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ORIGINAL ARTICLE

The joint impact of donor and recipient parameters on the outcome of heart transplantation in Germany after graft allocation

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Summary

Organ shortage in heart transplantation (HTx) results in increased use of grafts from donors with substantial risk factors. It is discussed controversially which donor characteristics may be detrimental. Therefore, we evaluated the joint impact of donor- and patient-related risk factors in HTx on patient survival by multiple analysis in a nationwide multicentre study after donor selection was carried out. The research database consists of data concerning hearts donated and transplanted in Germany between 2006 and 2008 as provided by Deutsche Stiftung Organtransplantation and the BQS Institute. Multiple Cox regression (significance level 5%, hazard ratio [95% CI]) was conducted (n = 774, recipient age $\geq$ 18 years). Survival was significantly decreased by donor age (1.021 [1.008–1.035] per year), nontraumatic cause of death (1.481 [1.079–2.034]), troponin >0.1 ng/ml (2.075 [1.473–2.921]), ischaemia time (1.197 [1.041–1.373] per hour), recipient age (1.017 [1.002–1.031] per year) and in recipients with pulmonary vascular resistance $\geq$320 dyn*s*cm^{-5} (1.761 [1.115–2.781]), with ventilator dependency (3.174 [2.211–6.340]) or complex previous heart surgery (1.763 [1.270–2.449]). After donor selection had been conducted, multiple Cox regression revealed donor age, nontraumatic cause of death, troponin and ischaemia time as well as recipient age, pulmonary hypertension, ventilator dependency and previous complex heart surgery as limiting risk factors concerning patient survival.

Introduction

Donor and recipient factors interact and jointly influence patient survival after heart transplantation (HTx). The individual decision to use a graft or not is guided by the question whether it will be suitable for the allocated recipient [1]. This policy is strongly influenced by the persisting organ shortage [2]. As a result, grafts from donors with comorbidities or from older donors are used increasingly. However, it is discussed controversially which donor and recipient factors should not be combined. Furthermore, it is still unknown whether German donor and recipient populations are comparable with those of other countries. Recently, we detected such differences while investigating

the joint impact of donor and recipient parameters on liver transplantation in Germany [3]. Therefore, it is necessary to analyse this concerning HTx in order to raise the safety and quality of donor and graft selection in the future. German data beyond the scope of single-centre experience were not available until now.

Materials and methods

Our study uses data from two institutional databases. For quality assurance and patient safety reasons, data on transplantation as well as data from follow-up surveys were reported to the BQS Institute for Quality and Patient Safety (BQS) from 2006 to 2008. Since 2006, a nationwide database has been implemented by the German organ procurement organization Deutsche Stiftung Organtransplantation (DSO). This database provides all donor data collected onsite and prospectively in the donor hospitals by coordinators for the purpose of allocation via Eurotransplant (ET) and donor characterization for the recipient centres with regard to the final decision about graft acceptance. Recipient data were provided by the recipients' HTx centre and according to national rules of quality assurance in medicine. Merging these two databases into one anonymized research database allowed us to analyse the impact of donor and recipient characteristics on early patient survival after HTx in Germany.

According to German law, data concerning selected medical and nursing procedures have to be collected for quality assurance and patient safety reasons. From 2001 to 2009, these data were reported to the German National Agency for Performance Measurement in Health Care (since 2010: BQS Institute for Quality and Patient Safety). Participation became mandatory for all hospitals by law [4].

The study was performed in accordance with the guidelines for Good Scientific and Good Epidemiological Practice of the German Society for Epidemiology (DGEPI 2008) [5]. Ethical approval was not needed as we fulfilled the criteria of 'Good Practice in Secondary Data Analysis' (GPS). According to this guideline, we considered all data protection requirements for secondary data analysis. Only anonymized data were used. Hence, no re-identification of persons was possible, and therefore, no informed consent of participants was necessary. Moreover, all phases of the study were subject to the strict data protection regulations of BQS, DSO and German law.

