Heart transplant survival and the use of donors with intracranial bleeding: United Network for Organ Sharing Registry propensity-score matched analysis

J. Sam Meyer, MSc,[a,b,c] Nancy Sweitzer, MD,[d] Dan Aravot, MD,[a,b] Carmelo A. Milano, MD, MHS,[e] and Yaron D. Barac, MD, PhD[a,b]

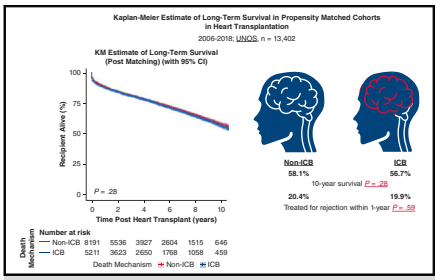
ABSTRACT

Objective: The transplantation of hearts from donors who experienced intracranial bleeding (ICB) has been associated with inferior long-term survival in both single-center analyses and, more recently, with the United Network for Ogan Sharing Registry. The purpose of this study was to further explore this relationship through propensity score matching in recipients receiving donor hearts from ICB and non-ICB donors in a large national registry.

Methods: We performed a retrospective cohort analysis of the United Network for Organ Sharing Registry Organ Procurement and Transplantation Network between 2006 and 2018 for adult candidates wait-listed for isolated heart transplantation. Recipients were stratified into 2 groups: ICB and non-ICB donors. Propensity score matching was performed to estimate causal effects by using observational data. Kaplan-Meier analysis was used to estimate survival posttransplant. Cox proportional hazards modeling was used to evaluate the independent effect of ICB as a cause of death.

Results: A total of 25,315 candidates met inclusion criteria. ICB heart donors (n = 5529) were older (median age, 42 vs 27 years; $P < .001$), less likely men (54.5% vs 75.2%; $P < .001$), and more often had a history of smoking (20.1% vs 11.7%; $P < .001$), and hypertension (34.2% vs 9.5%; $P < .001$). Before matching there was a significant difference in long-term posttransplant survival; for example, the non-ICB (60.7% [interquartile range, 59.5%-61.9%] vs 56.8% (interquartile range, 54.7%-59.0%]; $P < .0001$). However, when analyzing the propensity-score matched groups for outcomes, no difference was found between the cohorts both in terms of long-term survival as well as in rates of rejection.

Conclusions: In the largest propensity score matching analysis of heart transplants from donors who had experienced ICB, we found similar survival and rejection rates in heart transplant recipients. (JTCVS Open 2024;22:306-17)



Propensity score matching showed no difference in survival in heart recipients from ICB donors.

CENTRAL MESSAGE

In the largest UNOS registry analysis to date, propensity score matching showed no difference in survival, acute rejection, and treatment of rejection within 1 year between ICB and non-ICB hearts.

PERSPECTIVE

The outcomes of heart transplantation from donors with ICB are explored using both a novel statistical method and robust multicenter registry. This research has important implications for clinical practice and fills a gap in the literature, suggesting that using heart donors with ICB do not significantly influence long-term survival rates or rejection rates in recipients.

See Discussion on page 318.

From the [a]Division of Cardiovascular and Thoracic Surgery, Rabin Medical Center, Petach-Tikva, Israel; [b]Tel Aviv University, Sackler Faculty of Medicine, Tel Aviv, Israel; [c]Department of Biomedical Engineering, Ben-Gurion University of the Negev, Beer Sheva, Israel; [d]Division of Cardiology, Washington University School of Medicine, St Louis, Mo; and [e]Department of Surgery, Duke University Medical Center, Durham, NC.

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Address for reprints: Yaron D. Barac, MD, PhD, Division of Cardiovascular and Thoracic Surgery, Rabin Medical Center, Zeev Jabotinsky St 39, Petah Tikva 4941492, Israel (E-mail: yaronbar@clalit.org.il).

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Abbreviations and Acronyms
ICB = intracranial bleeding
CCS = cerebral-cardiac syndrome
SMD = standardized mean difference
TBI = traumatic brain injury
UNOS = United Network for Organ Sharing

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Heart transplantation is among the most highly effective therapies for end-stage heart disease, and occurrence continues to increase: In 2022, 4111 transplants took place in the United States alone.[1] However, even with this rise, wait list mortality remains an ongoing concern, and there is urgent need to expand the donor pool. Although donation after circulatory death has recently become available for heart transplant in the United States, donation after brain death remains the vast majority, and head trauma remains the single largest cause of death in heart donors. In the past, it was believed that recipients of transplants from donors with intracranial bleeding (ICB) at time of death had inferior survival, and several studies concluded that ICB is an independent risk factor for early posttransplant mortality.[2-6] This hypothesis has been linked to the well-established phenomenon of the cerebral-cardiac syndrome (CCS)—cardiac dysfunction following brain injury. CCS is believed to be caused by a catecholamine surge that occurs in response to rapidly elevating intracranial pressure.[7] However, the etiology of CCS both remains multifaceted and slowly elevating intracranial pressure due to ICB can occur in cases such as chronic subdural hematoma, arteriovenous malformations, coagulation disorders, and uncontrolled hypertension and may not generate the same sympathetic storm and cause structural myocardial damage attributed to CCS in the literature.[7] Thus, it is possible that the presence of a donor ICB alone does not uniformly predict inferior long-term function and these hearts can safely be used for donation. In a recent study, Barac and colleagues[8] demonstrated that traumatic brain injury (TBI) donor hearts had similar survival rates to non-TBI donors when using propensity score matching.[8] In this study, we aim to use propensity-score matched cohorts to assess the comparative outcomes of hearts from donors with ICB at the time of death and ascertain whether such hearts exhibit outcomes that are either noninferior or inferior to those from donors without ICB.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Data Source

A retrospective cohort analysis was performed using the United Network for Organ Sharing (UNOS) Registry Standard Analysis and Research database. The UNOS Registry administers the Organ Procurement and Transplantation Network under contract with the US Department of Health and Human Services. This database contains data on all transplant candidates undergoing listing for solid organ transplantation in the United States since October 1987. The data set used for this investigation included all recipients who were transplanted with a heart between 2006 and 2018 and their respective donors. The study was deemed exempt by our institutional review board (No. 172 Pro00073879; approved May 29, 2016; Informed consent was waived.

