ORIGINAL ARTICLE

The adapted Heart Donor Score

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SUMMARY

The Heart Donor Score (HDS) predicts donor organ discard for medical reasons and survival after heart transplantation (HTX) in the Eurotransplant allocation system. Our aim was to adapt the HDS for application in the United Network for Organ Sharing (UNOS) registry. To adjust for differences between the Eurotransplant and UNOS registries, the "adapted HDS" was created (aHDS) by exclusion of the covariates "valve function," "left-ventricular hypertrophy," and exclusion of "drug abuse" from the variable "compromised history." Two datasets were analyzed to evaluate associations of the aHDS with donor organ discard (n = 70 948) and survival (n = 19 279). The aHDS was significantly associated with donor organ discard [odds ratio 2.72, 95% confidence interval (CI) 2.68–2.76, $P < 0.001$; c-statistic: 0.937). The score performed comparably in donors <60 and ≥60 years of age. The aHDS was a significant predictor of survival as evaluated by univariate Cox proportional hazards analysis (hazard ratio 1.04, 95% CI 1.01–1.07, $P = 0.023$), although the association lost significance in a multivariable model. The aHDS predicts donor organ discard. Negative effects of most aHDS components on survival are likely eliminated by highly accurate donor selection processes.

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Introduction

Adult heart transplantation (HTX) is still limited by scarcity of available donor organs [1–3]. During the last decades, efforts have been made to extend the donor organ pool by increasing acceptance rates of marginal quality donors, characterized by older age, left-ventricular hypertrophy (LVH), or episodes of cardiac arrest, among others [4]. However, a large percentage of marginal quality donor organs is still discarded by heart transplant centers, likely due to concerns about potential penalization of sub-optimal outcomes after HTX [5].

To increase the efficiency of marginal quality donor organ utilization in the Eurotransplant allocation system, the Heart Donor Score (HDS) was developed by Smits *et al.* [6]. In the original publication, the HDS was demonstrated to be a predictor of donor organ discard for medical reasons and survival after HTX.

Our aim was to create an "adapted HDS" (aHDS) for application in the United Network for Organ Sharing (UNOS) registry. We were interested in the evaluation of donor characteristics that influence the decision processes toward acceptance or discard of donor hearts, the comparison of decision processes between Europe and the United States, and the evaluation of associations between these donor characteristics and survival after HTX.

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Patients and methods

The original HDS includes 12 donor characteristics: age, cause of death [cranial trauma, benign brain tumor, malignant brain tumor, circulatory, cerebrovascular accident (CVA), drug overdose, intoxication, carbon monoxide intoxication, meningitis, respiratory, subarachnoid bleeding, sepsis], compromised history (history of drug abuse, malignancy, sepsis, meningitis, positivity for hepatitis B surface antigen, hepatitis B core antibodies, or hepatitis C virus antibodies), hypertension, cardiac arrest, left-ventricular ejection fraction (LVEF), valve function, LVH, coronary angiography, serum sodium, norepinephrine support, and dopamine/dobutamine support [6].

For this analysis, Standard Transplant Analysis and Research files were requested from the UNOS registry. Exemption of full review was granted by the institutional review board of the Medical University of Vienna due to the de-identified nature of the datasets used for statistical analysis. To evaluate the score's performance in the prediction of donor organ discard for medical reasons, we worked with a dataset that included deceased donor organ offers reported to the UNOS registry as of June 8, 2018. To evaluate the score's performance in the prediction of survival after HTX, we analyzed a second dataset that included recipients of primary orthotopic HTX.

Creation of the adapted Heart Donor Score

Exploratory analyses of both UNOS datasets revealed substantial differences in comparison with the Eurotransplant original cohort. First, the HDS components "valve function" and "LVH" are exclusively reported for donors with LVEF <50% in the UNOS registry. As a consequence, both characteristics were missing in >95% of donors [7]. Second, the proportions of donors with a history of drug abuse were substantially higher in the UNOS registry in comparison with the Eurotransplant original cohort, a finding that is in line with recent reports about the "opioid crisis" in the United States [8].

Considering these differences, we created an "adapted HDS" (aHDS) by performing a multivariable logistic regression model based on the UNOS registry data [9,10]. The donor organ discard status ("accepted" versus "discarded for medical reasons") was defined as the outcome variable, and the original HDS components were included as covariates. The covariates "valve function" and "LVH" were not considered, and the covariate "compromised history" was redefined without "history of drug abuse." Beta estimates (log odds ratios) of this multivariable regression model were then used as points for calculation of the aHDS: Depending on the donor's individual covariate values the respective beta estimates were summed up to result in the individual aHDS value.

Prediction of donor organ discard for medical reasons

Figure S1 shows the derivation of the study cohort for this analysis. In the UNOS registry, several components of the aHDS were only available between the 1st of July, 2004 and the 28th of February, 2015. Therefore, all donors reported before and after this period were excluded. Moreover, all donors for donation after circulatory death and donors discarded for reasons unrelated to organ quality were excluded. Donors who succumbed to carbon monoxide intoxication were exceedingly rare ($n = 3$) and therefore excluded as well. Moreover, the aHDS components "cause of death" and "cardiac arrest" were missing for 100 donors and for one donor, respectively. After exclusion of all donors with missing values, the resultant study cohort for this analysis was comprised of 70 948 donors.

Univariate logistic regression analysis was performed to evaluate the aHDS' association with donor organ discard. Additionally, the previously described multivariable logistic regression model was used to evaluate associations of individual aHDS components with donor organ discard for medical reasons. A receiver operating characteristic curve was generated to visualize the aHDS' predictive performance. The area under the receiver operating characteristic curve (*c*-statistic) was calculated to quantify the aHDS' accuracy in the discrimination between accepted and discarded donor organs.

Additionally, sub-group analyses were conducted to analyze the performance of the aHDS in donors <60 and ≥60 years of age.

Prediction of survival after HTX

Figure S2 shows the derivation of the study cohort for this analysis. Recipients transplanted before the 1st of July, 2004 and after the 28th of February, 2015 were excluded due to the absence of several aHDS components in these periods, as described previously. All recipients under the age of 18 years, recipients of retransplants, multiorgan transplants, heterotopic transplants, and donation after circulatory death transplants were excluded. A single patient received a heart from a

donor who succumbed due to carbon monoxide intoxication; therefore, this patient was excluded as well. After exclusion of all patients with missing variables, the resultant study cohort for this analysis consisted of 19 279 HTX recipients.