Originally, the resulting database consists of 953 records. However, to obtain a homogeneous database, recipients younger than 18 years of age (57, 6.0%) or with more than one HTx (17, 1.8%) were excluded. Moreover, patients who received a graft that was not donated and transplanted in Germany (89, 9.3%) and patients with implausible survival times (34, 3.6%) were not considered.

Therefore, all in all, we analysed 774 (81.2% of 953) anonymized records of grafts donated from brain-dead donors (DBD) and transplanted to adults (age $\geq$ 18 years) in Germany between 2006 and 2008.

In a first step, the impact of relevant donor and recipient risk factors on survival was analysed by means of log-rank tests (concerning nominal and categorical factors) and univariate Cox regression (concerning interval-scaled factors). In a second step, a multiple Cox regression model was developed. For this model, risk factors that showed a *P*-value below 0.20 in univariate analysis were considered primarily. Factors that showed a *P*-value lower than 0.05 remained in the model (stepwise forward selection). All analyses were performed with IBM SPSS Statistics 19 (SPSS Inc., Chicago, IL, USA).

Some interval-scaled parameters were categorized because the methods of measurement differed between donor hospitals (e.g. either troponin T or I was determined, but not both) or were unavailable for a substantial number of donors (then missing values were considered as an informative category).

For each donor, all findings of electrocardiogram (ECG), echocardiography (ECHO) and coronary angiography (CORO) were categorized according to the national recommendations for donor heart evaluations [6–9].

Graft quality was judged according to the subjective opinion of the recovery surgeon at procurement. Hypotensive periods were defined according to the rules of the ET manual [10].

Patient survival times were calculated from the data on postoperative hospital stay and follow-up examination. Mean survival time was 79 days for persons who died during the study period and 365 days for censored cases.

Results

This study included 774 hearts exclusively donated and transplanted in Germany to adult recipients (age $\geq$ 18 years) between 2006 and 2008. All characteristics of the donor and recipient population were analysed as summarized in Tables 1 and 2.

On an univariate level of analysis, the following donor parameters were significantly associated with decreased patient survival (Table 1): increased donor age, prolonged ischaemia times (CIT), increased troponin I or T before recovery (cut-off: >0.1 ng/ml, Fig. 1), nontraumatic cause of death (COD) and the use of diuretics in donor maintenance within the time interval of ET donor report and recovery.

Paradoxically, grafts recovered from donors who experienced hypotensive periods were not associated with an

Table 1. Donor characteristics and transplant variables used in analysis of patient survival after adult heart transplantation (HTx). For interval-scaled parameters, median and interquartile range as well as significant *P*-values of univariate Cox regression are given. For nominal and categorical parameters, percentages as well as significant *P*-values of log-rank tests are shown.

