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ORIGINAL ARTICLE

Intracerebral bleeding in donors is associated with reduced short-term to midterm survival of heart transplant recipients

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Abstract

Aim The quality of the donor heart is known to have a crucial effect on outcome after heart transplantation (HTx). Although leading to brain death in the end, the initial cause of death of the donor and its potential influences on organ quality are heterogeneous. However, it is still controversial to which extent the donor cause of death is associated with outcome or survival post-HTx.

Methods and results We included all patients undergoing HTx in our centre between September 2010 and June 2021 (n = 218). Recipients were divided in five groups related to their donor cause of death: intracerebral bleeding ('ICB', n = 95, 44%), traumatic brain injury ('trauma', n = 54, 25%), hypoxic brain damage ('hypoxic', n = 34, 16%), cerebrovascular ('vascular', n = 15, 7%), or other cause (n = 20, 9%). Baseline characteristics, perioperative parameters, and survival after 30 and 90 days as well as 5 years after transplantation were collected.

Results Intracerebral bleeding in donors compared with traumatic brain injury is associated with higher probability of need for ECLS post-HTx (35% vs. 19%, P = 0.04) and significantly reduced survival up to 5 years post-HTx (i.e. 1 year survival: 61% vs. 95%, $P < 0.0001$). Although other conditions also show significant changes in outcome and survival, the effect is strongest for ICB, where survival is also reduced compared with all other causes (1 year: 61% vs. 89%, $P < 0.0001$).

Conclusions In this retrospective analysis, donor cause of death is associated with differing outcome and survival after HTx. Intracerebral bleeding hereby shows strongest decline in outcome and survival in comparison with all other causes.

Keywords Donor cause of death; Short-term survival; Intracerebral bleeding; Heart transplantation

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Introduction

The quality of the donor heart is known to have a crucial effect on outcome and complications after heart transplantation (HTx).[1] A potential donor risk factor for organ quality is the donor cause of death. Although leading to brain-stem death in the end, the initial cause of death of the donor and its potential influences on organ quality are heterogeneous. Different categorizations exist in literature, mainly dividing the donor cause of death either by traumatic and non-traumatic causes[2] or in categories such as anoxia/hypoxia, cerebrovascular events, or head trauma.[1,3] Therefore, different numbers are reported to the major and minor causes of death: according to the International Society for Heart and Lung Transplantation, between 2010 and 2018, 26% of all donors died from anoxia/hypoxic brain damage, 26% by cerebrovascular events, and 46% by traumatic brain injury.[4] However, depending on the inclusion of intracerebral

bleeding (ICB) in one or the other group, percentages are differing: in a US cohort of 358 donors for HTx, Cohen *et al.* reported 61% donors with traumatic brain injury but included all ICBs into this group, so that cerebrovascular events were only 3%.[3]

Apart from the donor cause of death classification, it is still controversial to which extent the donor cause of death is associated with outcome or survival post-HTx: while some studies report no significant influence of donor cause of death on early or late mortality,[1–3] others describe differences mainly between traumatic or non-traumatic donor cause of death.[5,6]

Therefore, this study aims to fill this gap by investigating a potential association of donor cause of death with morbidity and different medium-term to midterm survival up to 5 years after HTx.

Patients and methods

Ethics

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practices. All subjects participated voluntarily. The study was approved by our local ethics committee.

Patients and study design

Between September 2010 and June 2021, a total of n = 218 patients underwent HTx in our centre. Recipients were divided into five groups related to their donor cause of death: intracerebral bleeding ('ICB', n = 95, 44%), traumatic brain injury ('trauma', n = 54, 25%), hypoxic brain damage ('hypoxic', n = 34, 16%), cerebrovascular ('vascular', n = 15, 7%), or other cause (n = 20, 9%; including benign brain tumours, intoxication or cerebral infectious diseases like encephalitis, myelitis, and encephalomyelitis).

Data collection

All relevant recipient and donor variables were reviewed and compared between the five groups. Recipient and donor characteristics and recipient survival after up to 5 years, including 30 and 90 days and 1 year after transplantation, where applicable, were collected.