Survival up to 1 year after HTX was defined as the primary outcome variable for this analysis. Death and re-transplantation were considered as equal events. Patients were censored 1 year after HTX or on the 8th of June 2018, respectively. Survival of patients receiving a donor with an aHDS value below the median versus equal to or above the median was visualized using Kaplan–Meier survival curves. The log-rank test was used to compare survival curves of both groups. Univariate and multivariable Cox proportional hazards regression models were created to evaluate associations between the aHDS and survival after HTX. The *c*-statistic was calculated to quantify the aHDS' ability to predict survival after HTX. Additionally, a second multivariable Cox proportional hazards regression model including individual aHDS components was generated. Based on clinical experience and published evidence, we determined clinically relevant covariables to be incorporated in both multivariable models, including the components of the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) [11,12]. Proportions of explained variation (PEV) of individual predictors of the second multivariable model were calculated using the method of Schemper and Henderson [13]. The variable "creatinine clearance" was calculated using the Cockcroft–Gault method [14].

Additionally, Kaplan–Meier survival curves out to 10 years after HTX were generated to compare long-term survival rates between recipients of a donor with an aHDS value equal to or above the median versus below the median.

Continuous variables are described by mean values [±standard deviations (SD)]. Variables with skew distributions are depicted by the median (quartiles). Absolute frequencies and percentages are used for the description of categorical variables. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., 2016. Cary, NC, USA). Two-sided *P*-values <0.05 were considered statistically significant.

Results

Prediction of donor organ discard for medical reasons

The mean aHDS value was 3.62 (±1.36) for accepted organs and 8.67 (±2.84) for discarded organs, while the median aHDS values amounted to 3.59 (2.97–4.06) and 8.59 (6.76–11.11), respectively (Table 1, Fig. 1). Donors with an aHDS values ≥5 were more frequently discarded than accepted (Fig. 1).

The majority of accepted donors was younger than 45 years of age (84.5%; Table 1). Cranial trauma was the most common cause of death for accepted donors (58.1%), while discarded donors most commonly succumbed to CVA (51.4%). Notably, the proportions of donors with compromised history were substantially higher in the UNOS registry when compared with the Eurotransplant cohort as described in the original publication (accepted donors: 9.8% vs. 2.1%) [6]. Normal coronary angiography results were more common for accepted donors when compared with discarded donors (20.5% vs. 2.2%). High dosages of norepinephrine and dopamine/dobutamine support were rare for both accepted and discarded donors.

Univariate logistic regression analysis demonstrated that the aHDS was significantly associated with donor organ discard for medical reasons [odds ratio (OR; per increase of one point) 2.72, 95% confidence interval (CI) 2.68–2.76; OR (per increase of one SD) 30.6, 95% CI 29.0–32.2; $P < 0.001$]. A multivariable logistic regression model showed that all individual components of the aHDS with the exception of "cardiac arrest" ($P = 0.630$) were independently associated with donor organ discard for medical reasons (Table 2). Figure 2 visualizes the receiver operating characteristic curve of the aHDS with a *c*-statistic of 0.937.

Donors <60 years and ≥60 years of age

Table 3 shows baseline characteristics of donors <60 and ≥60 years of age. In donors<60 years of age, the mean aHDS value was 3.61 (±1.35) for accepted organs and 7.72 (±2.50) for discarded organs, while the median aHDS values amounted to 3.58 (2.97–4.05) and 7.71 (5.88–9.83), respectively (Table 3, Fig. 3). Donors ≥60 years of age presented with substantially higher aHDS values for both accepted organs (mean: 5.91 ± 1.72; median 5.58, 4.60–6.85) and discarded organs (mean: 11.63 ± 1.46; median: 12.09, 11.13–12.35; Fig. 4). Figure 4 clearly shows that the vast majority of donors ≥60 years of age was discarded. Accepted donors ≥60 years of age most commonly succumbed to CVA (65.6%) and rarely had a history of cardiac arrest (0.8%). Donors ≥60 years of age who presented with an LVEF <45% or with an unreported LVEF were uniformly discarded. The vast majority of older donors that were accepted had normal coronary

Table 1. Prediction of donor organ discard (baseline characteristics).

Variables	Offered organs N = 70 948 (100%)	
	Accepted organs n = 25 049 (35.3%)	Discarded organs N = 45 899 (64.7%)
aHDS (mean)	3.62 ± 1.36	8.67 ± 2.84
aHDS (median)	3.59 (2.97–4.06)	8.59 (6.76–11.11)
Age (year)		
<45	21 165 (84.5%)	16 859 (36.7%)
45–54	3203 (12.8%)	11 867 (25.9%)
55–59	559 (2.2%)	6022 (13.1%)
≥60	122 (0.5%)	11 151 (24.3%)
Cause of death		
Cranial trauma	14 542 (58.1%)	11 277 (24.6%)
Benign BT	121 (0.5%)	130 (0.3%)
Malignant BT	78 (0.3%)	110 (0.2%)
Circulatory	1518 (6.1%)	5914 (12.9%)
CVA	5053 (20.2%)	23 569 (51.4%)
Drug overdose	1287 (5.1%)	1899 (4.1%)
Intoxication	12 (0.1%)	12 (0.0%)
Meningitis	94 (0.4%)	155 (0.3%)
Respiratory	2277 (9.1%)	2677 (5.8%)
SAB	25 (0.1%)	81 (0.2%)
Sepsis	42 (0.2%)	75 (0.2%)
Donor history		
Uncompromised	22 590 (90.2%)	35 053 (76.4%)
Compromised	2459 (9.8%)	10 846 (23.6%)
Hypertension		
No	21 924 (87.5%)	23 952 (52.2%)
Yes	3011 (12.0%)	21 593 (47.0%)
Not available	114 (0.5%)	354 (0.8%)
Cardiac arrest		
No	23 367 (93.3%)	42 456 (92.5%)
Yes	1682 (6.7%)	3443 (7.5%)
LVEF (%)		
>55	18 383 (73.4%)	10 932 (23.8%)
45–55	5992 (23.9%)	6408 (14.0%)
<45	263 (1.1%)	6752 (14.7%)
Not available	411 (1.6%)	21 807 (47.5%)
Coronary angiography		
Normal	5132 (20.5%)	1018 (2.2%)
Irregularities	471 (1.9%)	2051 (4.5%)
1-vessel stenosis	32 (0.1%)	630 (1.4%)
>1-vessel stenosis	10 (0.0%)	616 (1.3%)
Not available	19 404 (77.5%)	41 584 (90.6%)
Serum sodium (mmol/l)		
<130	641 (2.6%)	965 (2.1%)
130–139	4201 (16.8%)	7648 (16.7%)
140–149	10 096 (40.3%)	19 855 (43.3%)
150–159	8072 (32.2%)	14 140 (30.8%)
160–164	1292 (5.2%)	2093 (4.6%)
165–169	501 (2.0%)	782 (1.7%)
≥170	208 (0.8%)	351 (0.8%)
Not available	38 (0.2%)	65 (0.1%)
Norepinephrine (µg/kg/min)		
<0.1	19 008 (75.9%)	31 776 (69.2%)
0.1–0.4	803 (3.2%)	4032 (8.8%)
0.41–0.8	115 (0.5%)	744 (1.6%)
>0.8	19 (0.1%)	82 (0.2%)
Not available	5104 (20.4%)	9265 (20.2%)
Dopamine/dobutamine (µg/kg/min)		
<5	17 527 (70.0%)	29 444 (64.1%)
5–7.5	1993 (8.0%)	3945 (8.6%)
7.51–10	846 (3.4%)	2546 (5.6%)
>10	258 (1.0%)	1226 (2.7%)
Not available	4425 (17.7%)	8738 (19.0%)

aHDS, adapted Heart Donor Score; BT, brain tumor; CVA, cerebrovascular accident; LVEF, left-ventricular ejection fraction; SAB, subarachnoid bleeding.

angiography results (75.4%). All donors ≥60 years of age with norepinephrine support >0.4 µg/kg/min or dopamine/dobutamine support >7.5 µg/kg/min were discarded (Table 3).