	Unit of analysis or factor level	*n*	(%)	Median	Interquartile range	*P*-Value
Donor characteristics and basic donor data						
Age	Year	774		44.0	33.0–51.0	<0.001
Gender	Female	336	(43.4)			NS
	Male	438	(56.6)			
Weight	kg	774		75.0	70.0–85.0	NS
Height	cm	774		175	170–182	NS
Stay in intensive care unit	Day	774		4.0	2.0–8.0	NS
Cause of death	Secondary (cerebral hypoxia)	69	(8.9)			0.003
	Nontraumatic	442	(57.1)			
	Traumatic	263	(34.0)			
Heart frequency	BPM	732		92.0	82.0–105.0	NS
Mean arterial blood pressure	mmHg	732		89.8	81.7–97.9	NS
Diuresis within last 24 h	l	704		4.1	3.0–5.7	NS
Cardiac resuscitation	None	714	(92.2)			NS
	Any	60	(7.8)			
	[if any: duration in min.]			[10.0]	[5.0–20.0]	
Hypotensive periods	None	735	(95.0)			0.028
	Any	39	(5.0)			
	[if any: duration in min.]			[15.0]	[10.0–60.0]	
Recovery						
Time between death and cross-clamp	Hour	774		12.6	10.3–16.2	NS
Time between ET report and cross-clamp	Hour	759		7.3	6.4–8.5	NS
Ischaemia time	Minute	773		201.0	165.0–238.0	0.003
Preservation solution	HTK	574	(74.2)			NS
	UW	182	(23.5)			
	Other	18	(2.3)			
Perfusion quality at recovery	Good	763	(98.6)			NS
	Inferior	11	(1.4)			
Graft quality at recovery	Good	717	(92.6)			NS
	Inferior	57	(7.4)			
Graft assessment after HTx	Good	727	(93.9)			<0.001
	Inferior	47	(6.1)			
Rescue allocation (see guideline [16])	No	613	(79.2)			NS
	Yes	161	(20.8)			
Laboratory data (at ET report)						
CK	IU/l IFCC	738		200.0	78.8–543.0	NS
CKMB	<5 IU/l	259	(34.9)			NS
	≥5 IU/l	483	(65.1)			
Troponin (T or I)	Not determined	202	(26.1)			0.002
	≤0.1 ng/ml	404	(52.2)			
	>0.1 ng/ml	168	(21.7)			
AST	IU/l IFCC	762		48.0	30.0–85.0	NS
ALT	IU/l IFCC	764		34.0	20.0–65.0	NS
Sodium	mM	769		147.0	141.0–153.0	NS
Creatinine	μM	770		70.7	54.8–96.4	NS
Bilirubin	μM	745		10.8	6.8–17.6	NS
Haemoglobin	mg/dl	767		10.1	9.0–11.6	NS
Leucocyte	G/l	770		12.7	9.8–16.9	NS
Prothrombin Time	As quick (%)	760		83.0	68.0–97.0	NS*
Anti-CMV	Negative	371	(48.0)			NS
	Positive	402	(52.0)			

Table 1. continued

	Unit of analysis or factor level	*n*	(%)	Median	Interquartile range	*P*-Value
Medication (at ET report)						
Blood transfusions (any since admission)	No	552	(71.3)			NS
	Yes	222	(28.7)			
Plasma expander (any since admission)	No	527	(68.1)			NS
	Yes	247	(31.9)			
Norepinephrine (actual doses)	None	242	(31.3)			NS
	≤0.1 μg/kg/min	304	(39.3)			
	≤0.2 μg/kg/min	129	(16.7)			
	>0.2 μg/kg/min	99	(12.8)			
Catecholamines (actual) [including norepinephrine]	No	220	(28.4)			NS
	Yes	554	(71.6)			
Catecholamines within last 24 h before ET report	No	143	(18.5)			NS
	Yes	631	(81.5)			
Steroids (actual)	No	501	(64.7)			NS
	Yes	273	(35.3)			
Steroids within last 24 h before ET report	No	480	(62.0)			NS
	Yes	294	(38.0)			
Antidiuretics (actual)	No	599	(77.4)			NS
	Yes	175	(22.6)			
Antidiuretics within last 24 h before ET report	No	468	(60.5)			NS
	Yes	306	(39.5)			
Diuretics (actual)	No	743	(96.0)			0.012
	Yes	31	(4.0)			
Diuretics within last 24 h before ET report	No	716	(92.5)			NS*
	Yes	58	(7.5)			
Insulin (actual)	No	644	(83.2)			NS
	Yes	130	(16.8)			
Antibiotics: prophylactic (since admission)	No	550	(72.4)			NS
	Yes	214	(27.6)			
Antibiotics: therapeutic (since admission)	No	493	(63.7)			NS
	Yes	281	(36.3)			
Additional diagnosis						
Previous malignancy‡	Not reported	742	(95.9)			NS
	Reported	32	(4.1)			
History of arterial hypertension	Not reported	594	(76.7)			NS
	Reported	180	(23.3)			
History of diabetes	Not reported	762	(98.4)			NS
	Reported	12	(1.6)			
History of arteriosclerosis	Not reported	730	(94.3)			NS
	Reported	44	(5.7)			
History of drug abuse‡	Not reported	751	(97.0)			NS
	Reported	23	(3.0)			
History of smoking	Not reported	519	(67.1)			NS
	Reported	255	(32.9)			
History of alcohol abuse	Not reported	633	(81.8)			NS
	Reported	141	(18.2)			
Hepatitis B‡	Anti-HBc and HBsAg negative	747	(96.5)			NS
	Anti-HBc or HBsAg positive	27	(3.5)			
Hepatitis C‡	Anti-HCV negative	766	(99.0)			NS
	Anti-HCV positive	8	(1.0)			
Acute thoracic trauma	Not reported	678	(87.6)			NS
	Reported	96	(12.4)			
Acute sepsis or meningitis‡	Not reported	758	(97.9)			NS
	Acute recovery	16	(2.1)			

