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Determining optimal donor heart ischemic times in adult cardiac transplantation

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Abstract

Objectives: Unsupervised statistical determination of optimal allograft ischemic time (IT) on heart transplant outcomes among ABO donor heart types.

Methods: We identified 36,145 heart transplants (2000–2018) from the United Network for Organ Sharing database. Continuous and categorical variables were analyzed with parametric and nonparametric testing. Determination of IT cutoffs for survival analysis was performed using Contal and O'Quigley univariable method and Vito Muggeo multivariable segmented modeling.

Results: Univariable and multivariable IT threshold determination revealed a cutoff at about 3 h. The hourly increase in survival risk with ≥3 h IT is asymmetrically experienced at the early 90 days (hazard ratio [HR] = 1.29, $p < .001$) and up to 1-year time point (HR = 1.16, $p < .001$). Beyond 1 year the risk of prolonged IT is less impactful (HR = 1.04, $p = .022$). Longer IT was associated with more postoperative complications such as stroke (2.7% vs. 2.3, $p = .042$), dialysis (11.6% vs. 9.1%, $p < .001$) and death from primary graft dysfunction (1.8% vs. 1.2%, $p < .001$). O blood type donor hearts with IT ≥ 3 h has significantly increased hourly mortality risk at 90 days (HR = 1.27, $p < .001$), 90 days to 1 year (HR = 1.22, $p < .001$) and >1 year (HR = 1.05, $p = .041$). For non-O blood types with ≥3 h IT hourly mortality risk was increased at 90 days (HR = 1.33, $p < .001$), but not at 90 days to 1 year (HR = 1.09, $p = .146$) nor ≥1 year (HR = 1.08, $p = .237$).

Conclusions: The donor heart IT threshold for survival determined from unbiased statistical modeling occurs at 3 h. With longer preservation times, transplantation with O donor hearts was associated with worse survival.

Abbreviations: BIVAD, biventricular assist device; BMI, body mass index; BSA, body surface area; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cell; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PGD, primary graft dysfunction; PVR, pulmonary vascular resistance; RVAD, right ventricular assist device; TAH, total artificial heart; UNOS-STAR, United Network for Organ Sharing-Standard Transplant Analysis and Research.

Paul C. Tang and Xiaoting Wu contributed equally to this study.

KEYWORDS
myocardial protection, reperfusion, transplantation-heart

1 | INTRODUCTION

It is well recognized that donor heart ischemic time (IT) is one of the most important factors influencing transplant outcomes and reflects increasing risk of primary graft dysfunction (PGD).[1,2] Indeed, PGD is a significant challenge that occurs in 10%–20% of heart transplant patients and accounts for 39% of early deaths.[3] Other well-recognized risk factors that impact transplant survival include donor cardiac function, recipient comorbidities, and acuity, as well as donor/recipient matching in terms of age, gender, and body habitus.[4] Based on surgical experience and impressions from decades of heart transplant experience, an IT of less than 4 h is widely accepted as a threshold for optimal transplant outcomes.[5–8] Based on this time-honored 4-h threshold, we previously reported that O blood type donor hearts were associated with poorer survival when ITs are prolonged.[9] Jawitz et al.[10] also found that donor O blood type was associated with decreased graft survival when compared with other blood types.

In this study, we seek to use unsupervised statistical methods to determine IT thresholds based on survival outcomes. This will improve the precision of our understanding of donor heart preservation responses by increasing the accuracy of the described relationship between ITs, cardiac function, and transplant outcomes. We also examine the differential impact of donor heart IT across varied post-transplant time strata to document follow-up time-dependent effects on survival.

2 | METHODS

2.1 | Patients

The University of Michigan Institutional Review Board has approved this study (IRB#HUM00182225, approved 5/14/2020). A waiver of informed consent was approved by the University of Michigan IRB. We analyzed 36,145 heart transplants from January 1st, 2000 to September 30st, 2018 from the United Network for Organ Sharing-Standard Transplant Analysis and Research (UNOS-STAR) database. To facilitate the comparability between recipient status, this covers the period before the recent change in donor heart allocation algorithm implemented in October 2018. The follow-up for the study population was a median of 5.04 years and mean of 6.20 years with a 95% confidence interval of 6.16–6.25 years. Patients less than 18 years of age, undergoing simultaneous lung transplants, or having missing key data (e.g., IT, age, and heart failure cause) were excluded from analysis (see Figure 1 for consort diagram). UNOS-STAR database consists of prospectively collected recipient/donor demographics, operative data, and postoperative outcomes for all thoracic transplant recipients in the United States.