Study Design and Outcomes

All first-time adult recipients of an isolated heart transplantation during the study dates were included (n = 25,315). Exclusion criteria included candidates younger than age18 years (n = 5123); those undergoing simultaneous lung, liver, or abdominal transplantation (n = 641); those undergoing retransplantation (n = 1257); and those with incomplete donor data or survival data (n = 1663). Additionally, all data for recipients who were retransplanted was excluded, including outcomes and patient characteristics from the initial transplantation. The study population was then stratified by donor cause of death (eg, ICB or non-ICB). The primary outcome was recipient long-term survival and its relation to both recipient and donor characteristics (Figure 1).

Propensity Score Matching

Propensity score matching was used to estimate causal effects by using observational data. To account for treatment effect, patients were propensity scored by using the *MatchIt* package for R for matching (R Foundation for Statistical Computing). Propensity scoring was performed with the following variables from the UNOS Registry Scientific Registry of Transplant Recipients data set: donor (age, race, and ischemic time) and recipient (age, sex, diabetes mellitus, recipient being treated with intravenous antibiotics or inotropes pretransplant, heart failure cause, transplant year, and sex mismatch). Recipients of ICB donors were matched to recipients of non-ICB donors 1:2 without replacement by nearest neighbor matching with a caliper of 0.15. Balance after matching was assessed using standardized mean differences (SMDs) with 0.15 as the upper limit indicating balance. The donor matched groups were not balanced for exact donor age because this factor reduced the ability to find matched cohorts with statistical power.

Statistical Analysis

Demographic data for both donors and recipients were compiled and described. Baseline characteristics and outcomes were compared between groups using the Mann-Whitney test for continuous variables and Pearson χ^2 test of independence for categorical variables. Differences between the groups were also evaluated using SMDs.

To adjust for factors that may influence the rate of each competing outcome, propensity score matching was performed to address differences in both recipient and donor demographics. Propensity score matching was performed across key baseline demographic variables (mentioned above), and a 1:2 (ICB:non-ICB) match was done.

Finally, posttransplant survival was estimated for those candidates in each propensity score matched group that underwent heart transplantation using the Kaplan-Meier method. Kaplan-Meier analysis was used to estimate survival posttransplant. Cox proportional hazards modeling was used to evaluate the independent effect of ICB as a cause of death.

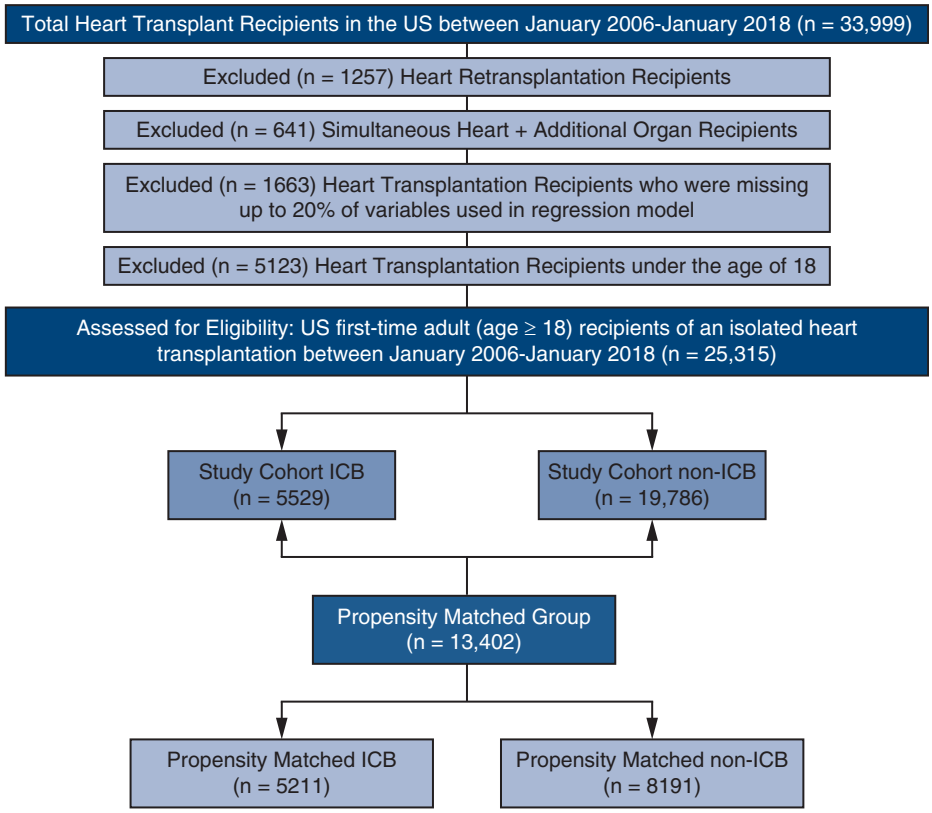

FIGURE 1. Study design. *ICB*, Intracranial bleeding.

Analyses were performed using RStudio, version 2022.02.3 for Windows and with SMD > 0.15 as the main imbalance indicator between the background variables.