Table 1. continued

	Unit of analysis or factor level	*n*	(%)	Median	Interquartile range	*P*-Value
Pancreatitis	Not reported	753	(97.3)			NS*
	Reported	21	(2.7)			
Acute pneumonia	Not reported	531	(68.6)			NS
	Reported	243	(31.4)			
Diagnostics						
Electrocardiogram	No abnormalities† [6]	710	(91.7)			NS
	Abnormalities† [6]	64	(8.3)			
Echocardiography LVF	Normal LVF (EF ≥ 50%)	679	(87.7)			NS
	Reduced LVF (EF < 50%)	25	(3.2)			
	Diastolic dysfunction	25	(3.2)			
	Status missing	45	(5.8)			
Echocardiography LVH	None (IVSd < 12 mm)	594	(76.7)			NS
	Moderate (IVSd 12–16 mm)	108	(14.0)			
	Severe (IVSd >16 mm)	27	(3.5)			
	Status missing	45	(5.8)			
Echocardiography heart valve§	No abnormalities	591	(76.4)			NS
	Insufficiency 1° only	130	(16.8)			
	Stenosis or >1° insufficiency	8	(1.0)			
	Status missing	45	(5.8)			
Echocardiography wall motion	Without abnormalities	702	(90.7)			NS
	Regional akinesia, hypokinesia	28	(3.6)			
	Status missing	44	(5.7)			
Coronary angiography	No coronary sclerosis	151	(19.5)			NS*
	Coronary sclerosis/stenosis	42	(5.4)			
	Not performed	581	(75.1)			

HTK, Custodiol® (Dr. Franz Köhler Chemie, Alsbach-Haehnlein, Germany); UW, University of Wisconsin – Belzer Viaspan® (Bristol-Meyers Squibb GmbH, Munich, Germany); LVF, left ventricular function; EF, ejection fraction; LVH, left ventricular hypertrophy; IVSd, interventricular septum diastolic. ET report: point of time where heart allocation was initiated by Eurotransplant, and recipient centres finalized their decision to realize HTx based on the donor data available.

NS: $P \geq 0.2$, NS*: $0.2 > P \geq 0.05$.

†Includes infarct-like QRS changes, bundle branch bloc, chronic atrial fibrillation, more than singular ventricular extrasystoles or Sokolow-Lyon index >3.5 cm according to the German Transplant Association [6].

‡One of these diagnosis classifies a donor as expanded criteria donor according to the German Medical Association [16,17].

§The following heart valve abnormalities existed in category stenosis or >1° insufficiency [6]: one case with minor aortic stenosis, one case with 2° aortic insufficiency and the other cases with 2° mitral or 2° tricuspid insufficiency. Category insufficiency 1° [6] covers only 1° insufficiency at any heart valve.

inferior patient survival as compared to grafts from donors without hypotensive periods (Fig. 2).

Concerning recipient parameters, in univariate analyses, a significant negative impact on patient survival could be observed for the following risk factors (Table 2): increased age, increased serum creatinine before HTx, history of diabetes, pulmonary vascular resistance (PVR) exceeding 320 dyn*s*cm^{-5} at HTx, previous complex heart surgery before HTx as well as dependency on different cardiac assist devices.

In multiple Cox regression (Table 3), patient survival was negatively influenced by increased donor age, increased troponin T or I (cut-off: >0.1 ng/ml), nontraumatic COD and prolonged ischaemia times. Hypotensive periods in donors were without negative impact. The following recipient-related factors were detrimental on patient survival: increased age and pulmonary vascular resistance (cut-off: ≥320 dyn*s*cm^{-5}), ventilator dependency before HTx, previous complex heart surgery as well as omitting calcineurin inhibitors or leucocyte proliferation inhibitors after HTx at hospital discharge.