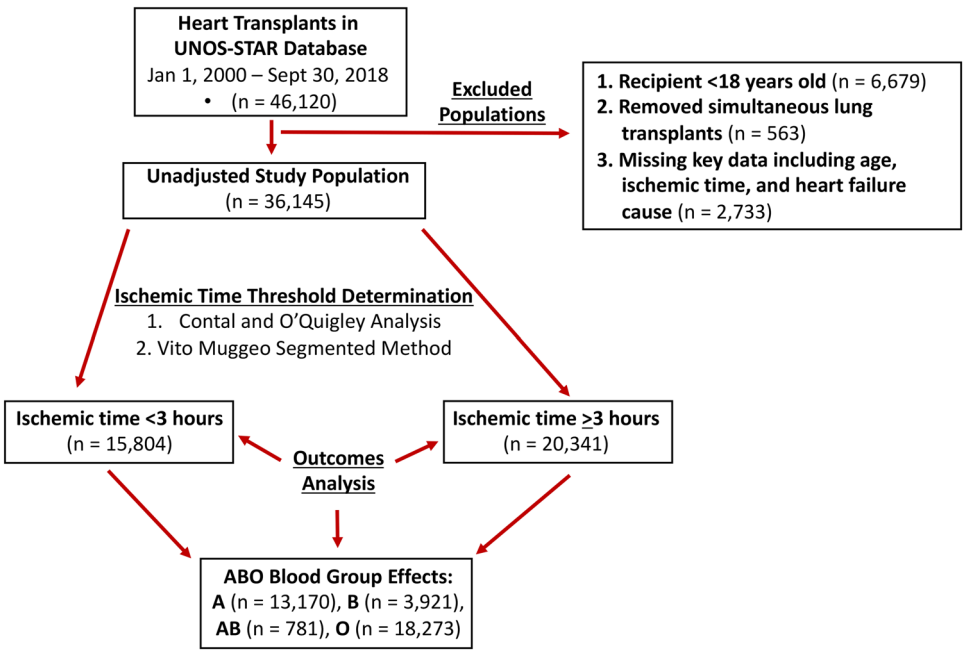

FIGURE 1 Consort Diagram for the Study Population showing study groups defined according to the 3 h ischemic time threshold. Groups excluded include pediatric populations, simultaneous heart-lung transplants, and those missing key data.

2.2 | Outcomes

We determined the demographics, and comorbidities of heart transplant donors and recipients. We also analyzed the left ventricular ejection fraction of donor hearts and parameters related to recipient acuity were also described. The primary endpoint of interest in the study was patient survival at 5, 10, and 15 years. Secondary endpoints include death from PGD and postoperative complications. Survival data were analyzed with Kaplan–Meier survival curves with log-rank statistics and Cox proportional hazards (PHs) regression. We also examined outcomes based on ABO status of donor hearts given our previous findings.[9]

2.3 | Statistical methods

IT cut-point determination based on survival was identified using two distinct methods. First, the Contal and O'Quigley method with log-rank test statistic was used to determine a cut point of IT without covariates adjustment. With the initial cutoff value from the Contal and O'Quigley method, segmented modeling (Vito Muggeo)[11] is further used to assess cut points of IT by adjusting for other covariates. Cox regression models with backward variable selection based on Akaike Information Criterion were used to determine risk factors in the segmented models. We adjusted for these significant variables in the subsequent Vito Muggeo segmented models and Cox regression models. For the segmented model, we utilized the initial cut-point value as determined by the Contal and O'Quigley method.