Analyzing only donors <60 years of age, the aHDS was significantly associated with donor organ discard for medical reasons (OR 2.71, 95% CI 2.66–2.75; $P < 0.001$). The *c*-statistic in this group amounted to 0.919. In donors ≥60 years of age, the aHDS was similarly associated with donor organ discard (OR 3.26, 95% CI 2.89–3.67; $P < 0.001$) with a *c*-statistic of 0.983.

Prediction of survival after HTX

Table 4 shows baseline characteristics of the study cohort for the survival analysis. The mean aHDS value of HTX recipients was 3.48 (±1.34), while the median aHDS value amounted to 3.53 (2.92–4.00). Most recipients received donors younger than 45 years of age (81.6%) with cranial trauma being the most common cause of death (58.7%). Most transplanted patients received a donor without compromised history (89.8%). Coronary angiography results were not available for the majority of transplanted donor hearts (73.4%). The median IMPACT Score of all recipients was 5.0 (3.0–7.0). The mean recipient age was 52.7 (±12.6) years and the mean ischemic time amounted to 3.24 (±1.05) hours.

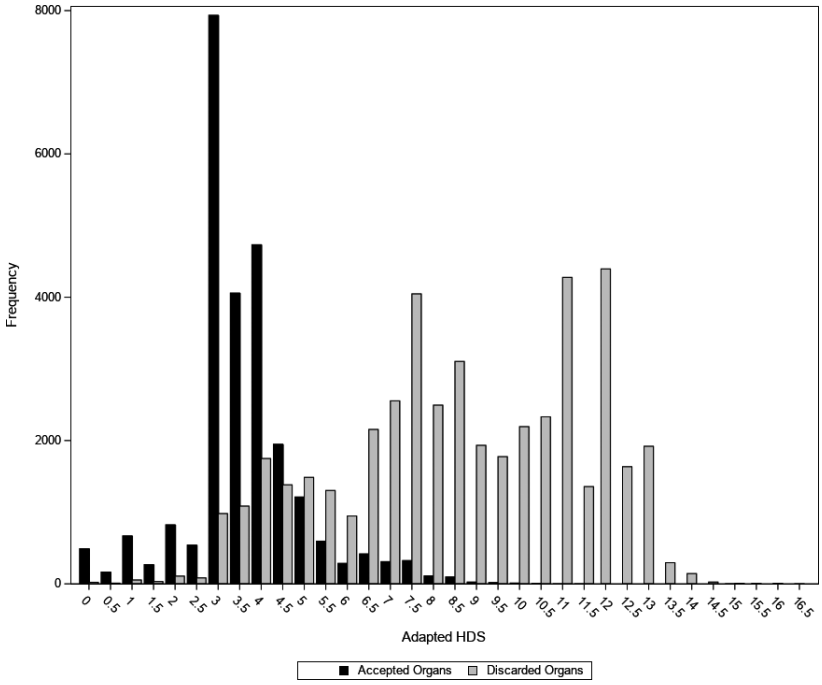

Figure 1 Distribution of the aHDS. The mean aHDS was 3.62 (±1.36) for accepted organs and 8.67 (±2.84) for discarded organs, while the median aHDS values amounted to 3.59 (2.97–4.06) and 8.59 (6.76–11.11), respectively.

Univariate Cox proportional hazards regression analysis showed a significant association of the aHDS with survival up to 1 year after HTX [hazard ratio (HR; per increase of one point) 1.04, 95% CI 1.01–1.07; HR (per increase of one SD) 1.05, 95% CI 1.01–1.10; $P = 0.023$] (Table 5). The *c*-statistic of this model amounted to 0.514. Figure 5 visualizes Kaplan–Meier survival curves of HTX recipients stratified along the median aHDS value of 3.53. Survival rates at 1 year after HTX amounted to 88.9% (95% CI, 88.2–89.5%) for patients receiving a donor with an aHDS value ≥3.53 and 89.9% (95% CI, 89.3–90.5%) for patients receiving a donor with an aHDS value <3.53 (log-rank test, $P = 0.021$). Figure S3 shows Kaplan–Meier survival curves out to 10 years after HTX. Survival rates at 3 years amounted to 82.4% (95% CI, 81.6–83.2%) for recipients of a donor with an aHDS value ≥3.53 and 83.3% (95% CI, 82.6–84.1%) for those with an aHDS value <3.53 (5 years: aHDS ≥3.53: 76.0%, 95% CI 75.1–76.9%); aHDS <3.53: 77.1%, 95% CI 76.2–78.0%).

Additionally, a multivariable Cox proportional hazards regression model including clinically relevant covariables was created: IMPACT Score, male donor sex, recipient body mass index, recipient diabetes, transplant year, transplant urgency, and ischemic time. Before statistical analysis, patients with missing variables were excluded (IMPACT Score: $n = 1080$; bilirubin: $n = 330$; creatinine clearance: $n = 73$; dialysis between listing and HTX: $n = 160$; infection: $n = 544$; ventricular assist device: $n = 205$; recipient body mass index: $n = 3$; recipient diabetes: $n = 74$; ischemic time: $n = 338$). Consequently, the model was calculated with 17 868 patients.

In the multivariable Cox proportional hazards regression model, the aHDS was not significantly associated with survival up to 1 year after HTX [HR (per increase of one point) 1.01, 95% CI 0.98–1.05; HR (per increase of one SD) 1.02, 95% CI 0.97–1.07; $P = 0.425$] (Table 5). A second multivariable Cox proportional hazards regression model that included all individual aHDS components showed that only donor age was independently and significantly associated with survival after HTX ($P < 0.001$) (Table 6). In this model, PEV values were highest for the variables "IMPACT Score" (1.20%) and "ischemic time" (0.22%).

Discussion

The present study provides several insights. First, our analysis shows that the aHDS accurately predicts donor organ discard for medical reasons in the UNOS registry, with a *c*-statistic of 0.937 (Fig. 2). Donors with an aHDS value ≥5 are more frequently discarded than accepted (Fig. 1). These findings are in line with a

Table 2. Prediction of donor organ discard (multivariable logistic regression analysis).