RESULTS

Demographic Characteristics

A total of 25,315 recipients met inclusion criteria for analysis (Table E1). Of these, 5529 (22%) were of the ICB group, and 19,786 (78%) were in the non-ICB group. At the time of transplant, the non-ICB recipients tended to be slightly younger (age 56 vs 57 years; $P < .001$) and the percentage of men was higher in the non-ICB group (75.7% vs 68.9%; $P < .001$). Although no difference was found between the groups in terms of their hospitalization status pretransplant, more ICB recipients were on intravenous inotropes when transplanted (41.1% vs 37.7%; $P < .001$). More ICB recipients had an intra-aortic balloon pump at transplant (6.8% vs 5.9%; $P < .001$) compared with the non-ICB group, and their median wait list time was shorter compared with the non-ICB group (84 vs 94 days; $P < .001$) (Table E1).

Non-ICB donors were mostly men (75.2% vs 54.5%; $P < .001$), were younger (median age, 27 vs 42 years; $P < .001$), had a lower body mass index (27.0 vs 28.2; $P < .001$), and experienced less diabetes mellitus, hypertension, and cancer compared with the ICB group. Furthermore, amongst non-ICB donors more used cocaine (19.1% vs 12.7%; $P < .001$) and fewer were cigarette smokers (11.7% vs 20.1%; $P < .001$) compared with the non-ICB group (Table E2). There was a larger tendency to perform sex mismatch of organs allocation in the ICB group compared with the non-ICB group (30.5% vs 23.2%; $P < .001$). Left ventricular ejection fraction was slightly higher in the ICB donor group (62.1 vs 61.5; $P < .001$) (Table E2).

Propensity-Score Matched Analysis

Using propensity score matching, a 1:2 balanced cohort was developed (Table E3) representing 5211 and 8191 candidates in the ICB and non-ICB cohorts, respectively (an exact 1:2 ratio could not be achieved). The groups were matched according to the variables mentioned in the Methods section but could not be balanced for the donor age at the time of transplant and therefore, balancing was performed without that variable. This resulted in SMD = 0.255, and median ages of 41 and 38 years for the ICB and non-ICB donor groups, respectively. The median follow-up time for the entire cohort before matching was 3.3 years (Q1-Q3, 1.0-6.8). After matching, the median follow-up time for the non-ICB group was 3.1 years (Q1-Q3, 1.0- 6.6), whereas for the ICB group, it was 4.0 years

(Q1-Q3, 1.1-7.1). Visual distribution of the propensity score matching can be found in Figure E1.

Unadjusted Analysis and Propensity Score Kaplan-Meier Survival Curves

The cohort long-term posttransplant survival was estimated using the Kaplan-Meier method. Using nonpropensity score matched groups, the non-ICB group had higher 10-year survival rates than the ICB group (60.7% vs 56.8%; $P < .0001$) (Figure 2). However, using the propensity score-matched groups, no difference in 10-year survival was found in the Kaplan-Meier analysis (Figure 3). In addition, propensity-score matched cohorts showed no difference in rates of acute rejection or rejection within 1 year (Figure 4). Propensity score matching balanced 10 variables: donor age, donor race, donor ischemic time, recipient age, recipient sex, presence of diabetes mellitus, treatment with antibiotics or inotropes within 2 weeks of transplant, cause of heart failure, sex mismatch, and treatment year. In addition, to illustrate the effect on survival after correcting for confounders, a Kaplan-Meier curve was generated for a typical recipient—this being the median age and mode body mass index of our sample cohort (Figure 5).

Cox Proportional Hazards

To account for potential confounders and identify independent predictors of recipient survival, a multivariate Cox proportional hazard model was created that included predictors that were not included in the propensity score balancing: Donor age and body mass index > 25 (recipient). Younger donor age was associated with improved recipient survival (hazard ratio, 1.01 per year; 95% CI, 1.007-1.013; $P < .001$) (Table 1). To evaluate the proportional hazards assumption of our Cox proportional hazards model, we conducted tests based on Schoenfeld residuals. The global test of the proportional hazards assumption for our Cox model yielded a χ^2 test statistic of 7.5738 ($df = 3$; $P = .056$), suggesting the assumption is reasonably met overall. Individual tests for Schoenfeld residuals showed the following results: mechanism of death (ICB) had a test statistic of 0.0868 ($df = 1$; $P = .768$), indicating no evidence against the assumption; donor age had a test statistic of 3.7864 ($df = 1$; $P = .052$), suggesting a borderline potential violation; and body mass index > 25 had a test statistic of 2.2049 ($df = 1$; $P = .138$), indicating no evidence against the assumption. Thus, although the global test supports the proportional hazards assumption, donor age may require further investigation due to its borderline result.

To illustrate the similar effect of recipient survival for both mechanisms of death after correction for confounders in the model, we created a figure with predicted survival curves for a typical recipient; that is, with a median age of sample (39 years) and mode of body mass index (>25) (Figure 3). This model predicted identical survival rates at 10 years: (56.8% [95% CI, 55.0%-58.7%] for non-ICB vs 56.6% [95% CI, 54.6%-58.7%] for ICB).