After identifying the cut point of IT, multivariable Cox PHs model was performed to identify determinants of patient survival. IT was modeled using a spline term with a knot at the identified cut point. Further testing showed that the Cox model was non-proportional given the significant interaction with time ($p < .001$). Due to non-proportionality, time-varying coefficients for IT were modeled in the Cox regression models as a linear spline term utilizing the identified IT cut point. Survival time was divided into separate intervals as follows: 90 days, 90 days to 1 year, 1–5, 5–10, and >10 years. Hazard ratios (HRs) of IT for mortality were similar after 1 year (1–5, 5–10, and >10 years). Therefore, HRs for IT were reported for time intervals: <90 days, 90 days to 1 year, and >1 year.

The initial candidate variables examined included (1) pre-transplant recipient variables (gender, heart failure cause, diabetes, dialysis, creatinine, bilirubin, extracorporeal membrane oxygenation [ECMO], intra-aortic balloon pump, left ventricular assist device [LVAD], right ventricular assist device, biventricular mechanical support [e.g., total artificial heart and biventricular assist devices], mean pulmonary artery pressure, and days spent in listing status [1A, 1B, and 2]), (2) donor factors (age, gender, hypertension, diabetes, and presence of coronary artery disease), and (3) the donor versus recipient ratio for body surface area. Recipient, donor, and matching characteristics are outlined and summarized in Supporting Information: Table 1.

Variables chosen based on Akaike Information Criterion with backward variable selection included: (1) recipient factors: age, gender, heart failure cause, diabetes, dialysis, creatinine, bilirubin, biventricular support, ECMO, mean pulmonary artery pressure; (2) donor factors: donor age, ABO blood type; and (3) Body surface area ratio between donor versus recipient.

Pearson X^2 test or Fisher's exact test was used to analyze categorical variables. Independent Student's *t*-test or Wilcoxon-rank sum test was used to compare continuous variables after determining data distribution. We excluded patients if key data (e.g., IT and heart failure cause) was absent, excluded variables with large numbers of missing data (e.g., panel reactive antibodies and pulmonary function tests), and included variables with <20% missing data points. Missing continuous variables were treated with mean imputation and binary variables were considered as negative (no) if missing.

SAS version 9.4 (SAS Institute Inc.) was used to perform the univariable Contal and O'Quigley cut-point analysis. R version 3.5.2.(r-project.org) was used to perform Vito Muggeo Segmented Broken-Line multivariable modeling.[12,13] Other statistical analysis was performed using the Statistical Package for the Social Sciences software version 25 (SPSS Inc.).

3 | RESULTS

3.1 | Unsupervised determination of IT thresholds for survival

Contal and O'Quigley's univariate analysis for the entire study population ($n = 36,145$) revealed an IT cutoff threshold of 3.40 h ($p < .001$) for survival. We then utilized the 3.4 h threshold as the initial value for the Vito Muggeo Segmented multivariable method for determining IT thresholds which were adjusted for variables identified by backward variable selection.

Segmented modeling revealed an adjusted IT threshold for survival for the entire study population was approximately 3 h (i.e., 2.73 h, Table 1, Supporting Information: Figure 1). Within the individual blood groups, segmented analysis using an initial value of 3 h demonstrated that IT thresholds for individual blood groups were

TABLE 1 Ischemic time thresholds from adjusted Vito Muggeo multivariable segmented modeling for survival.

Groups	Hours of graft ischemia (SE)
Study population ($n = 36,145$)	2.73 (0.41)
A blood type ($n = 13,170$)	2.09 (0.50)
B blood type ($n = 3,921$)	2.99 (0.39)
AB blood type ($n = 781$)	2.97 (0.78)
O blood type ($n = 18,273$)	3.11 (0.74)

Note: Identified cutoff for the study population and donor blood types B, AB, and O were approximately 3 h. Blood type A cutoff was earlier at 2.1 h.

2.09 h (SE = 0.50) for group A (n = 13,170), 2.99 h (SE = 0.39) for group B, 2.97 h (SE = 0.78) for group AB and 3.11 h (SE = 0.74) for group O (Table 1). Given the recurring IT threshold of approximately 3 h for survival, subsequent analysis focuses on the 3 h cutoff.