Variable	Beta-estimate	Odds ratio	95% CI of odds ratio	*P*-value
Age (year)				
<45	0	1.00	–	**<0.001**
45–54	1.85	6.34	5.87–6.84	
55–59	2.61	13.62	11.91–15.56	
≥60	3.67	39.29	31.45–49.09	
Cause of death				
Cranial trauma	0	1.00	–	**<0.001**
Benign BT	0.13	1.14	0.80–1.63	
Malignant BT	−0.01	0.99	0.66–1.49	
Circulatory	1.09	2.98	2.72–3.26	
CVA	0.93	2.53	2.38–2.70	
Drug overdose	0.88	2.40	2.17–2.66	
Intoxication	0.96	2.60	0.90–7.51	
Meningitis	0.32	1.38	0.99–1.92	
Respiratory	0.50	1.65	1.51–1.80	
SAB	0.59	1.81	0.90–3.67	
Sepsis	0.40	1.49	0.90–2.48	
Donor history				
Uncompromised	0	1.00	–	**<0.001**
Compromised	0.81	2.24	2.09–2.41	
Hypertension				
No	0	1.00	–	**<0.001**
Yes	1.06	2.90	2.71–3.10	
Not available	0.79	2.20	1.60–3.01	
Cardiac arrest				
No	0	1.00	–	0.630
Yes	0.02	1.02	0.93–1.12	
LVEF (%)				
>55	0	1.00	–	**<0.001**
45–55	0.76	2.14	2.03–2.26	
<45	4.25	69.79	61.13–79.68	
Not available	3.50	33.24	29.84–37.03	
Coronary angiography				
Normal	0	1.00	–	**<0.001**
Irregularities	3.73	41.76	36.15–48.25	
1-vessel stenosis	4.97	143.52	97.37–211.55	
>1-vessel stenosis	5.95	384.82	200.75–737.68	
Not available	2.98	19.65	17.81–21.68	
Serum sodium (mmol/l)				
<130	−0.19	0.83	0.70–0.97	**0.038**
130–139	−0.07	0.93	0.87–1.00	
140–149	0	1.00	–	
150–159	−0.05	0.95	0.90–1.00	
160–164	−0.03	0.97	0.87–1.09	
165–169	0.06	1.06	0.89–1.26	
≥170	0.22	1.25	0.97–1.60	
Not available	−0.18	0.83	0.45–1.53	
Norepinephrine (μg/kg/min)				
<0.1	0	1.00	–	**<0.001**
0.1–0.4	0.79	2.21	1.97–2.48	
0.41–0.8	0.82	2.28	1.73–3.01	
>0.8	0.60	1.83	0.90–3.69	
Not available	0.05	1.05	0.98–1.12	

Table 2. Continued.

Variable	Beta-estimate	Odds ratio	95% CI of odds ratio	*P*-value
Dopamine/dobutamine (μg/kg/min)				
<5	0	1.00	–	**<0.001**
5–7.5	0.16	1.18	1.08–1.29	
7.51–10	0.58	1.79	1.59–2.01	
>10	0.89	2.44	2.02–2.96	
Not available	0.15	1.16	1.08–1.24	

BT, brain tumor; CVA, cerebrovascular accident; LVEF, left-ventricular ejection fraction; SAB, subarachnoid bleeding.
Bold indicates statistical significance ($P < 0.05$).

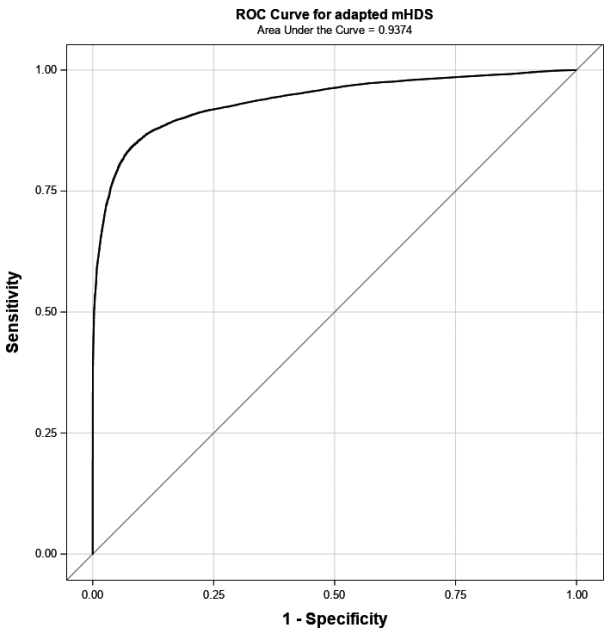

Figure 2 Prediction of donor organ discard. The receiver operating characteristic curve of the aHDS is visualized. The area under the receiver operating characteristic curve (*c*-statistic) amounts to 0.937.

report from the 2015 American Society of Transplantation Conference on Donor Heart Selection, showing that experts in the transplant community rank the variables "donor age," "LVEF," "LVH," "ischemic time," and "high inotrope use" among the most important risk factors during the donor selection process [5]. Additionally, "donor-recipient sex mismatch," "coronary artery disease," and "malignancy" are considered important risk factors. Most of these variables are components of the aHDS, and our results confirm that they are significantly associated with donor organ discard in this real-world registry (Table 2). A previously published analysis of the UNOS registry reported comparable results. In this study, "older age," "lower LVEF," "tumor as a cause of death," and "presence of inotropic support" were significantly associated with donor organ discard [15]. Similarly, a study utilizing the California Transplant Donor Network database showed that "age over 50 years," "CVA as a cause of death," "hypertension," "reduced LVEF," and other variables were predictive of donor organ discard [16].

Second, our analysis suggests that similar donor characteristics are considered by transplant physicians in Europe and the United States during the decision processes toward acceptance or discard of specific donor hearts. However, the past 3 decades have seen a trend toward substantially increasing median donor age in Europe (31–45 years), but not in North America (28–31 years) [17]. Indeed, Table 2 demonstrates that "age ≥60 years" has an OR of 39.29 for donor organ discard in the UNOS registry, and Table 3 shows that only 1.1% of donors ≥60 years are accepted for HTX. Future studies are required to analyze how these changing acceptance practices regarding "donor age" in Europe will translate into outcomes after HTX.

Third, our analyses show that the aHDS is similarly predictive of donor organ discard in donors <60 and ≥60 years of age. Importantly, Table 3 suggests that only highly selected donors ≥60 years of age were accepted for HTX, given that only 0.8% of them presented with a history of cardiac arrest, none of them presented with an LVEF <45% or an unreported LVEF, and none of them required higher dose norepinephrine or dopamine/dobutamine support (Table 3). In the literature, interactions between donor age and other donor variables have been reported. For example, prolonged ischemic time in combination with a donor heart of advanced age is associated with significantly inferior survival in comparison with the same ischemic time in a younger donor heart [17]. Therefore, transplant physicians most likely accepted donors ≥60 years of age only if their risk profile was otherwise low in order to avoid excessive accumulation of donor risk.