Discussion

This is the first national investigation for Germany which takes into account joint donor and recipient factors on a multicentre level. In contrast to other studies, the analysed donor data were real-time data used for organ allocation and terminal decisions by recipient centres to realize HTx. The corresponding recipient data were collected for quality assurance reasons according to German law. To ensure data consistency, our study was limited to HTx

Table 2. Recipient characteristics used in analysis of patient survival after adult heart transplantation (HTx). For interval-scaled parameters, median and interquartile range as well as significant *P*-values of univariate Cox regression are given. For nominal and categorical parameters, percentages as well as significant *P*-values of log-rank tests are shown.

Basic recipient data	Unit of analysis or factor level	*n*	(%)	Median	Interquartile range	*P*-Value
Age	Year	774		54.0	45.0–60.0	0.008
Weight	kg	771		77.0	68.0–87.0	NS
Height	cm	763		175	170–180	NS*
Gender	Female	143	(18.5)			NS
	Male	631	(81.5)			
Ratio donor/recipient weight	≥1	413	(53.6)			NS
	<1	358	(46.4)			
Ratio donor/recipient height	≥1	413	(53.6)			NS
	<1	358	(46.4)			
HLA-panel-reactive antibodies	≥5%	39	(5.0)			NS
	<5%	735	(95.5)			
Rejections (primary hospital stay after HTx)	>0	106	(15.5)			NS
	=0	580	(84.5)			
Heart disease	Dilatative cardiomyopathy	438	(56.6)			NS
	Other	336	(43.4)			
Waiting list status high urgency (according [16])	Yes	556	(71.8)			NS
	No	218	(28.2)			
Recipient ventilated before HTx	Yes	26	(3.4)			<0.001
	No	748	(96.6)			
HTx combined with other organs	Yes	18	(2.3)			NS
	No	756	(97.7)			
Diabetes before HTx	Yes	154	(19.9)			0.047
	No	620	(80.1)			
Assist device	None	559	(72.2)			0.046
	LVAD	108	(14.0)			
	BVAD, TAH, ECMO, IABP	107	(13.8)			
Pulmonary vascular resistance	Not reported	158	(20.4)			0.002
	<320 dyn*s*cm^{-5}	562	(72.6)			
	≥320 dyn*s*cm^{-5}	54	(7.0)			
Heart surgery before HTx	None	472	(61.0)			0.041
	Coronary ± valve	124	(16.0)			
	Valve/inborn vitium/other	178	(23.0)			
Creatinine before HTx	mg/dl	773		1.3	1.0–1.7	0.011
Hospital stay after HTx	Day	774		22.0	1.0–57.3	NS
Immunosuppression						
Induction therapy	Any	340	(43.9)			NS*
	None	434	(56.1)			
Initial: cyclosporine†	Yes	434	(56.1)			NS
	No	340	(43.9)			
Initial: tacrolimus†	Yes	173	(22.4)			NS
	No	601	(77.6)			
Initial: azathioprine†	Yes	148	(19.1)			0.005
	No	626	(80.9)			
Initial: mycophenolate†	Yes	418	(54.0)			NS
	No	356	(46.0)			
Initial: steroids	Yes	731	(94.4)			NS*
	No	43	(5.6)			
Initial: m-TOR inhibitor	Yes	15	(2.9)			NS
	No	502	(97.1)			
Initial: other‡	Yes	48	(6.2)			0.016
	No	726	(93.8)			
Discharge: cyclosporine†	Yes	362	(46.8)			NS*
	No	412	(53.2)			

Table 2. continued

Basic recipient data	Unit of analysis or factor level	*n*	(%)	Median	Interquartile range	*P*-Value
Discharge: tacrolimus†	Yes	368	(47.5)			<0.001
	No	406	(52.5)			
Discharge: azathioprine†	Yes	30	(3.9)			NS
	No	744	(96.1)			
Discharge: mycophenolate†	Yes	616	(79.6)			<0.001
	No	158	(20.4)			
Discharge: steroids	Yes	721	(93.2)			<0.001
	No	53	(6.8)			
Discharge: m-TOR inhibitor	Yes	26	(5.0)			NS
	No	491	(95.0)			
Discharge: other‡	Yes	69	(8.9)			0.004
	No	705	(91.1)			

NS = $P \geq 0.2$, NS*: $0.2 > P \geq 0.05$.