Cox proportional hazards multivariable analysis on backward selected variables showed that for recipients of donor hearts with IT ≥ 3 h (Table 2), improved survival was associated with nonischemic heart failure etiology (HR = 0.79, p < .001) and higher donor/recipient BSA ratio (HR = 0.75, p = .003). However, greater mortality was associated with pre-transplant dialysis (HR = 1.32, p < .001), pre-transplant biventricular support (HR = 1.27, p < .001), pre-transplant ECMO (HR = 2.19, p < .001), and donor O blood type (HR = 1.07, p = .004). Donor blood types A, B, and AB did not impact survival in the group (p > .10). For transplants utilizing donor hearts exposed to IT < 3 h (Table 3), greater mortality was similarly associated with pre-transplant dialysis (HR = 1.29, p < .001), pre-transplant biventricular support (HR = 1.30, p = .002), as well as heart failure from failed cardiac graft (HR = 1.47, p = .023) and ischemic cardiomyopathy (HR = 1.33, p < .001). As we previously reported,[9] donor blood type was not associated with mortality in this group (p > .05) with shorter ITs.

3.2 | Impact of donor heart IT on early and late survival

Multivariable Cox regression was divided into separate follow-up year strata as follows: <90 days, 90 days to 1 year, 1–5, 5–10, and >10 years. We found that the HR for mortality related to IT had the greatest impact at <90 days (<3 h: HR = 1.10, ≥3 h: HR = 1.27) and 90 days to 1 year (<3 h: HR = 1.01, ≥3 h: HR = 1.14). On the other hand, the HR was similar for 1–5 years (<3 h: HR = 1.03, ≥3 h: HR = 1.06), 5–10 years (<3 h: HR = 0.98, ≥3 h: HR = 1.00) and >10 years (<3 h: HR = 1.07, ≥3 h: HR = 1.00). Therefore, subsequent Cox regression multivariable analysis examined survival for the follow-up time strata of <90 days, 90 days to 1 year, and >1 year.

For the entire study population, the risk of mortality within 90 days after surgery when increasing 1 h of IT for IT < 3 and ≥3 h were 1.11 (95% CL: 1.01–1.23, p = .026) and 1.29 (95% CL: 1.23–1.36, p < .001, Table 4), respectively. The risk of mortality for 90 days to 1 year when increasing 1 h of IT for IT < 3 and ≥3 h were 1.00 (95% CL: 0.89–1.13, p = .952 and 1.16 (95% CL: 1.08–1.25, p < .001), respectively. In contrast, the mortality risk at greater than 1 year when increasing 1 h of IT for IT < 3 and ≥3 h were comparable at 1.02 (95% CL: 0.97–1.07, p = .381) and 1.04 (95% CL: 1.01–1.08, p = .022), respectively (Table 4). Kaplan–Meier survival analysis shows inferior survival for the transplants utilizing donor hearts with ITs ≥ 3 h (Figure 2A). The 90 days, 1 year, 5, 10, and 15 years survival for patients undergoing heart transplant utilizing donor hearts exposed to <3 and ≥3 h of IT are shown in Supporting Information: Table 2. HRs of IT over stratified survival times from a linear spline term for IT with a knot at the traditional 4 h are shown in Supporting Information: Table 3. Survival based on stratified IT is reported in Supporting Information: Figure 2.

3.3 | Influence of donor heart ABO blood type on survival

Recipient, donor, and matching characteristics for each of the blood groups for IT < 3 and ≥3 h are shown in Supporting Information:

TABLE 2 Ischemic time ≥ 3 h: Cox proportional hazards multivariable analysis.

Ischemic time ≥ 3 h	Coefficients	SE	Wald	*df*	*p* Value	Hazard ratio
Recipient: Age	0.01	0.001	17.87	1	<.001	1.01
Creatinine (mg/dl)	0.07	0.01	28.81	1	<.001	1.07
Bilirubin (mg/dl)	0.03	0.003	73.27	1	<.001	1.03
Diabetes	0.10	0.03	10.59	1	.001	1.11
Dialysis	0.27	0.06	22.58	1	<.001	1.32
Preop BIVAD or TAH	0.24	0.06	14.70	1	<.001	1.27
Preop ECMO	0.78	0.13	34.56	1	<.001	2.19
Nonischemic cardiomyopathy	−0.24	0.03	95.20	1	<.001	0.79
PA mean (mmHg)	0.01	0.001	13.77	1	<.001	1.01
Donor: Age	0.01	0.001	99.97	1	<.001	1.01
O Blood type	0.07	0.02	8.24	1	.004	1.07
Matching: Donor/recipient BSA ratio	−0.29	0.10	8.94	1	.003	0.75