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Table 3. Donors <60 and ≥60 years of age (baseline characteristics).

Variables	Age < 60 years *N* = 59 675 (100%)		Age ≥ 60 years *N* = 11 273 (100%)	
	Accepted organs *n* = 24 927 (41.8%)	Discarded organs *N* = 34 748 (58.2%)	Accepted organs *n* = 122 (1.1%)	Discarded organs *N* = 11 151 (98.9%)
aHDS (mean)	3.61 ± 1.35	7.72 ± 2.50	5.91 ± 1.72	11.63 ± 1.46
aHDS (median)	3.58 (2.97–4.05)	7.71 (5.88–9.83)	5.58 (4.60–6.85)	12.09 (11.13–12.35)
Age (year)				
<45	21 165 (84.9%)	16 859 (48.5%)	0 (0%)	0 (0%)
45–54	3203 (12.9%)	11 867 (34.2%)	0 (0%)	0 (0%)
55–59	559 (2.2%)	6022 (17.3%)	0 (0%)	0 (0%)
≥60	0 (0%)	0 (0%)	122 (100%)	11 151 (100%)
Cause of death				
Cranial trauma	14 510 (58.2%)	9697 (27.9%)	32 (26.2%)	1580 (14.2%)
Benign BT	121 (0.5%)	117 (0.3%)	0 (0.0%)	13 (0.1%)
Malignant BT	77 (0.3%)	97 (0.3%)	1 (0.8%)	13 (0.1%)
Circulatory	1511 (6.1%)	4722 (13.6%)	7 (5.7%)	1192 (10.7%)
CVA	4973 (20.0%)	15 552 (44.8%)	80 (65.6%)	8017 (71.9%)
Drug overdose	1287 (5.2%)	1867 (5.4%)	0 (0.0%)	32 (0.3%)
Intoxication	12 (0.1%)	12 (0.0%)	0 (0.0%)	0 (0.0%)
Meningitis	93 (0.4%)	150 (0.4%)	1 (0.8%)	5 (0.0%)
Respiratory	2277 (9.1%)	2420 (7.0%)	0 (0.0%)	257 (2.3%)
SAB	24 (0.1%)	50 (0.1%)	1 (0.8%)	31 (0.3%)
Sepsis	42 (0.2%)	64 (0.2%)	0 (0.0%)	11 (0.1%)
Donor history				
Uncompromised	22 494 (90.2%)	26 614 (76.6%)	96 (78.7%)	8439 (75.7%)
Compromised	2433 (9.8%)	8134 (23.4%)	26 (21.3%)	2712 (24.3%)
Hypertension				
No	21 849 (87.7%)	20 615 (59.3%)	75 (61.5%)	3337 (29.9%)
Yes	2964 (11.9%)	13 862 (39.9%)	47 (38.5%)	7731 (69.3%)
Not available	114 (0.5%)	271 (0.8%)	0 (0.0%)	83 (0.7%)
Cardiac arrest				
No	23 246 (93.3%)	31 917 (91.9%)	121 (99.2%)	10 539 (94.5%)
Yes	1681 (6.7%)	2831 (8.2%)	1 (0.8%)	612 (5.5%)
LVEF (%)				
>55	18 279 (73.3%)	9869 (28.4%)	104 (85.3%)	1063 (9.5%)
45–55	5974 (24.0%)	5875 (16.9%)	18 (14.8%)	533 (4.8%)
<45	263 (1.1%)	6448 (18.6%)	0 (0.0%)	304 (2.7%)
Not available	411 (1.7%)	12 556 (36.1%)	0 (0.0%)	9251 (83.0%)
Coronary angiography				
Normal	5040 (20.2%)	938 (2.7%)	92 (75.4%)	80 (0.7%)
Irregularities	465 (1.9%)	1907 (5.5%)	6 (4.9%)	144 (1.3%)
1-vessel stenosis	31 (0.1%)	566 (1.6%)	1 (0.8%)	64 (0.6%)
>1-vessel stenosis	8 (0.0%)	547 (1.6%)	2 (1.6%)	69 (0.6%)
Not available	19 383 (77.8%)	30 790 (88.6%)	21 (17.2%)	10 794 (96.8%)
Serum sodium (mmol/l)				
<130	637 (2.6%)	818 (2.4%)	4 (3.3%)	147 (1.3%)
130–139	4185 (16.8%)	5913 (17.0%)	16 (13.1%)	1735 (15.6%)
140–149	10 043 (40.3%)	14 570 (41.9%)	53 (43.4%)	5285 (47.4%)
150–159	8031 (32.2%)	10 751 (30.9%)	41 (33.6%)	3389 (30.4%)
160–164	1288 (5.2%)	1680 (4.8%)	4 (3.3%)	413 (3.7%)
165–169	498 (2.0%)	651 (1.9%)	3 (2.5%)	131 (1.2%)
≥170	208 (0.8%)	310 (0.9%)	0 (0.0%)	41 (0.4%)
Not available	37 (0.2%)	55 (0.2%)	1 (0.8%)	10 (0.1%)
Norepinephrine (μg/kg/min)				
<0.1	18 914 (75.9%)	24 091 (69.3%)	94 (77.1%)	7685 (68.9%)

Table 3. Continued.

Variables	Age < 60 years *N* = 59 675 (100%)		Age ≥ 60 years *N* = 11 273 (100%)	
	Accepted organs *n* = 24 927 (41.8%)	Discarded organs *N* = 34 748 (58.2%)	Accepted organs *n* = 122 (1.1%)	Discarded organs *N* = 11 151 (98.9%)
0.1–0.4	800 (3.2%)	2985 (8.6%)	3 (2.5%)	1047 (9.4%)
0.41–0.8	115 (0.5%)	567 (1.6%)	0 (0.0%)	177 (1.6%)
>0.8	19 (0.1%)	65 (0.2%)	0 (0.0%)	17 (0.2%)
Not available	5079 (20.4%)	7040 (20.3%)	25 (20.5%)	2225 (20.0%)
Dopamine/dobutamine (μg/kg/min)				
<5	17 432 (69.9%)	22 049 (63.5%)	95 (77.9%)	7395 (66.3%)
5–7.5	1985 (8.0%)	3034 (8.7%)	8 (6.6%)	911 (8.2%)
7.51–10	846 (3.4%)	1951 (5.6%)	0 (0.0%)	595 (5.3%)
>10	258 (1.0%)	949 (2.7%)	0 (0.0%)	277 (2.5%)
Not available	4406 (17.7%)	6765 (19.5%)	19 (15.6%)	1973 (17.7%)

aHDS, adapted Heart Donor Score; BT, brain tumor; CVA, cerebrovascular accident; LVEF, left-ventricular ejection fraction; SAB, subarachnoid bleeding.