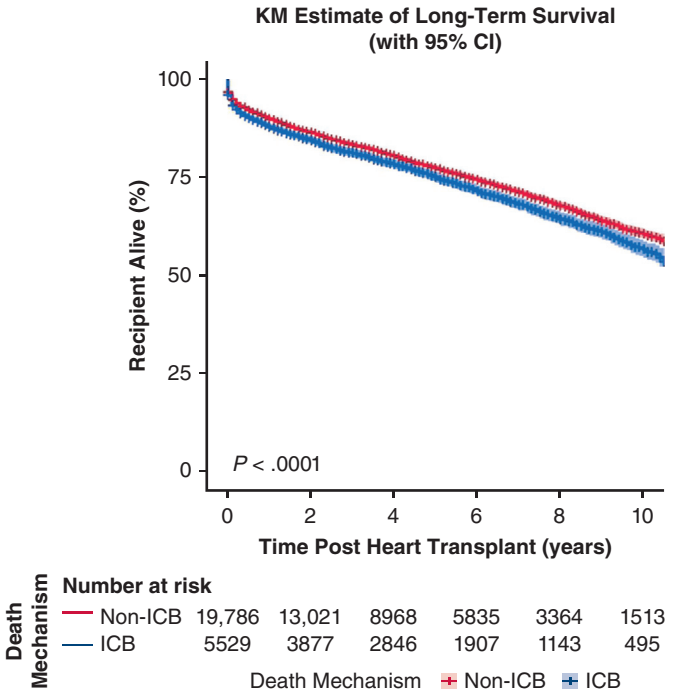

FIGURE 2. Ten-year Kaplan-Meier (*KM*) estimate of long-term survival of recipients after heart transplantation in the entire cohort, stratified by intracranial bleeding (*ICB*).

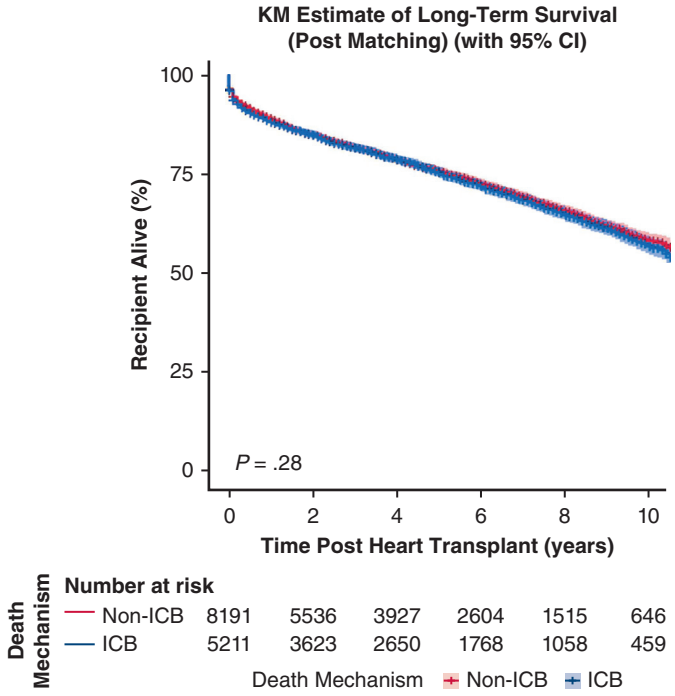

FIGURE 3. Ten-year Kaplan-Meier (*KM*) estimate of long-term survival of recipients after heart transplantation in the propensity-matched cohort, stratified by intracranial bleeding (*ICB*).

DISCUSSION

In the United States, the majority (roughly 45%) of heart transplants come from donors whose cause of death was head trauma. Anoxic brain injury or cerebrovascular accident have historically made up another 38%.[1] It has long been believed, and demonstrated by multiple studies, that hearts from donors with an ICB demonstrated lower long-term survival.[2-6] Recently, it was shown that there is actually a modest survival benefit when using TBI hearts,[9] and a recent study by Barac and colleagues[8] found no survival difference between TBI and non-TBI hearts when using propensity-score matched groups. Our UNOS Registry-based propensity score-matched retrospective study demonstrated similar posttransplant survival between ICB and non-ICB hearts. Additionally, no difference in rates of acute rejection or treatment for rejection within 1 year were found. Given that the majority of rejection happens within a year, this is a reassuring finding.

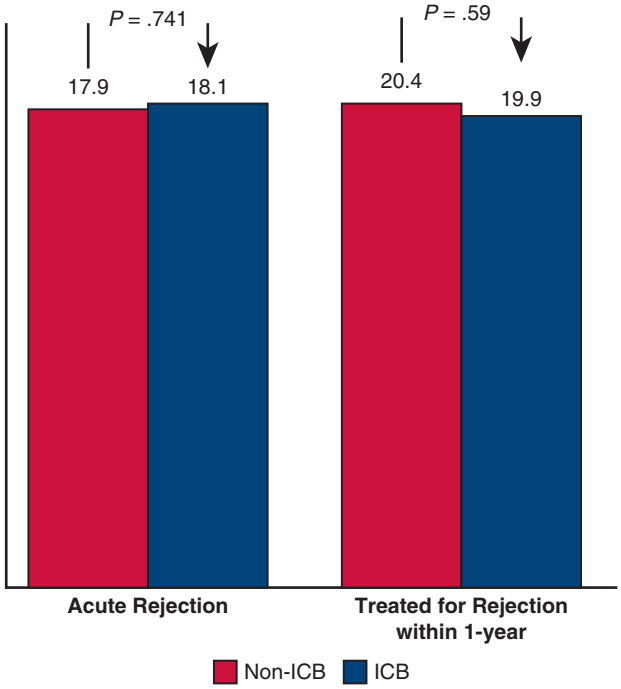

FIGURE 4. Rates of acute rejection and treatment for rejection within 1 year. *ICB*, Intracranial bleeding.