Note: Notable risk factors for mortality were pre-transplant high creatinine, diabetes, dialysis, biventricular mechanical support, extracorporeal membrane oxygenation (ECMO), and O donor blood type. Nonischemic cardiomyopathy and a high body surface area (BSA) were associated with improved survival.

Abbreviations: BIVAD, biventricular assist device; PA, pulmonary artery; TAH, total artificial heart.

TABLE 3 Ischemic time < 3 h: Cox proportional hazards multivariable analysis.

Ischemic time < 3 h	Coefficients	SE	Wald	*df*	*p* Value	Hazard ratio
Recipient: Age	0.003	0.001	5.25	1	0.022	1.003
Male	−0.10	0.03	8.72	1	0.003	0.91
Creatinine (mg/dl)	0.05	0.01	16.62	1	<0.001	1.05
Bilirubin (mg/dl)	0.02	0.01	22.82	1	<0.001	1.02
Diabetes	0.12	0.04	10.27	1	0.001	1.13
Dialysis	0.25	0.07	12.52	1	<0.001	1.29
Preop BIVAD or TAH	0.26	0.09	9.16	1	0.002	1.30
Cardiac graft failure	0.38	0.17	5.19	1	0.023	1.47
Ischemic cardiomyopathy	0.28	0.03	83.64	1	0.000	1.33
PA mean (mmHg)	0.01	0.001	10.53	1	0.001	1.01
Donor: Age	0.01	0.001	85.51	1	<0.001	1.011

Note: Notable risk factors for mortality were pre-transplant diabetes, dialysis, biventricular mechanical support, cardiac graft failure from prior transplant, and ischemic cardiomyopathy. Recipient male gender was associated with improved survival.

Abbreviations: BIVAD, biventricular assist device; PA, pulmonary artery; TAH, total artificial heart.

Tables 4 and 5, respectively. For the O blood type donor hearts with IT ≥ 3 h, there was a significant increase in mortality for each hourly IT increase at all three follow-up time strata at 90 days (HR = 1.27, $p < .001$), 90 days to 1 year (HR = 1.22, $p < .001$), and 1 year or greater (HR = 1.05, $p = .04$). The majority of the mortality risk was during the initial postoperative period up to 1 year. For IT < 3 h, each additional hour of IT confers a mortality risk (HR = 1.173, $p = .002$) at 90 days but not beyond that time frame ($p < .300$, Table 4).

The relationship of O donor hearts with survival is distinct from that of other blood types. For A blood type donor hearts, there was a significant increase in 90 days transplant mortality at 90 days for ≥3 h IT (HR = 1.34, $p < .001$) but not beyond this time period. There was no significant increase in mortality risk for <3 h IT ($p > .05$). B donor blood type transplants experiencing IT ≥ 3 h had increased hourly mortality risk for 90 days (HR = 1.27, $p = .005$) and 90 days to 1 year (HR = 1.25, $p = .032$) but not for 1 year and beyond (HR = 1.07, $p = .174$). IT < 3 h did not influence mortality risk for early time points at 90 days (HR = 0.92, $p = .305$) nor 90 days to 1 year (HR = 0.86, $p = .092$). Transplants using AB donor hearts showed a trend toward significantly increased hourly IT risk with IT ≥ 3 h at 90 days (HR = 1.46, $p = .053$) but did not show significant risk elevation at other IT or follow-up strata ($p > .050$, Table 4). Stratified survival times for a traditional 4 h IT threshold for the different donor blood types are shown in Supporting Information: Table 2. We also show the relative mortality risks at the 3 h threshold for O and combined non-O donor hearts in Supporting Information: Table 6. The 90 days, 1 year, 5, 10, and 15 years survival for patients undergoing heart transplant for the study population, and different donor hearts blood types exposed to <3 and ≥3 h of IT are shown in Supporting Information: Table 2. Kaplan–Meier analysis confirms that O donor hearts experience inferior survival compared to blood types A ($p = .023$, Figure 2B), B ($p = .027$, Figure 2C), and AB ($p = .038$, Figure 2D). Supporting Information: Figure 3 shows no differences in survival amongst the non-O blood types ($p > .200$, Supporting Information: Figure 3).