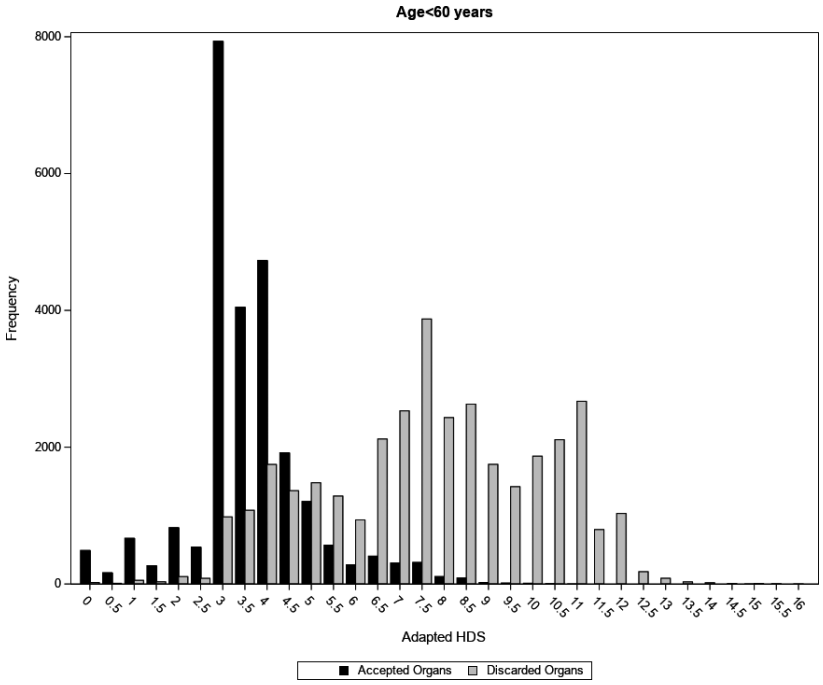

Figure 3 Donors <60 years of age. In donors <60 years of age, the mean aHDS value was 3.61 (±1.35) for accepted organs and 7.72 (±2.50) for discarded organs, while the median aHDS values amounted to 3.58 (2.97–4.05) and 7.71 (5.88–9.83), respectively.

Fourth, survival analyses show that the aHDS individually predicts survival after HTX, although the effect becomes nonsignificant after adjustment for the IMPACT Score and other recipient and procedural variables (Table 5). Detailed analysis of individual aHDS components demonstrates that donor age is significantly and independently associated with 1-year survival after HTX (Table 6). This finding is in line with a multitude of published analyses, including the widely recognized "donor risk score" by Weiss *et al.* [18] Fig. 5 illustrates that the 1-year survival rates of recipients stratified along the median aHDS are significantly different, although this difference likely is of minimal clinical relevance (88.9% vs. 89.9%). Moreover, PEV values in Table 6 are comparably small for most aHDS components.

We believe that two hypotheses are feasible to explain the absence of an independent association of the aHDS

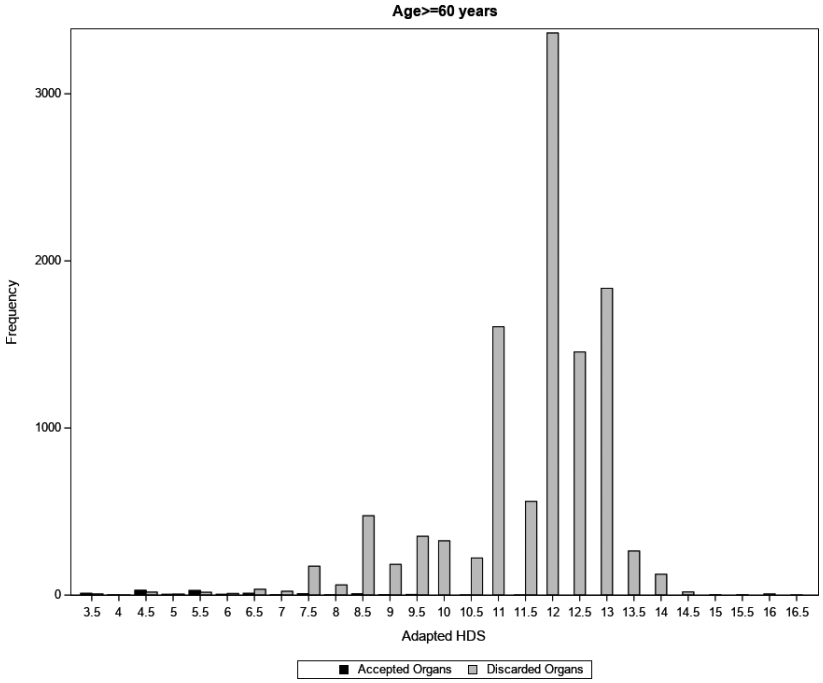

Figure 4 Donors ≥60 years of age. Donors ≥60 years of age presented with substantially higher aHDS values for both accepted organs (mean: 5.91 ± 1.72; median 5.58, 4.60–6.85) and discarded organs (mean: 11.63 ± 1.46; median: 12.09, 11.13–12.35).

with survival. Primarily, our notion is that donor selection processes and decision making of transplant physicians in the United States are highly accurate, thereby eliminating the potentially negative effects of most aHDS components and leaving only donor age with a significant and independent influence on 1-year survival after HTX (Table 6).

Alternatively, the components of the aHDS with the exception of "donor age" might be of inferior importance for survival after HTX. This explanation would be in line with a recently growing body of literature, showing that marginal quality donor hearts might be safely accepted without compromising outcomes after HTX. Specifically, our group has shown that higher dose norepinephrine donor support is not associated with impaired survival or higher rates of primary graft dysfunction, prolonged ventilation, or renal replacement therapy after HTX [19]. Moreover, studies have shown that recipients of donors with even markedly reduced LVEF are not at risk of impaired long-term survival, dopamine donor support is actually associated with superior survival after HTX, and recipients of donor hearts with documented single-vessel disease have similar survival when compared with recipients of donor hearts without coronary atherosclerosis [20–23].

We believe that the aHDS might be used clinically to standardize donor acceptance criteria and define "high-risk donors," thereby potentially reducing variability in acceptance practices between transplant centers [24]. As suggested by Smith et al., standardization of the donor selection process might enable transplant centers to increase the utilization rates of marginal quality donor organs without compromising survival rates after HTX [25]. Moreover, the aHDS might be implemented to raise efficiency of the allocation process. Chances of acceptance or discard might be estimated for specific donor hearts early on in the allocation process, thereby offering a possibility to efficiently guide resource allocation, including transport for organ procurement or operative suite utilization.