Statistical analysis and figure making

Qualitative (dichotomous) variables were compared by the Pearson χ^2 test or, when its application conditions were not met, by Fisher's exact test. If one of the two groups contained a zero value for an event, Yates' correction was added. Quantitative variables were compared by the Students' t-test. The tests were performed bilaterally, and the threshold of significance was set at 0.05. Statistical analysis was performed using GraphPad Prism and IBM SPSS Statistics software (SPSS). Figures were created using GraphPad Prism, Microsoft PowerPoint, and IBM SPSS.

Results

Recipient data

All included recipients (n = 218, refer to methods) were divided in five groups related to their donor cause of death: Intracerebral bleeding ('ICB', n = 95, 44%), traumatic brain injury ('trauma', n = 54, 25%), hypoxic brain damage ('hypoxic', n = 34, 16%), cerebrovascular ('vascular', n = 15, 7%) or other cause (n = 20, 9%). In the group with donor traumatic brain injury, recipients were younger, with significance only compared with ICB or hypoxic brain damage (50.1 vs. 55.7 resp. 57.9 years, P = 0.004 and 0.002). The percentage of male recipients was slightly different between the groups, with the smallest amount in ICB (63%) and highest in the hypoxic brain damage group (91%).

Groups also differed in high-urgency waiting list status, with significance only in recipients with donor ICB compared with traumatic brain damage (36% vs. 61%, P = 0.003).

With few exceptions, all other baseline characteristics were comparable, including other parameters of size mismatch and comorbidities. Furthermore, no statistically relevant differences could be observed in laboratory values, including recipient sodium and potassium levels as well as creatinine, bilirubin, and haemoglobin (refer to *Table 1*).

Donor data

Donors with ICB or cerebrovascular death were older, with significance for comparison between ICB and traumatic as well as hypoxic brain damage (47.5 vs. 38.2 resp. 40.6 years, $P < 0.0001$ and P = 0.002) and between cerebrovascular death and traumatic brain damage (47.3 vs. 38.2 years, P = 0.02). The percentage of male donors differed between the groups, with the smallest amount in ICB (39%) and highest in the hypoxic brain damage group (74%).

Hypoxic brain damage donors had more often cardiopulmonary resuscitation before brain death (74%, P for all comparisons < 0.0001). Donors with traumatic brain damage had less occurrence of arterial hypertension, significant in comparison with ICB (30% vs. 68%, P = 0.002) and hypoxic brain damage (30% vs. 78%, P = .02), Additionally, donors with ICB had significantly higher sodium levels than those with traumatic brain damage (150.3 vs. 147.2 mmol/L, P = .03).

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Table 1 Preoperative recipient parameters