3.4 | Impact of IT on postoperative outcomes

Transplants utilizing donor hearts with 3 h or greater of IT was associated with a higher incidence of postoperative stroke (2.3% vs. 2.7%, $p = .042$), dialysis (9.1% vs. 11.6%, $p < .001$) and permanent pacemaker implant (3.0% vs. 3.4%, $p = .043$, Table 5). Longer IT was also associated with more deaths resulting from PGD (1.2% vs. 1.8%, $p < .001$) and acute rejection (1.6% vs. 1.9%, $p = .034$, Table 5). There was no difference in the incidence of death from hyperacute (0.1% vs. 0.1%, $p = .237$) or chronic rejection (1.8% vs. 1.9%, $p = .415$, Table 5).

4 | DISCUSSION

Donor heart IT is well recognized as one of the most important determinants of transplant outcomes. Clinical experience and supporting observational studies have designated an IT of less than approximately 4 h as the threshold for optimizing donor heart function and outcomes.[5–8] Extending beyond 4 h IT is notable for increased risk for PGD, an important driver for post-transplant mortality.[1,2] The increased magnitude of inflammation, cell death, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation beyond the 4 h preservation threshold was also supported by previous studies in human donor hearts by our group.[14]

In the current study, we utilize the UNOS-STAR heart transplant data set to perform "big data" driven unsupervised determination of

TABLE 4 Spline Cox regression model for survival

Mortality risk	Hazard ratio (per 1 h increase in ischemic time [IT])	Lower 95% CL	Upper 95% CL	*p* Value
For entire study population				
IT < 3 h: 90 days	1.11	1.01	1.23	.026
(*n* = 15,804) 90 days to 1 year	1.00	0.89	1.13	.952
≥1 year	1.02	0.97	1.07	.381
IT h: 90 days	1.29	1.23	1.36	<.001
(*n* = 20,341) 90 days to 1 year	1.16	1.08	1.25	.000
≥1 year	1.04	1.01	1.08	.022
A donor blood type				
IT < 3 h: 90 days	1.112	0.993	1.245	.066
(*n* = 5396) 90 days to 1 year	1.007	0.879	1.153	.921
≥1 year	1.032	0.959	1.111	.398
IT ≥ 3 h: 90 days	1.344	1.239	1.459	<.001
(*n* = 7774) 90 days to 1 year	1.065	0.928	1.222	.369
≥1 year	1.023	0.969	1.081	.404
B donor blood type				
IT < 3 h: 90 days	0.917	0.778	1.082	.305
(*n* = 1436) 90 days to 1 year	0.855	0.712	1.026	.092
≥1 year	0.871	0.763	0.994	.04
IT ≥ 3 h: 90 days	1.267	1.074	1.495	.005
(*n* = 2485) 90 days to 1 year	1.248	1.019	1.529	.032
≥1 year	1.069	0.971	1.176	.174
AB donor blood type				
IT < 3 h: 90 Days	1.064	0.674	1.681	.79
(*n* = 184) 90 days to 1 year	1.265	0.786	2.036	.334
≥1 year	1.201	0.787	1.835	.396
IT ≥ 3 h: 90 days	1.457	0.995	2.133	.053
(*n* = 597) 90 days to 1 year	0.556	0.277	1.116	.099
≥1 year	0.913	0.743	1.122	.387
O donor blood type				
IT < 3 h: 90 days	1.173	1.058	1.301	.002
(*n* = 8788) 90 days to 1 year	1.041	0.919	1.18	.525
≥1 year	1.030	0.969	1.094	.345
IT ≥ 3 h: 90 days	1.27	1.19	1.355	<.001
(*n* = 9485) 90 days to 1 year	1.223	1.117	1.338	<.001
≥1 year	1.051	1.002	1.103	.04

Note: Mortality risk from prolonged IT is concentrated in the early post-transplant period in the first year. O blood type donor hearts were associated with significantly increased hazard for death within the first post-transplant year ($p < .001$) as well as beyond ($p = .04$).