Limitations

Several limitations need to be considered when interpreting the presented results. First, retrospective registry analyses are subject to selection bias. Most donors presenting with characteristics at the extremes of the range (e.g., age >80 years, LVEF <10%) have likely not been reported to the UNOS registry from the outset. Therefore, the true influence of extreme donor characteristics and consequently aHDS values on outcomes after HTX is inherently in-examinable. Second, the recent changes in the United States heart allocation system could not be considered in this analysis of the period 2004–2015. Third, the recently increasing utilization of hepatitis C positive donors and donation after circulatory death

Table 4. Prediction of survival after HTX (baseline characteristics).

Variables	HTX recipients *N* = 19 279 (100%)
aHDS (mean ± SD)	3.48 ± 1.34
aHDS (median [quartiles])	3.53 (2.92–4.00)
aHDS components	
Donor age (year)	
<45	15 739 (81.6%)
45–54	2924 (15.2%)
55–59	502 (2.6%)
≥60	114 (0.6%)
Cause of death	
Cranial trauma	11 312 (58.7%)
Benign BT	93 (0.5%)
Malignant BT	62 (0.3%)
Circulatory	1027 (5.3%)
CVA	4312 (22.4%)
Drug overdose	1106 (5.7%)
Intoxication	11 (0.1%)
Meningitis	67 (0.4%)
Respiratory	1243 (6.5%)
SAB	21 (0.1%)
Sepsis	25 (0.1%)
Donor history	
Uncompromised	17 315 (89.8%)
Compromised	1964 (10.2%)
Hypertension	
No	16 448 (85.3%)
Yes	2728 (14.2%)
Not available	103 (0.5%)
Cardiac arrest	
No	18 074 (93.8%)
Yes	1205 (6.2%)
LVEF (%)	
>55	13 988 (72.6%)
45–55	4991 (25.9%)
<45	144 (0.8%)
Not available	156 (0.8%)
Coronary angiography	
Normal	4780 (24.8%)
Irregularities	320 (1.7%)
1-vessel stenosis	28 (0.2%)
>1-vessel stenosis	8 (0.0%)
Not available	14 143 (73.4%)
Serum sodium (mmol/l)	
<130	335 (1.7%)
130–139	3015 (15.6%)
140–149	7851 (40.7%)
150–159	6490 (33.7%)
160–164	1008 (5.2%)
165–169	390 (2.0%)
≥170	165 (0.9%)
Not available	25 (0.1%)
Norepinephrine (μg/kg/min)	
<0.1	14 299 (74.2%)
0.1–0.4	614 (3.2%)
0.41–0.8	83 (0.4%)
>0.8	14 (0.1%)
Not available	4269 (22.1%)
Dopamine/dobutamine (μg/kg/min)	
<5	13 785 (71.5%)
5–7.5	1449 (7.5%)
7.51–10	555 (2.9%)
> 10	159 (0.8%)
Not available	3331 (17.3%)
IMPACT score (1080 missing)	5.0 (3.0–7.0)
IMPACT score components	
Recipient age (year)	52.7 ± 12.6
Bilirubin (mg/dl; 330 missing)	0.8 (0.5–1.2)
Creatinine clearance (ml/min; 73 missing)	78.8 (60.0–102.8)
Dialysis between listing and HTX (160 missing)	
No	18 741 (98.0%)
Yes	378 (2.0%)
Female sex	4790 (24.8%)
Diagnosis	
Dilatative cardiomyopathy	9108 (47.3%)
Ischemic cardiomyopathy	7931 (41.1%)
Congenital heart disease	583 (3.0%)
Other	1657 (8.6%)
Infection (544 missing)	
No	16 695 (89.1%)
Yes	2040 (10.9%)
Intra-aortic balloon pump	
No	18 263 (94.7%)
Yes	1016 (5.3%)
Mechanical ventilation	
No	18 917 (98.1%)
Yes	362 (1.9%)
Ethnicity	
Caucasian	13 304 (69.0%)
African American	3718 (19.3%)
Hispanic	1471 (7.6%)
Other	786 (4.1%)
Temporary circulatory support	
No	18 934 (98.2%)
Yes	345 (1.8%)
Ventricular assist device (205 missing)	
No ventricular assist device	12 610 (66.1%)
Old generation pulsatile	1510 (7.9%)
New generation continuous	257 (1.4%)
Abbott HeartMate II® or HeartWare® HVAD®	4697 (24.6%)
Other variables	
Donor male sex	13 828 (71.7%)

Table 4. Continued.

Variables	HTX recipients N = 19 279 (100%)
Recipient body mass index (kg/m^2; 3 missing)	26.95 ± 4.81
Recipient diabetes (74 missing)	
No	14 108 (73.5%)
Yes	5097 (26.5%)
Transplant year	2010 (2007–2012)
Transplant urgency	
Status 1A	10 137 (52.6%)
Status 1B	7054 (36.6%)
Status 2	2088 (10.8%)
Ischemic time (h) (338 missing)	3.24 ± 1.05

aHDS, adapted Heart Donor Score; BT, brain tumor; CVA, cerebrovascular accident; HTX, heart transplantation; IMPACT, Index for Mortality Prediction after Cardiac Transplantation; LVEF, left-ventricular ejection fraction; SAB, subarachnoid bleeding.

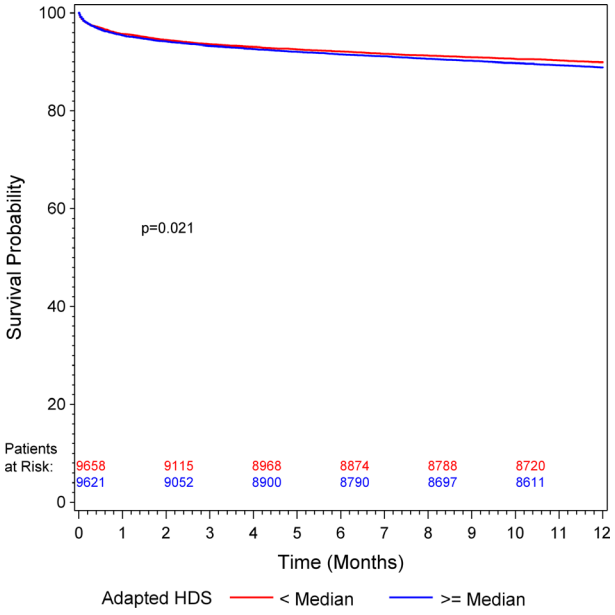

Figure 5 Prediction of Survival after HTX. Kaplan–Meier survival curves of transplanted patients stratified along the median donor aHDS value of 3.53 (2.92–4.00) are visualized. Survival at 1 year after HTX amounted to 88.9% in recipients of a donor with an aHDS value ≥3.53 and 89.9% in those with an aHDS value <3.53 (log-rank test, P = 0.021).