The effect of brain death on the heart has been extensively studied. Given that 30-day posttransplant mortality is generally due to cardiac dysfunction, it is important to ensure that brain death is not contributing to increased posttransplant mortality. Cardiac dysfunction following brain injury is a well-recognized phenomenon, and several potential mechanisms have been proposed. Shivalkar and colleagues[7] observed that a sudden increase in intracranial pressure caused massive catecholamine release, and Yeh and colleagues[10] demonstrated that this led to ischemic electrocardiogram changes and ventricular remodeling, and these changes might occur in as soon as 6 hours following injury.[11] However, ventricular dysfunction caused by brain death may be reversible, and work by Khush and colleagues[12] has shown

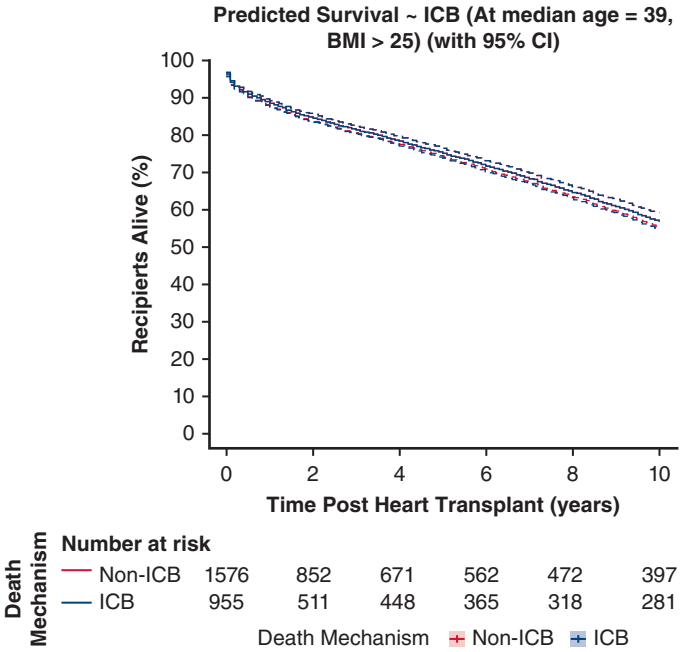

FIGURE 5. Predicted survival for a typical recipient. *ICB*, Intracranial bleeding; *BMI*, body mass index.

both that these hearts can still be viable transplant candidates and that commonly measured clinical parameters can predict reversibility. Others have proposed that the mechanism of cardiac injury might be a rapid decline in levels of thyroid hormone, often seen in critically ill patients, produces a stunned myocardium.[13] It has been proposed that treating brain-dead donors with thyroxine can improve transplant function and randomized trials are ongoing.[14,15]

The effect of brain injury has been shown in rats and humans to influence blood pressure, cardiac contractility, and the accumulation of reactive oxygen species.[16] Li and colleagues[17] showed in mice that ICB induced significant cardiac damage, including oxidative stress and expression of inflammatory markers, in the absence of preexisting cardiac disease. Additionally, brain injury has been shown to induce cardiac uncoupling (a decrease in heart rate variability), which has been shown to predict mortality after a TBI.[18] Yamani and colleagues[3] specifically looked at donors with spontaneous intracranial bleeding compared to trauma victims, and found that hearts from ICB donors had an increased risk of dysfunction within 30 days posttransplant, suggesting that ICB uniquely contributes to cardiac dysfunction.[3] However, work by Oras and colleagues[19] and Barac and colleagues[20] found that left ventricle dysfunction is common in heart donors and should not necessarily preclude use of such hearts.

Single-center studies have shown that there is reduced posttransplant survival when using ICB hearts, and Shumer and colleagues[5] and others,[2-4,6] demonstrated similar findings in a large UNOS database analysis. It should be taken into account that a recent publication by the International Society for Heart and Lung Transplantation, using its own registry, found increased survival when TBI was the cause of donor death compared to cerebrovascular accident and other reasons.[9] Recently, Crawford and colleagues[21] found similar survival rates after lung transplant between TBI and non-TBI donors, and Barac and colleagues[8] using propensity-score matched groups, found similar results with heart transplants. Taken together with the findings of this study, the importance of accounting for as many variables as possible when matching donors and recipients should be emphasized.

In concurrence with the literature, our nonmatched analysis demonstrated that the non-ICB group had higher

TABLE 1. Propensity-score matched Cox-proportional hazards model (corrected for donor age and donor body mass index)

Term	Hazard ratio	SE	Statistic	*P* value	95% CI
DEATH_MECH_DON = ICB	1.005	0.035	0.157	.875	0.940-1.076
AGE_DON (y)	1.010	0.002	6.204	.000	1.007-1.013
BMI_DON_CALC_Gr25 = TRUE	1.034	0.036	0.932	.351	0.964-1.109

DEATH_MECH_DON, Donor mechanism of death; *ICB*, intracranial bleeding; *AGE_DON*, donor age; *BMI_DON_CALC_Gr25 = TRUE*, calculated donor body mass index greater than 25.

survival rates than the ICB group. However, propensity score matching revealed no difference in 10-year survival between the ICB and the non-ICB cohort. Similar rates of acute rejection and of treatment for rejection within one year were also found between the groups (Figure 6).

A previous study by these authors[8] demonstrated that using propensity matching, survival rates were similar among heart transplant recipients between donors whose cause of death was TBI versus other causes. However, this study sought to explore the mechanism of death. In the UNOS database, the cause of death entry records the primary medical condition or disease that led to the death of the organ donor, such as cardiogenic shock. The mechanism of death entry, on the other hand, details the specific physiological processes or events that ensued due to the cause, like myocardial infarction, arrhythmias, and subsequent hemodynamic instability. In the context of our study, this differentiation was significant as TBI, or head trauma as referred to in the UNOS database only accounted for the cause of death of 10.4% of all patients whose mechanism of death was ICB or intracranial hemorrhage in the database. The intricacies of TBI and ICB vary, encompassing distinct biological and physiological processes. Thus, examining the isolated influence of the mechanism of ICB provides a nuanced understanding, potentially revealing novel insights into its unique influence on posttransplant survival. Such investigation is pivotal for refining risk assessment models, optimizing donor-recipient matching, and advancing clinical practice in heart transplantation.