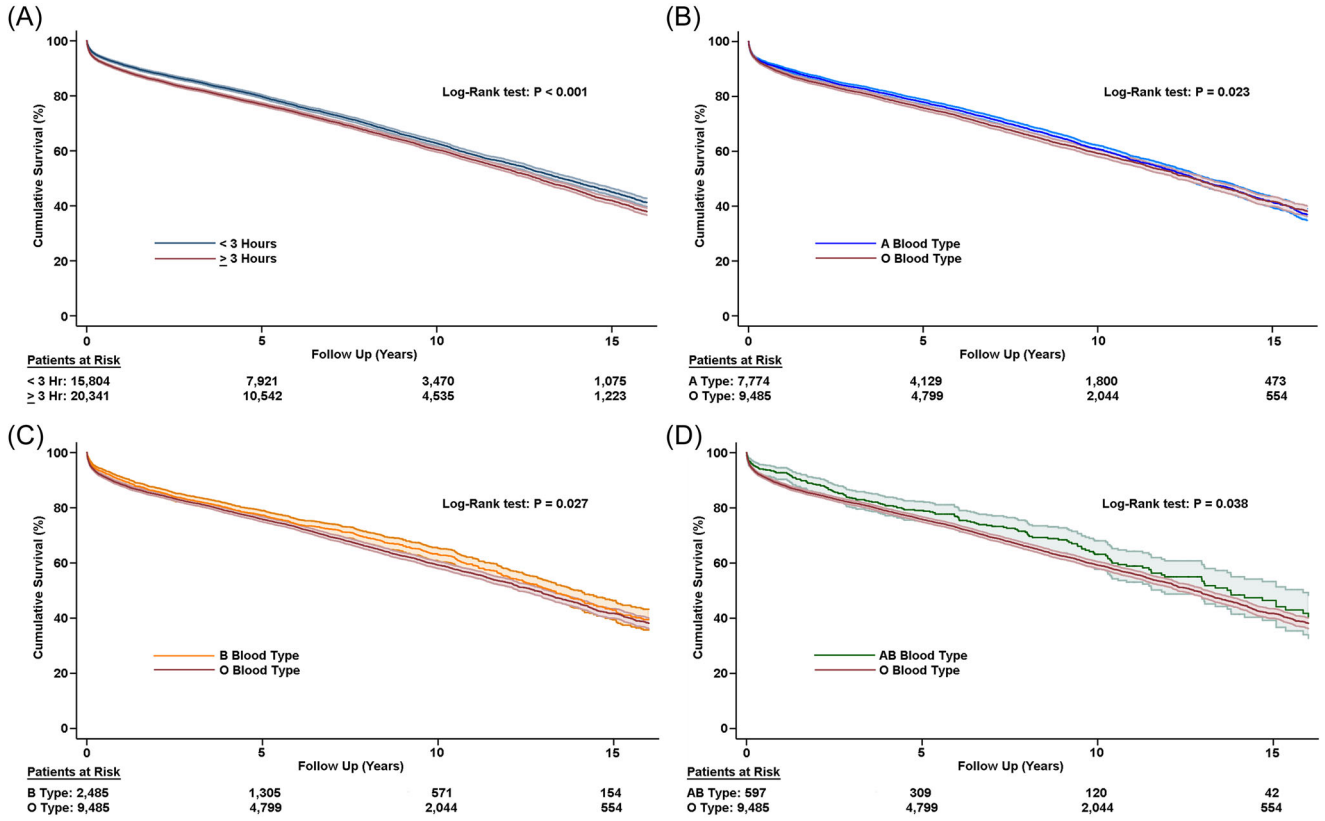

FIGURE 2 Transplant survival plot showing inferior survival for greater than 3 h ischemic time (IT) and donor hearts of O blood type. (A) <3 h versus ≥3 h of IT for the total study population and transplant survival after ≥3 h IT of O donor blood types versus donor blood types (B) A, (C) B, and (D) AB. 95% Confidence bands are shown.