Recipient variables	Gr 1 ICB $n = 95$	Gr 2 Trauma $n = 54$	Gr 3 Hypoxic $n = 34$	Gr 4 Vascular $n = 15$	Gr 5 Other $n = 20$	*P* value 1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Age (years)	55.7 ± 10.7	50.1 ± 12.2	57.9 ± 9	54.5 ± 10.7	58.3 ± 6.6	**0.004**	0.30	0.70	**0.002**	0.21	0.28
Gender (% male)	63	76	91	80	80	0.11	**0.002**	0.20	0.09	1.0	0.35
Height (cm)	172.2 ± 9.3	177.2 ± 7.3	177.2 ± 6.6	173.3 ± 8.5	172.1 ± 6.1	**0.001**	**0.01**	0.68	1.0	0.09	0.09
Weight (kg)	76 ± 17.4	79.6 ± 13.2	83.9 ± 15.5	77.4 ± 11	74.3 ± 11.7	0.19	**0.02**	0.77	0.18	0.56	0.16
Body mass index (kg/m^2)	25.4 ± 4.9	25.5 ± 4	27 ± 5	25.8 ± 3.7	24.9 ± 3.5	0.94	0.11	0.76	0.12	0.76	0.43
Predicted heart mass ratio (%)	1	1	1	1	1	0.35	0.70	0.83	0.23	0.73	0.63
Cardiac reoperation (%)	62	61	82	60	55	0.9	0.03	0.88	0.06	0.54	0.15
High-urgency waiting list (%)	36	61	47	60	30	**0.003**	0.25	0.07	0.27	1.0	0.54
Ventricular assist device (%)	52	52	71	40	35	0.97	0.06	0.40	0.12	0.56	0.06
CPR pre-HTx (%)	12	13	24	0	10	0.84	0.10	0.38	0.20	0.35	0.12
Haemodialysis (%)	6	2	3	7	5	0.21	0.48	0.98	0.70	0.33	0.54
Diabetes mellitus (%)	33	13	18	0	15	**0.01**	0.11	**0.02**	0.51	0.32	0.20
Laboratory values											
Haemoglobin (g/dL)	12 ± 2.1	12.1 ± 2	11.5 ± 2.6	11.5 ± 2.1	12.5 ± 2.7	0.75	0.34	0.40	0.27	0.31	0.94
Creatinine (mg/dL)	1.4 ± 1.2	1.4 ± 0.9	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	0.90	0.67	0.86	0.46	0.72	0.82
Bilirubin (mg/dL)	0.8 ± 0.9	0.9 ± 0.7	0.8 ± 1.1	1.2 ± 1.1	0.8 ± 0.4	0.83	0.99	0.22	0.87	0.26	0.39
Lactate dehydrogenase (U/L)	352 ± 388.8	290.6 ± 170.9	501.8 ± 611.2	262.9 ± 79.3	274.1 ± 72.9	0.31	0.13	0.40	**0.03**	0.57	0.16
Sodium (mmol/L)	137.4 ± 3.5	138 ± 3.8	139.1 ± 2.8	138.4 ± 3.2	137.9 ± 4.5	0.44	0.08	0.41	0.32	0.78	0.56
Potassium (mmol/L)	4.2 ± 0.5	4.4 ± 0.6	4.3 ± 0.3	4.2 ± 0.6	4.3 ± 0.3	0.06	0.46	0.85	0.30	0.16	0.48

CPR, cardiopulmonary resuscitation.

Preoperative recipient data regarding the donor cause of death [intracerebral bleeding ('ICB', $n = 95$, 44%), traumatic brain injury ('trauma', $n = 54$, 25%), hypoxic brain damage ('hypoxic', $n = 34$, 16%), cerebrovascular ('vascular', $n = 15$, 7%), or other cause ($n = 20$, 9%)]. Mean and standard deviation values for continuous variables or percentages for discrete variables are shown. Significance was calculated by the Pearson χ^2 test or, when its application conditions were not met, by Fisher's exact test for qualitative variables and the Student's *t*-test for quantitative variables. Bold *P* values represent statistical significance.

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With few exceptions, all other baseline characteristics and laboratory values were comparable, including other parameters of size mismatch, left ventricular ejection fraction and comorbidities, as well as donor potassium levels and lactate dehydrogenase (refer to *Table 2*).

Perioperative morbidity and mortality

Regarding perioperative and postoperative parameters, both groups did not differ in cold graft ischaemia time, duration of surgery, time on mechanical ventilation, length of postoperative hospital or IMC/ICU stay, or need for transfusion of packed red blood cells (refer to *Table 3*). However, in the group of donor hypoxic brain damage, total graft ischaemia time was lower, with significance in comparison with traumatic and cerebrovascular brain damage (198.8 vs. 218.6 resp. 229.2 min; $P = 0.03$ resp. 0.02). Also, in the donor traumatic brain damage group, the need for transfusion of fresh frozen plasma during surgery and platelets on IMC/ICU was lower.