†For further multiple analysis, immunosuppressives were summarized: cyclosporine and tacrolimus into one group of calcineurin inhibitors and azathioprine and mycophenolate into one group of leucocyte proliferation inhibitors.

‡The kind of other immunosuppressive drugs had not been specified by the recipient centres.

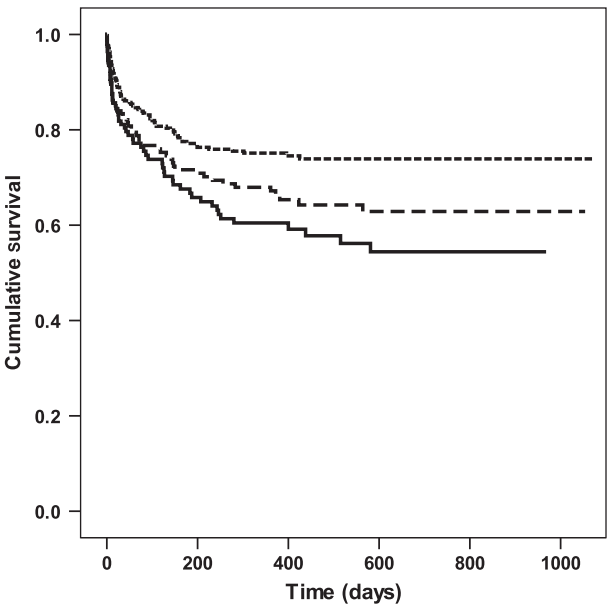

Figure 1 Survival function of the donor-related risk factor 'troponin'. Dotted line: troponin T or I <=0.1 ng/ml (*n* = 404); dashed line: troponin not determined (*n* = 202); solid line: troponin T or I > 0.1 ng/ml (*n* = 168); log-rank test: *P* = 0.002.

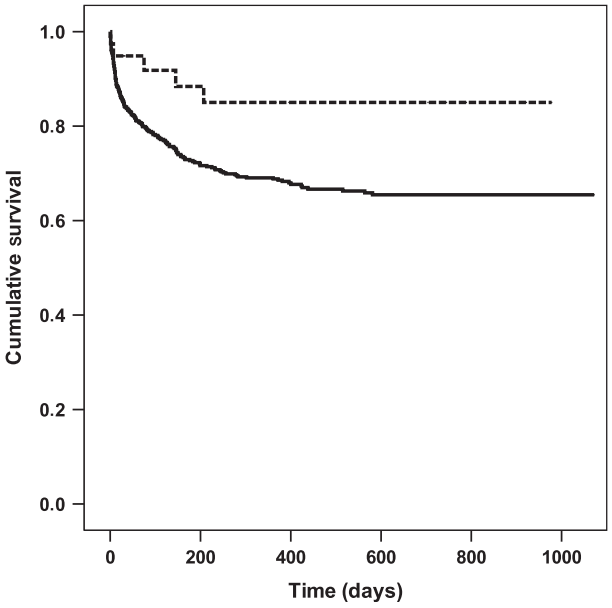

Figure 2 Survival function of the donor-related risk factor 'hypotensive periods'. Dotted line: any hypotensive period (*n* = 39); solid line: no hypotensive periods (*n* = 735); log-rank test: *P* = 0.028. After the process of appropriate donor selection before heart transplantation, hypotensive periods are without negative impact on recipient survival.

performed in Germany with grafts recovered in Germany only.