Like ICB, TBI had long been believed to negatively influence posttransplant survival, but propensity score matching shows that it is perhaps time to call that assumption into question. Failure to utilize propensity matching might account for the results of previous series that demonstrated inferior survival using ICB hearts. Propensity score matching is a method to estimate the effect of a treatment, intervention, or other factors by accounting for covariates that may influence a group receiving the treatment. This allows for an observational study that has some characteristics of a randomized controlled trial and thus can be an invaluable tool when randomized controlled trials are not feasible. This method can greatly increase the validity of observational studies and can be used to reexamine long-standing clinical practice not based on randomized controlled trials.

There are several limitations to our study. Because this is a retrospective analysis, time elapsed between the ICB and the donation is unknown. Given the potential reversibility of cardiac injury in a short timeframe, this is a significant factor. These data are also only from North America, and it is well recognized that the donor pool in Europe is different, specifically regarding age.

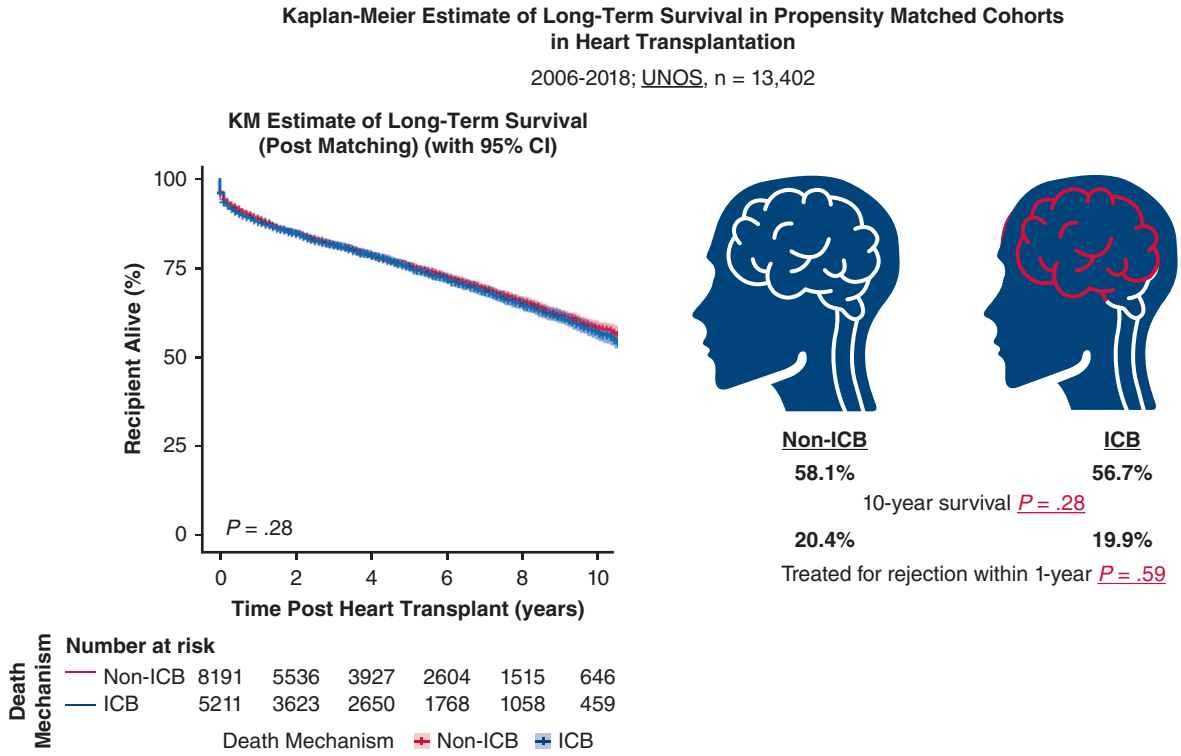

FIGURE 6. Visualization of key findings in a Kaplan-Meier (*KM*) estimate of long-term survival in propensity matched cohorts in heart transplantation. *UNOS*, United Network for Organ Sharing; *ICB*, intracranial bleeding.

Additionally, in our model donor age could not be included because the age distribution of donors with ICB is significantly different than the age of patients without ICB. This exclusion may limit our risk adjustment. Similarly, our exclusion of retransplant patients may introduce bias related to survival and rejection data; however, this methodology is commonly used in studies analyzing the UNOS database.[15,22,23] Another factor that cannot be disregarded is that our data must be reconciled with the more than 20 years of data that have guided clinical practice regarding transplant from ICB donors. Further studies should examine specific subgroups within ICB donors to address concerns about posttransplant survival.

In summary, in the largest UNOS Registry analysis to date, a propensity-score matched approach showed no survival difference between ICB and non-ICB hearts. Future studies should further examine the time from ICB incidence to death, as well as further elucidating the precise nature of ICB-related cardiac injury.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/heart-transplant-survival-and-the-use-of-donors-with-intracranial-bleeding-unos-registry-propensity-matched-analysis.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: heart transplant, intracranial bleeding, brain injury, UNOS, propensity matching