Regarding common postoperative morbidities, patients did not differ in the likelihood of kidney failure with haemodialysis post-HTx, neurological complications, the incidence of acute graft rejection (>1R), or occurrence of severe infection or sepsis. However, the need for mechanical life support post-HTx was higher in the donor-ICB group, with comparison with traumatic brain damage being significant (35% vs. 19%, $P = 0.04$). Additionally, the mortality under mechanical life support was also significantly different in both groups (32% vs. 0%, $P = 0.04$). The rate of primary isolated right ventricular failure was comparable between all groups.

Concerning early mortality, overall survival was comparable between groups, with exception of the donor-ICB group. Here, survival in direct individual comparison with the other groups is reduced, with strongest and significant reduction between ICB and traumatic brain damage 30 days (83% vs. 100%, $P = 0.002$), 90 days (77% vs. 100%, $P = 0.0002$), and 1 year (61% vs. 95%, $P < 0.0001$) after HTx (refer to *Table 3*). When comparing survival of recipients with donor ICB vs. all other donor cause of death, survival reduction is also significantly reduced 30 days (83% vs. 97%, $P = 0.0012$), 90 days (77% vs. 94%, $P = 0.0006$), and 1 year (61% vs. 89%, $P < 0.0001$) after HTx. These results were confirmed by Kaplan–Meier survival analysis (refer to *Figure 1*). The recipients' cause of death was not different between the groups (refer to *Table 3*).

Discussion

Only limited knowledge exists on the association of perioperative morbidity and mortality in heart transplant recipients and donor cause of death. We therefore aimed to enlighten possible differences between different causes of donor brain-stem death (ICB or hypoxic, traumatic, and cerebrovascular brain damage) on outcome after HTx and thus retrospectively analysed 218 HTx recipients in a 10 year study period.

Here, our main finding is that in our heart transplant cohort, ICB as donor cause of death is associated with reduced short-term to midterm survival after HTx. In comparison with all other causes, survival in the donor-ICB group is significantly reduced 30 days (83% vs. 97%, $P = 0.0012$), 90 days (77% vs. 94%, $P = 0.0006$) and 1 year (61% vs. 89%, $P < 0.0001$) after HTx, with strongest effect between ICB and traumatic brain damage. Comparing the current study with literature, survival in the non-ICB donor cause of death groups is comparable with larger HTx cohorts (89–93%[7–9]).

In our study cohort, the majority of all donor cause**s** of death were ICB (44%), followed by traumatic brain injury (25%), hypoxic (16%), and cerebrovascular brain damage (7%); 9% had other or unknown causes. When taking into account the differences in the underlying categorization in other studies, this goes in line with published data from larger HTx cohorts.[3,4] In addition, the nature of the donor cause of death varies between regions and countries worldwide, with for example an almost absence of gun-shot wounds and acute explosive brain death in Europe.[10]

The influence of donor cause of death on survival after HTx remains controversial in published literature.[1–3,5,6,11] Only a few studies exist that explicitly analyse the influence of donor ICB on outcome after HTx, suggesting to have impact on outcome and mortality after HTx[12]; however, all those cohorts included retrospective patient data from different HTx eras, leading to a potential bias.

The same can be observed for other solid organ transplantations such as kidney or lung transplantation.[13–16] Recently, a novel risk assessment score for allocation in HTx by Schramm *et al*. showed no predictive value by including the donor cause of death as a risk factor in their multivariate model; however, ICB was the only different and nearly significant donor cause of death in all groups regarding short-term to midterm survival.[17]

Concerning perioperative recipient and donor characteristics, donor cause of death groups were slightly differing in size parameters, age, and gender. However, those differences 'match' in both recipients and donors, most likely due to the choice of allocation to avoid mismatches. Additionally, we found a predominance of male donors in the trauma group in accordance with previous studies,[13] and absolute age differences were small, making relevance for survival unlikely.