Coordination, recovery and transplant teams are aware of the risks associated with unchangeable factors (e.g. donor age) and changeable factors (e.g. donor treatment). At recipient centres, it is decided whether a graft offered for a particular recipient will be of a benefit or not taking into account the actual health status of the recipient. Therefore, our analyses may be affected by a selection bias caused by donor characterization and the allocation process.

In Cox regression analysis (Table 3), increasing donor age and prolonged CIT were associated with lower patient survival rates. This corresponds well with the findings of previous studies [9,11–13]. Donor age may be taken as a surrogate parameter for other comorbidities that limit success in HTx and which are not perfectly described by other

Table 3. Results of multiple Cox regression analysis concerning patient survival after first heart transplantation (n = 774, recipient age ≥18 years). Data analysis was preceded by a donor–recipient selection process during graft allocation.

	Unit of analysis or factor level	SE	Hazard ratio	95%-CI		*P*-Value
Donor-related risk factors						
Donor age	Year	0.007	1.021	1.008	1.035	0.002
Ischaemia time	Hour	0.071	1.197	1.041	1.375	0.011
Cause of death	Nontraumatic (versus traumatic/secondary)	0.162	1.481	1.079	2.034	0.015
Hypotensive periods reported	Any	0.458	0.407	0.166	0.999	0.050
Donor Troponin I or T	≤0.1 ng/ml	Reference category				
	>0.1 ng/ml	0.175	2.075	1.473	2.921	<0.001
	Not determined	0.173	1.339	0.955	1.878	0.090
Recipient-related risk factors						
Recipient age	Year	0.007	1.017	1.002	1.031	0.024
Ventilator dependent before HTx	Yes	0.269	3.744	2.211	6.340	<0.001
Pulmonary vascular resistance	<320 dyn*s*cm^{-5}	Reference category				
	≥320 dyn*s*cm^{-5}	0.233	1.761	1.115	2.781	0.015
	Not reported	0.172	1.338	0.956	1.873	0.090
Heart surgery before transplantation	None	Reference category				
	Coronary surgery, heart valve replacement	0.202	1.011	0.680	1.503	0.956
	Repeated heart surgery, vitium correction, other	0.168	1.763	1.270	2.449	0.001
Immunosuppression						
Calcineurin inhibitor at hospital discharge*		0.211	0.380	0.251	0.574	<0.001
Proliferation inhibitor at hospital discharge†		0.159	0.441	0.323	0.603	<0.001

*Tacrolimus or cyclosporine.
†Mycophenolate or azathioprine.

donor characteristics. After adjustment for covariables, the nontraumatic COD of a donor was an additional risk factor for failure as compared to secondary or traumatic COD, which were both of equivalent risk in univariate analysis and therefore summarized into one group. With the donor selection process completed, other cardiovascular risk factors (Table 1) were without effect on patient survival, although they are assumed to be associated with cerebrovascular diseases and nontraumatic COD.

Again, extended CIT limited patient survival. This raises concerns whether everything was performed to mitigate this problem in a recipient population experiencing more and more previous cardiac surgery or implantation of assist devices.

Increased donor troponin levels themselves should not preclude HTx as after appropriate recipient selection and short CIT, experienced centres achieve acceptable results [9]. However, interpretation of the results of such tests requires further studies. The complications of temporary neurocardiac injury after devastating cerebral injuries with or without cardiac arrest must be taken into account as one reason for reversible increase in heart enzymes.

As the level of creatinine phosphokinase–muscle–brain fraction (CK-MB) was without significant impact on patient survival, the suggestion to characterize donor hearts by determining CK-MB [10,14] may be outdated. CK-MB values may be increased due to brain tissue necrosis or the fact that measurement differs between laboratories. Other more heart-tissue-specific parameters exist (e.g. troponin T [15]).

