is based on urgency status, that is, the regular 'transplantable' (T) and the 'high-urgency' (HU) status, as well as the collected waiting time. Because the vast majority of our patients were transplanted in the HU status (*Table 1*), it is not surprising that in our model this parameter was not an independent predictor of 1 year mortality.

Given the mostly HU status, German transplant physicians have to compromise on donor-specific and recipient-specific risk factors and the acceptance of a donor heart offer is frequently based on personal experience, recent

centre-specific outcomes, and associated risk tolerance. There is a donor scoring system based on ET data, which utilizes 10 pre-procurement donor factors predicting donor heart discard and identifying a cut-off associated with recipient 3 year post-transplant mortality.[5] Although the utilized donor data are relatively old and date back to the years 2005–2008, and the calculated outcomes may not necessarily account for transplant candidate characteristics nowadays, this donor scoring system may be helpful in at least roughly assessing donor-derived risk. This assumption is supported by the fact that cold ischaemic time remained the only donor-specific risk factor in the BO score. The US and French scores also consider a donor age greater than 55 years as a risk factor for survival. In our study cohort, however, strict matching of recipient/donor age may have resulted in donor age becoming non-significant in the multivariable analysis. Nevertheless, we still believe that advanced donor age may represent a certain risk for post-transplant outcome.

Only a few risk factors such as recipient age and diagnosis are identical in all three risk scores. In our cohort, age and ischaemic time were among the parameters that varied the most and thus had the greatest influence on clinical outcome. Data are in line with the clinical experience that advanced recipient age is an important risk factor of poor clinical outcome and that short organ preservation times are crucial for successful transplant outcomes. Long ischaemic time is also an important risk factor in the US score, but not in the French score. In our cohort and the US cohort, about 25% and 20% of patients, respectively, had ischaemic times $>$ 4 h. Because no data on the frequency of long ischaemic times are presented in the French paper,[4] it remains unclear whether or not statistical power was sufficient to detect a potential impact of ischaemic time on clinical outcome. Notably, overall 1 year survival in both our and the French cohort was only 78%,[4] but was 88% in the US cohort.[7] Obviously, unknown risk factors remain, and this assumption is also supported by the fact that, even in the prediction cohorts, the c-index of the three risk scores ranged between 0.64 and 0.73 only. Several obvious recipient risk factors such as transplant indication, advanced age, MCS support, and poor liver and kidney function were already considered in all three risk scores. Notably, signs of secondary organ failure are considered for warranting HU status in the ET region. We consider MCS support as a risk factor for outcome, as heart transplants in MCS patients are technically challenging not only because of the status post previous surgery. Still, clear-cut data comparing heart transplants in non-MCS patients with and without any previous cardio-thoracic surgery will help to elucidate such assumptions. We felt that particularly short-term MCS devices render heart transplantation at risk for frequently disturbed coagulation system. This remains speculation as we bridge candidates very seldom by ECMO or Impella, owing to the fairly long waiting times in Germany.[10]

It is hard to clearly delineate why our transplant procedures involve a higher risk compared with the US data.[7] Although a highly important issue, particularly when discussing ischaemic times, we may assume that surgical quality per se may not be the reason for differences between our and the US data. Warm ischaemic times could be indicative, but were seemingly acceptable here. Although our results after heart transplantation are comparable with the French data,[4] our current analysis impressively demonstrates that we have accepted a relatively high collective risk. It is noteworthy that the dramatic organ shortage in Germany has led to a waitlist mortality rate of approximately 20% per year and roughly 70% of all donor heart offers are allocated to HU-status patients.[11] This current allocation algorithm does not follow the German legislation for organ transplantation, which demands evaluation of the prospective transplant benefit in a particular candidate in addition to urgency. For this purpose, the German authorities are currently developing a cardiac allocation score (CAS). Similar to the lung allocation score (LAS),[12] it shall facilitate donor organ allocation respecting both urgency and transplant benefit, that is, the calculated 1 year survival after transplant. However, neither the LAS nor the currently discussed CAS model includes donor organ quality aspects and their particular effects on transplant outcome. Patient survival after heart transplantation, however, is a quality indicator for transplant programmes.

A few other risk assessment tools are also available. The Seattle Heart Failure Model (SHFM) gained a lot of attention because it is a relatively simple calculator predicting the impact of distinct therapeutic options on 1, 2, and 5 year survival of HF patients.[13] Although durable MCS is an included option in the calculations, the SHFM does not specifically consider cardiac transplantation. The Index for Mortality Prediction After Cardiac Transplantation (IMPACT) has been validated in a large cohort of US heart transplant patients.[5,14] IMPACT may accurately predict post-transplant survival, but, as a matter of methodology, it is highly specific to the US transplant policies only and may not directly apply to Germany and the ET area. Furthermore, the novel MCS therapy modalities, for example, small intrapericardially implantable ventricular assist devices, may have a distinct impact on transplant outcomes compared with the more 'historical' pumps, but they are not accounted for in IMPACT. Notably, the recent ET data indicate that MCS patients account for almost 50% of all transplanted patients. Neither the SHFM nor IMPACT includes donor organ-associated risk.[14,15]

Our study has both strengths and limitations. Strengths include the relatively large dataset from a high-volume centre, the creation of a risk score for patients in the ET region, and the comparison of three risk scores from different transplant regions. One limitation is that generalizability of the BO score may be limited due to centre-specific

characteristics. This may also explain the slightly better c-index of the BO score compared with the c-indices of the US score and the French score. Because the latter scores are based on multicentric prediction cohorts, the risk of unexplained confounding may be higher than in a monocentric prediction cohort. A further limitation is that machine learning algorithms such as random forest or long short-term memory network may potentially result in better accuracy than conventional logistic regression. Likewise, we do not present a validation cohort. According to the TRIPOD statement,[8] however, internal validation is very important, and this is what we did by performing bootstrapping. External validation should use samples from a later period or another hospital or country. Therefore, future studies have to investigate the reliability of our score for other cohorts. Notably, a strength of our investigation is that we could confirm reliability of the US and French scores for the ET region. It should also be mentioned that some pre-transplant data, such as intra-aortic balloon pump implants and inotropic support, were not assessed. However, more than 80% of our patients were on inotropic support, because this is a prerequisite for high-urgency listing. Additionally, no data regarding morbidity and long-term mortality are presented. It is noteworthy that mortality in heart transplant recipients is highest within the first post-operative year. One-year mortality is thus the most important outcome variable. Moreover, the assessment of preoperative parameters may be limited in predicting mortality beyond the first post-operative year because other parameters such as medication adherence and lifestyle factors may become more important. This assumption is in line with higher c-indices for 30 day mortality than for 1 year mortality. Finally, the BO score may become less reliable with the introduction of a new allocation score or the development of novel MCS therapy modalities.

In conclusion, our current study has revealed that risk assessment tools may accurately categorize the risk of heart transplantations in international donor–recipient combinations. The tools may easily support decision-making during donor heart allocation also in the ET region. Future studies have to show whether or not region-specific risk scores are able to improve discrimination ability. Further evaluation is also needed regarding implementation of these tools into a centre transplant policy helps to improve heart transplantation outcomes, excluding excessive cumulative risk. Further developments will have to include as yet unaccounted risk factors for even more reliable predictions.

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Conflict of interest

None of the authors declared a conflict of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Study flowchart.
Table S1. Results of the bootstrapped regression for 1-year mortality using 1,000 samples with random replacement.

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