Apart from size, age and gender, almost all other recipient characteristics were comparable, with the exception of those with donor ICB were more often on the high-urgency waiting list for HTx, leading to a potential bias. Donors were only differing in some parameters including predominantly higher CPR pre-brain death and lowered haemoglobin levels in

Table 2 Preoperative donor parameters

Donor variables	Gr 1 ICB $n = 95$	Gr 2 Trauma $n = 54$	Gr 3 Hypoxic $n = 34$	Gr 4 Vascular $n = 15$	Gr 5 Other $n = 20$	*P* value 1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Age (years)	47.5 ± 10.5	38.2 ± 13.5	40.6 ± 12	47.3 ± 10.1	37.6 ± 12.2	<**0.0001**	**0.002**	0.95	0.40	**0.02**	0.07
Gender (% male)	39	72	74	53	60	**0.0002**	**0.001**	0.40	1.0	0.21	0.20
Height (cm)	172.6 ± 8.1	177 ± 8.0	177.2 ± 8.7	173.9 ± 6.8	175.8 ± 9.8	**0.002**	**0.01**	0.57	0.91	0.17	0.20
Weight (kg)	77.6 ± 14.5	80.6 ± 12.3	82.7 ± 16.9	82.3 ± 18.2	76.6 ± 10.3	0.21	0.10	0.28	0.51	0.69	0.94
Body mass index (kg/m^2)	25.9 ± 4.1	25.6 ± 3	27.2 ± 7.4	27.1 ± 5.3	24.9 ± 3.3	0.63	0.22	0.32	0.17	0.16	0.97
Left ventricular ejection fraction (%)	62 ± 10	60 ± 8	61 ± 8	58 ± 6	57 ± 9	0.31	0.91	0.26	0.39	0.53	0.22
CPR pre-brain death (%)	18	13	74	13	50	0.49	<**0.0001**	1.0	<**0.0001**	1.0	<**0.0001**
Norepinephrine, peak dose (μg/kg/min)	0.2	0.2	0.2	0.1	0.3	0.92	0.56	0.07	0.70	0.16	0.06
Arterial Hypertension (%)	68	30	78	55	20	**0.002**	0.71	0.49	**0.02**	0.27	0.37
Diabetes mellitus (%)	9	18	75	33	10	0.21	0.10	0.28	0.51	0.69	0.94
Laboratory values											
Haemoglobin (g/dL)	10.3 ± 2.4	8.8 ± 2.1	11.2 ± 2.39	10.2 ± 3.02	11.5 ± 2.84	**0.0002**	0.10	0.83	<**0.0001**	**0.05**	0.25
Lactate dehydrogenase (U/L)	388.3 ± 611.14	495 ± 329.2	589.7 ± 406.59	412.4 ± 256.27	517.4 ± 424.66	0.27	0.09	0.89	0.27	0.43	0.18
Sodium (mmol/L)	150.3 ± 7.6	147.2 ± 9.1	148.6 ± 8.4	149.3 ± 5.3	150.6 ± 10	**0.03**	0.28	0.65	0.48	0.39	0.76
Potassium (mmol/L)	4.2 ± 0.5	4.2 ± 0.8	4.2 ± 0.5	3.9 ± 0.6	4.1 ± 0.6	0.59	0.78	0.12	0.58	0.21	0.25