Interestingly, in our multiple Cox regression, many donor factors discussed as risk factors [1,6,9,12,15] were without significant effect on patient survival: cardiac resuscitation (independent of duration), application of norepinephrine or other catecholamines (independent of standard dosage), donor medication, minor abnormalities in diagnostics (e.g. ECHO, ECG) or cardiovascular risk factors, anti-CMV status of the donor as well as other donor-derived disease transmission risks according to the definition of extended donor criteria (EDC) by a national guideline [16]. Paradoxically, hypotensive periods in a donor – as rated by recipient centres during their acceptance of a graft for HTx and as defined within the ET manual [10] – did not limit patient survival (Fig. 2). The most probable explanation of these results is that careful donor and recipient selection was carried out, especially concerning donors with recovery from cardiocirculatory instability while adhering the recommendations [1,8,9,12,15]. Wittwer and Wahlers concluded [1] that the course from devastating cerebral injury beyond brain death is a cardiac stress test. In case of normal ECG and ECHO, hearts with minor coronary vessel abnormalities may be accepted for transplantation. This more or less functional approach may be underlined by our observations.

Two unexpected observations deserve some attention: Firstly, donor CORO was performed in only 24.9% of the cases, while donor median donor age was 44 years. The restrictive use of CORO may be explained by a targeted evaluation of donors and restricted availability. In univariate analysis, (unadjusted) patient survival was similar in cases with and without pathologies detected by CORO. However, it was lower than in cases without CORO performed. Of course, to perform CORO is the final step in risk assessment of a graft potentially compromised by other risks such as, donor age – which is significant in multiple analysis. Secondly, the need to use diuretics during donor maintenance within the hours before recovery was a risk factor in univariate analysis. This needs further evaluation, as this may indicate some underestimated problems in donor maintenance.

Concerning recipient-related risk factors, multiple Cox regression analysis (Table 3) revealed that increased age as well as pulmonary hypertension ($\geq$320 dyn*s*cm^{-5}), previous (especially more complex) heart surgeries and ventilator dependency are of negative impact on patient survival. Size, weight and gender matches were without significant effect, which may probably be caused by adequate donor–recipient matching. This confirms current recommendations [1,9].

According to national guidelines [16,17], rescue allocation took place in 21.8% of the grafts used for HTx. 71.8% of the recipients were listed as 'high urgent candidates' for HTx. PRA exceeded 5% in 5.0% of the cases. This may indicate additional risks. However, these factors were without significant effect on patient survival in multiple analysis. Rescue allocation had to be initiated by Eurotransplant when the graft had been turned down three times for medical reasons by recipient centres.

The assessment of graft quality at recovery is subjective as traditionally performed by the recovery surgeon. The grading is made according to the policy of the organ reports to be used in the ET area. Graft quality at recovery was without significant impact on patient survival. The functional assessment performed after reperfusion at HTx by the implanting team is a different observation with prognostic value (Table 1).

Immunosuppressive drugs were used and combined after HTx until hospital discharge heterogeneously. Omitting the use of calcineurin or leucocyte proliferation inhibitors at hospital discharge is of negative impact on patient survival. Evaluation of immunosuppressive therapy after HTx was not part of this study and should be further investigated.

A limitation of the study is the short follow-up period. However, when implementing the national concept of mandatory quality assurance in medicine, it was decided to follow up recipients only for 3 years. In the future, such quality assurance programmes should include longer time periods within a transplant registry. On the other hand, this study contributes valuable knowledge on how to merge multiple institutional databases without conflict of interests and with appropriate protection of patient rights. The methodological know-how gained by this study can be used to establish an effective follow-up register of transplantations while using different institutional databases.

Conclusion

After careful donor selection, advanced donor and recipient age, nontraumatic COD as well as prolonged CIT persisted to be risk factors for survival. Additionally, recipient-related risks were increased pulmonary hypertension and previous complex heart surgery. When interpreting the results of the Cox regression model, it must be considered that donor and recipient selection during the donation–allocation–transplantation process took place before the data were analysed.

Authorship

MK: data analysis, research design, performance of the research and writing of the paper. C-LF-F: performance of the research, writing the paper and data analysis. MK and C-L.F-F: equally contributed to the study. IS: data analysis and performance of the research. SB, SRZ and FP: research design and performance of the research. GK: research design and writing of the paper. NRF: research design, performance of the research and writing the paper.

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