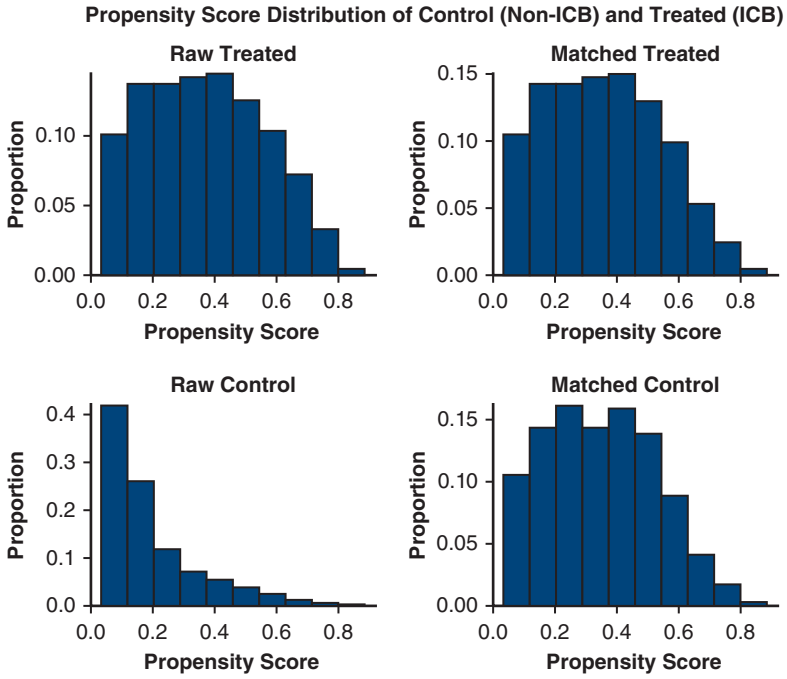

FIGURE E1. Side-by-side histogram showing propensity score distribution of control (no intracranial bleeding [*ICB*]) and treated (*ICB*) groups.

TABLE E1. Demographic characteristics of recipients of heart transplantation, segregated by presence of intracranial bleeding (ICB) in the donor

Variable	Overall	No ICB	ICB	*P* value	Test	Standardized mean difference
No.	25,315	19,786	5529			
ABO blood type				.033		0.045
A	10,297 (40.7)	8084 (40.9)	2213 (40.0)			
O	9908 (39.1)	7660 (38.7)	2248 (40.7)			
AB	1409 (5.6)	1129 (5.7)	280 (5.1)			
B	3701 (14.6)	2913 (14.7)	788 (14.3)			
Age (y)	56.0 (46.0-63.0)	56.0 (46.0-63.0)	57.0 (47.0-63.0)	<.001	Nonnormal	0.105
Cerebrovascular disease	1364 (5.4)	1045 (5.3)	319 (5.8)	.157		0.022
Time on wait list, median (d)	92.0 (27.0-259.0)	94.0 (28.0-263.0)	84.0 (24.0-245.0)	<.001	Nonnormal	0.053
Diabetes mellitus	6919 (27.4)	5427 (27.5)	1492 (27.0)	.543		0.010
Dialysis	639 (2.5)	517 (2.6)	122 (2.2)	.100		0.026
ECMO at transplant	190 (0.8)	155 (0.8)	35 (0.6)	.290		0.018
Ethnicity				.293		0.029
Hispanic	2053 (8.1)	1576 (8.0)	477 (8.6)			
White	16,967 (67.0)	13,292 (67.2)	3675 (66.5)			
Black	5188 (20.5)	4066 (20.5)	1122 (20.3)			
Other	1107 (4.4)	852 (4.3)	255 (4.6)			
Male sex	18,795 (74.2)	14,983 (75.7)	3812 (68.9)	<.001		0.152
IABP at transplant	1549 (6.1)	1173 (5.9)	376 (6.8)	.018		0.036
ICU	2 (10.5)	0 (0.0)	2 (40.0)	.098		1.155
Intravenous antibiotics in 2 wk before transplant	2554 (10.3)	2031 (10.4)	523 (9.6)	.084		0.027
Intravenous inotropes at transplant	9731 (38.4)	7456 (37.7)	2275 (41.1)	<.001		0.071
Malignancy	2006 (7.9)	1541 (7.8)	465 (8.4)	.136		0.023
Recipient creatinine (mg/dL)	1.2 (0.9-1.4)	1.2 (0.9-1.4)	1.2 (0.9-1.4)	.525	Nonnormal	<0.001
Recipient bilirubin (mg/dL)	0.7 (0.5-1.1)	0.7 (0.5-1.1)	0.7 (0.5-1.2)	.221	Nonnormal	0.019
Heart failure cause				.064		0.035
Nonischemic dilated cardiomyopathy	12,867 (50.8)	10,122 (51.2)	2745 (49.7)			
Ischemic cardiomyopathy	8154 (32.2)	6359 (32.1)	1795 (32.5)			
Other	4286 (16.9)	3300 (16.7)	986 (17.8)			
Ventilator at transplant	387 (1.5)	299 (1.5)	88 (1.6)	.712		0.007
VAD_ALL = 1	25,315 (100.0)	19,786 (100.0)	5529 (100.0)	NA		<0.001
ACUTE_REJ_EPI = NO	20,649 (81.6)	16,124 (81.5)	4525 (81.9)	.550		0.009
Calculated - treated for rejection within 1 y	4090 (20.4)	3210 (20.6)	880 (19.8)	.237		0.021

Values are presented as n (%) or median (interquartile range). *ECMO*, Extracorporeal membrane oxygenation; *IABP*, intra-aortic balloon pump; *ICU*, intensive care unit; *VAD_ALL = 1*, ventricular assist device allocation level 1; *NA*, not available; *ACUTE_REJ_EPI=NO*, acute rejection episode.

TABLE E2. Demographic characteristics of heart transplant donors, segregated by intracranial bleeding (ICB) as cause of brain death