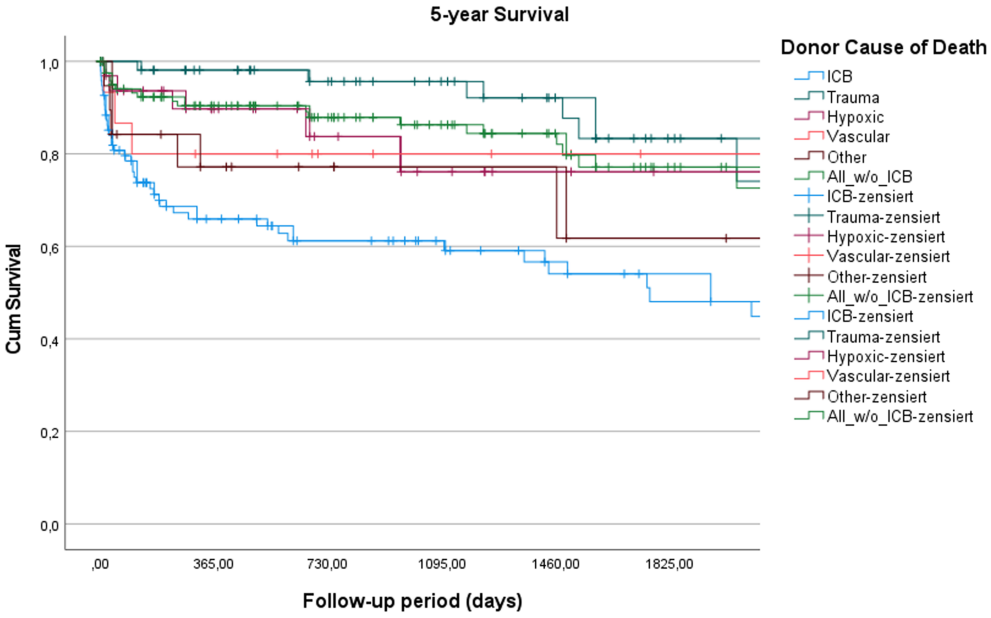
Preoperative donor data regarding the donor cause of death [intracerebral bleeding ('ICB', $n = 95$, 44%), traumatic brain injury ('trauma', $n = 54$, 25%), hypoxic brain damage ('hypoxic', $n = 34$, 16%), cerebrovascular ('vascular', $n = 15$, 7%), or other cause ($n = 20$, 9%)]. Significance was calculated by the Pearson χ^2 test or, when its application conditions were not met, by Fisher's exact test for qualitative variables and the Student's *t*-test for quantitative variables. Bold *P* values represent statistical significance.

Table 3 Perioperative and postoperative parameters and survival, grouped by donor cause of death [intracerebral bleeding ('ICB', *n* = 95, 44%), traumatic brain injury ('trauma', *n* = 54, 25%), hypoxic brain damage ('hypoxic', *n* = 34, 16%), cerebrovascular ('vascular', *n* = 15, 7%), or other cause (*n* = 20, 9%)]