(DCD) donors for HTX is not accounted for by this analysis. However, hepatitis C positive donors currently only account for 1.1% of donors in the International Society of Heart and Lung Transplantation registry, and DCD-HTX remains to be exclusively performed by specialized centers. Therefore, these donors currently do not account for substantial percentages of transplant activity in the United States or in Europe [17,26]. Fourth, the anonymized nature of the datasets underlying this retrospective registry analysis limited the possibilities to perform structured audits for data entry errors.

Table 5. Prediction of survival after HTX (univariate and multivariable cox proportional hazards regression analyses).

Variable	Hazard ratio	95% Confidence interval	*P*-value
Univariate analysis			
aHDS			**0.023**
Per increase of one point	1.04	1.01–1.07	
Per increase of one SD	1.05	1.01–1.10	
Multivariable model			
aHDS			0.425
Per increase of one point	1.01	0.98–1.05	
Per increase of one SD	1.02	0.97–1.07	
IMPACT score (log2-transformed)	1.47	1.40–1.54	**<0.001**
Male donor sex	0.91	0.82–1.01	0.065
Recipient body mass Index (kg/m^2)	1.02	1.01–1.03	**<0.001**
Recipient diabetes	1.03	0.93–1.14	0.622
Transplant year	0.98	0.96–0.99	**0.003**
Transplant urgency			
Status 1A	0.94	0.81–1.10	0.294
Status 1B	0.89	0.76–1.04	
Status 2	1.00	–	
Ischemic time (h)	1.15	1.10–1.20	**<0.001**

aHDS, adapted Heart Donor Score; IMPACT, Index for Mortality Prediction after Cardiac Transplantation; SD, standard deviation. Bold indicates statistical significance (P < 0.05).

Table 6. Prediction of survival after HTX (multivariable cox proportional hazards regression analysis of aHDS components).

Variable	Hazard ratio	95% Confidence interval	*P*-value	Proportion of explained variation (%)
Age (year)				
<45	1.00	–	**<0.001**	0.09
45–54	1.31	1.13–1.52		
55–59	1.47	1.13–1.90		
≥60	1.27	0.75–2.14		
Cause of death				
Cranial trauma	1.00	–	0.060	0.09
Benign BT	1.49	0.86–2.59		
Malignant BT	1.01	0.45–2.29		
Circulatory	0.93	0.74–1.16		
CVA	1.04	0.91–1.18		
Drug overdose	0.93	0.75–1.15		
Intoxication	3.11	1.00–9.70		
Meningitis	0.56	0.21–1.53		
Respiratory	1.24	1.03–1.49		
SAB	2.32	0.96–5.61		
Sepsis	0.77	0.19–3.10		
Donor history				
Uncompromised	1.00	–	0.684	0.00
Compromised	1.03	0.89–1.20		
Hypertension				
No	1.00	–	0.202	0.00
Yes	1.07	0.94–1.23		
Not available	1.49	0.89–2.48		
Cardiac arrest				
No	1.00	–	0.299	0.01
Yes	1.00	0.74–1.10		
LVEF (%)				
>55	1.00	–	0.720	0.01
45–55	0.98	0.88–1.09		
<45	0.83	0.47–1.48		
Not available	0.77	0.43–1.36		
Coronary angiography				
Normal	1.00	–	0.332	0.02
Irregularities	1.36	1.01–1.83		
1-vessel stenosis	0.82	0.26–2.55		
>1-vessel stenosis	1.09	0.15–7.82		
Not available	0.98	0.86–1.11		
Serum sodium (mmol/l)				
<130	1.02	0.71–1.47	0.656	0.02
130–139	0.96	0.84–1.10		
140–149	1.00	–		
150–159	1.00	0.90–1.12		
160–164	0.94	0.75–1.17		
165–169	1.23	0.91–1.67		
≥170	1.03	0.64–1.64		
Not available	1.96	0.81–4.76		
Norepinephrine (μg/kg/min)				
<0.1	1.00	–	0.235	0.03
0.1–0.4	1.34	1.05–1.70		
0.41–0.8	0.97	0.49–1.96		
>0.8	0.81	0.11–5.75		
Not available	1.02	0.90–1.15		

Table 6. Continued.

Variable	Hazard ratio	95% Confidence interval	*P*-value	Proportion of explained variation (%)
Dopamine/dobutamine (μg/kg/min)				
<5	1.00	–	0.257	0.02
5–7.5	1.16	0.98–1.37		
7.51–10	1.05	0.80–1.38		
>10	1.05	0.63–1.75		
Not available	1.13	0.99–1.30		
IMPACT score (log2-transformed)	1.46	1.39–1.54	**<0.001**	1.20
Donor male sex	0.96	0.87–1.07	0.478	0.00
Recipient body mass index (kg/m^2)	1.02	1.01–1.03	**<0.001**	0.07
Recipient diabetes	1.02	0.92–1.14	0.668	0.00
Transplant year	0.98	0.96–0.99	**0.005**	0.04
Transplant urgency				
Status 1A	0.98	0.84–1.14	0.355	0.01
Status 1B	0.92	0.78–1.07		
Status 2	1.00	–		
Ischemic time (h)	1.15	1.10–1.20	**<0.001**	0.22

BT, brain tumor; CVA, cerebrovascular accident; HTX, heart transplantation; IMPACT, Index for Mortality Prediction after Cardiac Transplantation; LVEF, left-ventricular ejection fraction; SAB, subarachnoid bleeding.

Bold indicates statistical significance ($P < 0.05$).

Conclusions

Four conclusions can be drawn from this analysis. First, the aHDS accurately predicts donor organ discard for medical reasons in the UNOS registry and might be applied to standardize donor selection processes. Second, transplant physicians in the United States and in Europe base their decisions regarding donor organ discard or acceptance on similar donor characteristics. Third, the aHDS is similarly predictive in donors <60 years or ≥60 years of age. Only highly selected donors ≥60 years of age are accepted for HTX. Fourth, donor selection processes of transplant physicians in the United States seem to be highly accurate, thereby eliminating the potentially negative effects of most aHDS components and leaving only donor age with a significant and independent influence on 1-year survival after HTX.

Authorship

PA and AOZ: conceptualized the study. PA: prepared the datasets for statistical analysis and drafted the manuscript. AK: performed all statistical analyses. JMS: is the first author of the original publication of the HDS and provided scientific and statistical advice. AZA-Z and EO-J: critically reviewed and co-edited the manuscript. GL: provided resources as well as scientific advice.

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Conflict of interest

Dr Zuckermann serves on the speakers' bureau of Paragonix, Novartis, Mallincrodt, Sanofi-Genzyme, Franz Köhler Chemie and on the advisory board for Chiesi. Dr Aliabadi-Zuckermann received travel grants from Sanofi and institutional grant support from Fresenius. Dr Laufer is a consultant for Edwards Lifesciences. All other authors have nothing to disclose.

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SUPPORTING INFORMATION

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

Figure S1. Derivation of the study cohort for donor organ discard.

Figure S2. Derivation of the study cohort for survival.

Figure S3. Survival out to 10 years after HTX.

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