Variable	Overall	No ICB	ICB	*P* value	Test	Standardized mean difference
No.	25,315	19,786	5529			
ABO blood type				.007		0.053
A	9127 (36.1)	7228 (36.5)	1899 (34.3)			
O	12,864 (50.8)	9954 (50.3)	2910 (52.6)			
B	2767 (10.9)	2156 (10.9)	611 (11.1)			
AB	557 (2.2)	448 (2.3)	109 (2.0)			
Donor age (y)	30.0 (22.0-41.0)	27.0 (21.0-36.0)	42.0 (33.0-49.0)	<.001	Nonnormal	1.004
Donor cause of death				<.001		3.762
Head trauma	13,403 (52.9)	12,829 (64.8)	574 (10.4)			
Anoxia	6154 (24.3)	6154 (31.1)	0 (0.0)			
Cerebrovascular/stroke	5049 (19.9)	212 (1.1)	4837 (87.5)			
Other	551 (2.2)	500 (2.5)	51 (0.9)			
CNS tumor	158 (0.6)	91 (0.5)	67 (1.2)			
Donor creatinine (mg/dL)	1.0 (0.8-1.4)	1.0 (0.8-1.4)	0.9 (0.7-1.3)	<.001	Nonnormal	0.145
Diabetes mellitus	860 (3.4)	558 (2.8)	302 (5.5)	<.001		0.133
Donor ethnicity				<.001		0.099
Black	4073 (16.1)	3148 (15.9)	925 (16.7)			
Hispanic	4148 (16.4)	3130 (15.8)	1018 (18.4)			
White	16,323 (64.5)	12,944 (65.4)	3379 (61.1)			
Other	771 (3.0)	564 (2.9)	207 (3.7)			
Donor male sex	17,895 (70.7)	14,884 (75.2)	3011 (54.5)	<.001		0.446
Cancer	377 (1.5)	212 (1.1)	165 (3.0)	<.001		0.136
Cigarette use	3390 (13.5)	2287 (11.7)	1103 (20.1)	<.001		0.233
Cocaine use	4401 (17.7)	3710 (19.1)	691 (12.7)	<.001		0.176
Diabetes mellitus	860 (3.4)	558 (2.8)	302 (5.5)	<.001		0.133
Hypertension	3757 (14.9)	1879 (9.5)	1878 (34.2)	<.001		0.625
Graft ischemic time (h)	3.2 (2.4-3.8)	3.2 (2.4-3.8)	3.2 (2.4-3.8)	.629	Nonnormal	0.004
Donor bilirubin (mg/dL)	0.7 (0.5-1.2)	0.8 [0.5-1.2)	0.7 (0.4-1.0)	<.001	Nonnormal	0.127
Donor body mass index	27.3 (5.8)	27.0 (5.7)	28.2 (6.3)	<.001		0.205
Sex mismatch	6288 (24.8)	4599 (23.2)	1689 (30.5)	<.001		0.165
Left ventricular ejection fraction	61.6 (6.9)	61.5 (7.0)	62.1 (6.8)	<.001		0.096

Values are presented as n (%) or median (interquartile range). *CNS*, Central nervous system.

TABLE E3. Propensity-matched demographic characteristics of recipients and donor of heart transplantation, segregated by presence of intracranial bleeding (ICB) in the donor

Variable	Overall	No ICB	ICB	*P* value	Test	Standardized mean difference
No.	13,402	8191	5211			
Age (y)	56.0 (47.0-63.0)	56.0 (46.0-63.0)	57.0 (47.0-63.0)	.020	Nonnormal	0.046
Gender	9410 (70.2)	5800 (70.8)	3610 (69.3)	.061		0.033
Diabetes mellitus	3702 (27.6)	2278 (27.8)	1424 (27.3)	.554		0.011
Intravenous antibiotics in 2 wk before transplant	1326 (9.9)	824 (10.1)	502 (9.6)	.438		0.014
INOTROPES_TRR	5463 (40.8)	3321 (40.5)	2142 (41.1)	.531		0.011
Heart failure cause				.630		0.017
Nonischemic dilated cardiomyopathy	6724 (50.2)	4129 (50.4)	2595 (49.8)			
Ischemic cardiomyopathy	4367 (32.6)	2669 (32.6)	1698 (32.6)			
Other	2311 (17.2)	1393 (17.0)	918 (17.6)			
TX_YEAR				.067		0.080
2006	1003 (7.5)	596 (7.3)	407 (7.8)			
2007	1021 (7.6)	614 (7.5)	407 (7.8)			
2008	997 (7.4)	599 (7.3)	398 (7.6)			
2009	1063 (7.9)	637 (7.8)	426 (8.2)			
2010	1135 (8.5)	664 (8.1)	471 (9.0)			
2011	988 (7.4)	595 (7.3)	393 (7.5)			
2012	1050 (7.8)	642 (7.8)	408 (7.8)			
2013	1020 (7.6)	623 (7.6)	397 (7.6)			
2014	1141 (8.5)	695 (8.5)	446 (8.6)			
2015	1072 (8.0)	657 (8.0)	415 (8.0)			
2016	1253 (9.3)	787 (9.6)	466 (8.9)			
2017	1118 (8.3)	735 (9.0)	383 (7.3)			
2018	541 (4.0)	347 (4.2)	194 (3.7)			
Donor age (y)	39.0 (30.0-46.0)	38.0 (29.0-45.0)	41.0 (32.0-48.0)	<.001	Nonnormal	0.255
Donor ethnicity				.224		0.037
Black	2124 (15.8)	1260 (15.4)	864 (16.6)			
Hispanic	2476 (18.5)	1515 (18.5)	961 (18.4)			
White	8348 (62.3)	5146 (62.8)	3202 (61.4)			
Other	454 (3.4)	270 (3.3)	184 (3.5)			
Graft ischemic time (h)	3.2 (2.4-3.8)	3.2 (2.4-3.8)	3.2 (2.4-3.8)	.971	Nonnormal	<0.001
Sex mismatch	3926 (29.3)	2348 (28.7)	1578 (30.3)	.047		0.035
ACUTE_REJ_EPI = NO	10,990 (82.0)	6725 (82.1)	4265 (81.9)	.741		0.006
Calculated: Treated for rejection within 1 y	2161 (20.2)	1328 (20.4)	833 (19.9)	.590		0.011

Values are presented as median (interquartile range) or n (%) unless otherwise noted. *INOTROPES_TRR*, Inotrope stress test result; *TX_YEAR*, transplant year; *ACUTE_REJ_EPI = NO*, acute rejection episode.