Outcome and survival	Gr 1 ICB *n* = 95	Gr 2 Trauma *n* = 54	Gr 3 Hypoxic *n* = 34	Gr 4 Vascular *n* = 15	Gr 5 Other *n* = 20	*P* value					
						1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Total graft ischaemia time (min)	217.4 ± 57	218.6 ± 40.7	198.8 ± 38.6	229.2 ± 46.4	221.7 ± 44.9	0.89	0.09	0.45	**0.03**	0.40	**0.02**
Graft cold ischaemia time (min)	151.9 ± 56.4	152.9 ± 38.2	132.3 ± 39	165.5 ± 43.3	161.4 ± 43.8	0.90	0.07	0.38	0.06	0.28	0.06
Postoperative hospital stay (days)	43.5 ± 35.2	46 ± 29.1	49.3 ± 42.1	39.5 ± 25.5	44.8 ± 27.1	0.66	0.46	0.68	0.69	0.44	0.43
Postoperative IMC/ICU stay (days)	22.1 ± 26.9	24.3 ± 21.7	28.6 ± 32.4	22.7 ± 27.5	24.1 ± 21.5	0.61	0.27	0.93	0.47	0.82	0.55
Mechanical ventilation (h)	148.2 ± 187.2	132.1 ± 180	155.3 ± 195.9	131 ± 163.9	190.4 ± 259.8	0.62	0.86	0.74	0.60	0.98	0.69
Duration of surgery (min)	453.4 ± 124.5	419.3 ± 104.1	440.8 ± 122.6	416 ± 95	424.4 ± 107.7	0.09	0.62	0.27	0.39	0.91	0.50
Blood transfusions (during surgery)											
Packed red blood cells (mL)	3857.1 ± 2934	3283.2 ± 2230.6	4167 ± 3710.4	3798 ± 3294.2	3621.2 ± 3091.1	0.24	0.65	0.94	0.19	0.50	0.75
Platelets (mL)	1148.6 ± 788.5	1034 ± 792.3	1356.7 ± 990.5	1173.3 ± 1049.5	1125.9 ± 819.3	0.42	0.25	0.92	0.12	0.59	0.58
Fresh frozen plasma (mL)	1560.7 ± 1496.9	860 ± 1052.6	2241.7 ± 2480.3	1916.7 ± 2479.4	1764.7 ± 1945	**0.005**	0.08	0.46	**0.001**	**0.02**	0.69
Blood transfusions (on IMC/ICU)											
Packed red blood cells (mL)	3734.5 ± 4797.3	2700 ± 2953.5	3629.7 ± 4363.1	3708 ± 3993.2	4995 ± 6494	0.16	0.92	0.98	0.26	0.29	0.95
Platelets (mL)	1251.5 ± 2409.2	531.3 ± 858.4	1107.3 ± 2390.1	1202.7 ± 1485.3	1512.5 ± 2891.4	**0.04**	0.78	0.94	0.12	**0.03**	0.89
Fresh frozen plasma (mL)	5892.7 ± 8010	4792.5 ± 4471.8	5783.3 ± 6114.8	5700 ± 5796	9468.8 ± 9513.9	0.36	0.95	0.93	0.41	0.53	0.97
Postoperative morbidity											
Infection/Sepsis (%)	23	19	29	27	33	0.68	0.48	0.75	0.29	0.49	1.0
Rejection within stay (%)	9	6	10	7	0	0.75	1.0	1.0	0.66	1.0	1.0
Haemodialysis post-HTx (%)	56	55	55	47	75	0.86	1.0	0.58	1.0	0.77	0.75
Neurological complications (%)	20	9	20	27	33	0.16	1.0	0.51	0.19	0.10	0.71
Re-thoracotomy post-HTx (%)	32	21	27	40	48	0.18	0.66	0.56	0.59	0.18	0.50
Isolated right ventricular failure post-HTx, *n* (%)	8 (8)	3 (6)	3 (9)	2 (13)	2 (10)	0.52	0.94	0.54	0.55	0.30	0.63
ECLS post-HTx (%)	35	19	33	20	25	**0.04**	0.85	0.25	0.13	0.92	0.35
Died on support (% of whole group)	11	0	6	7	5	**0.01**	0.73	1.0	0.15	0.22	1.0
ECLS-related mortality (% of ECLS per group)	32	0	18	33	20	**0.04**	0.31	0.97	0.18	0.23	0.52
Survival											
30 day survival, *n* (%)	77/92 (83.7)	53/53 (100)	29/31 (93.5)	14/15 (93.3)	18/19 (94.7)	**0.002**	0.17	0.33	0.26	0.50	0.98
90 day survival, *n* (%)	68/88 (77.3)	53/53 (100)	27/29 (93.1)	13/15 (86.7)	13/16 (81.3)	**0.0002**	0.06	0.41	0.24	0.07	0.48
1 year survival, *n* (%)	47/77 (61.0)	38/40 (95.0)	19/22 (86.4)	11/14 (78.6)	10/14 (71.4)	**<0.0001**	**0.05**	0.21	0.23	0.07	0.54
Recipient cause of death											
Sepsis/Infection, *n* (%)	14/40 (35)	3/6 (50)	2/5 (40)	2/6 (33)	3/5 (60)	0.48	0.83	0.94	0.74	0.56	0.82
Cancer, *n* (%)	2/40 (5)	1/6 (17)	1/5 (20)	2/6 (33)	0/5 (0)	0.28	0.20	0.08	0.89	0.51	0.62
Major bleeding, *n* (%)	7/40 (18)	0/6 (0)	1/5 (20)	1/6 (17)	0/5 (0)	0.57	1.0	1.0	0.45	1.0	1.0
PGF, *n* (%)	8/40 (20)	0/6 (0)	1/5 (20)	1/6 (17)	1/5 (20)	0.57	1.0	1.0	0.45	1.0	1.0
Rejection, *n* (%)	3/40 (8)	0/6 (0)	0/5 (0)	0/6 (0)	1/5 (20)	1.0	1.0	1.0	1.0	1.0	1.0
Other, *n* (%)	6/40 (15)	2/6 (33)	0/5 (0)	0/6 (0)	0/5 (0)	0.28	1.0	0.58	0.45	0.45	1.0

Mean and standard deviation values for continuous variables or percentages for discrete variables were shown. Significance was calculated by the Pearson χ^2 test or, when its application conditions were not met, by Fisher's exact test for qualitative variables and the Student's *t*-test for quantitative variables. Bold *P* values represent statistical significance.

Figure 1 Five-year Kaplan–Meier survival after HTx depending on donor cause of death. Kaplan–Meier survivals for intracerebral bleeding ('ICB'), traumatic brain injury ('trauma'), hypoxic brain damage ('hypoxic'), cerebrovascular ('vascular'), or other cause (n = 20, 9%) are shown. Apart from those, Kaplan–Meier survivals for sum of all donor causes of death without ICB are shown additionally ('All w/o ICB'). Data under the graph representing patients at risk at specific time points in all groups.



hypoxic brain damage. Interestingly, donor sodium levels were significantly higher in the donor-ICB group, with mean hypernatremia levels of 150 mmol/L. As donor hypernatremia has been associated with reduced survival post-HTx,[18] this could partly explain the association of ICB and reduced survival in this subgroup.

With respect to perioperative morbidity, the need for mechanical life support in recipients with donor ICB and mortality under support was significantly higher. This finding suggests a higher short-term risk of cardiocirculatory failure in recipients with donor-ICB, supporting our findings in overall reduced survival. Related to that but not different between the groups was the rate of primary isolated right ventricular failure, however possibly limited by the low absolute numbers. The groups also differed in some parameters, such as total graft ischaemia time being longer in the hypoxic group and reaching significance formally. However, those differences are small in absolute numbers, even between the highest absolute difference in the traumatic vs. hypoxic brain damage group (218.6 ± 40.7 vs. 198.8 ± 38.6). Thereby, it seems to be unlikely clinically relevant or have a major effect on survival. As the recipients' cause of death could be another possible mechanism in understanding the role of donor ICB, we compared those between all groups, however with no difference. Again, this analysis is obviously limited by low absolute numbers in each recipient cause of death category per group.

Apart from heart transplant donors, ICB is a major health problem, accounting for 10–15% of all strokes worldwide each year, with the highest mortality rate among all strokes with 38% of 1 year survival.[19,20] From a pathophysiological perspective, different pathways delivering primary and secondary damage in ICB patients were described, including mechanical compression caused by hematoma as well as inflammation, oxidative stress, cytotoxicity, and the neurotoxicity of thrombin.[21] Some of those mechanisms, including inflammation and oxidative stress, could potentially influence other organs including the heart. Baroldi *et al*. could show that in 89% of patients with ICB, myocardial necrosis could have been detected.[22] Several other animal and clinical studies, although rather old, have suggested association of intracerebral haemorrhage and adverse effects on the heart.[23–29] In addition to the mentioned biochemical aspects, one of the physical mechanisms seems to be a rapid and more explosive rise in intracerebral pressure causing cardiac hemodynamic perturbations and myocardial injury.[22–25,30,31] Some or all of those potential mechanisms could be responsible for the reduced survival we see in recipients with donor ICB; however, we cannot technically prove this hypothesis due to the nature of this study.

This study's major and obvious limitation is that it is composed from a single centre and only includes retrospective data. Therefore, future studies with larger cohorts, preferably from the newest era of HTx and potentially with prospective design, are needed to confirm or decline the association of donor cause of death including ICB on outcome and survival after HTx.

Conclusion

In this retrospective analysis, donor cause of death is associated with differing outcome and survival after HTx. ICB hereby shows the strongest decline in outcome and survival compared with all other causes. Future studies are yet to be performed to confirm those findings in a prospective and larger scale.

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Conflict of interest

The authors have no conflicts of interest to declare.

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