TABLE 5 Post-transplant outcomes.

Ischemic time (IT)	<3 h (*n* = 15,804)	≥3 h (*n* = 20,341)	*p* Value
Postoperative stroke	370 (2.3%)	545 (2.7%)	.042
Postoperative dialysis	1446 (9.1%)	2369 (11.6%)	<.001
Postoperative pacemaker	477 (3.0%)	691 (3.4%)	.043
Death from primary graft failure	189 (1.2%)	366 (1.8%)	<.001
Death from hyperacute rejection	13 (0.1%)	25 (0.1%)	.237
Death from acute rejection	251 (1.6%)	383 (1.9%)	.034
Death from chronic rejection with graft vasculopathy	277 (1.8%)	380 (1.9%)	.415

Note: Longer IT was associated with post-transplant stroke, dialysis, permanent pacemaker implant as well as death from primary graft dysfunction and acute rejection.

optimal IT cutoffs for transplant survival. Our results using univariable and multivariable unbiased segmentation models show that the "step-up" in mortality risk actually occurs significantly earlier than previously appreciated after about 3 h of preservation. To examine the 3 h cutoff further, Cox survival analysis showed that pre-transplant dialysis and biventricular support were important risk factors for mortality on either side of the 3 h threshold. However, pre-transplant ECMO (HR = 2.19) and O donor blood type (HR = 1.07) were specific mortality risk factors for the group with IT ≥ 3 h. This is consistent with prior studies showing the adverse impact of pre-transplant mechanical support[15–17] and dialysis[18] on survival and findings by our group that donor blood group O confers heightened transplant risk with prolonged IT.[9]

Our study finds that mortality risk from each additional hour of preservation with a donor heart IT of ≥3 h has the greatest impact on the early post-transplant period up to 1 year. This hourly increase in mortality risk with IT ≥ 3 h at 90 days, 90 days to 1 year, and >1 year were HR = 1.29, HR = 1.16, and HR = 1.04, respectively. This was in

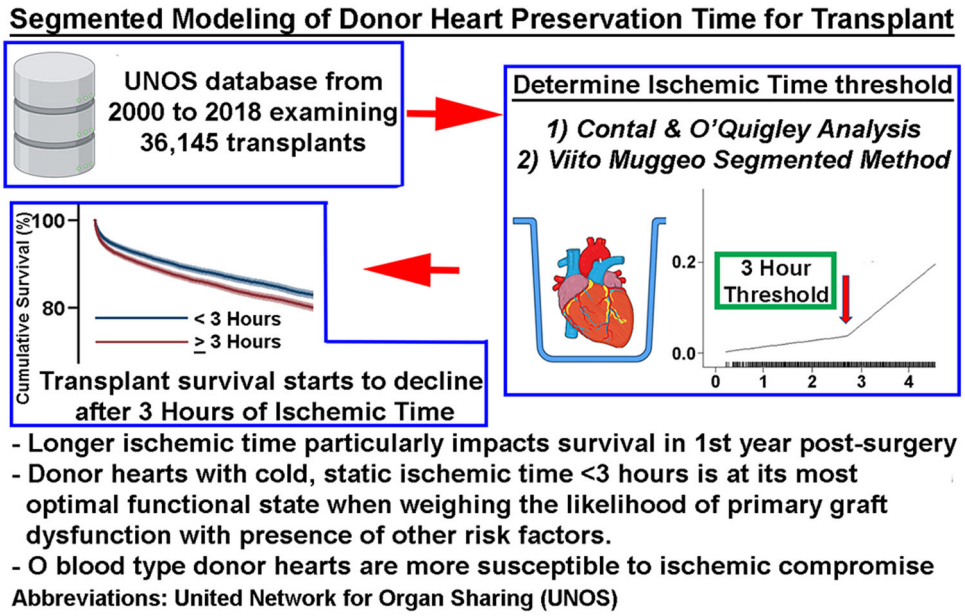

FIGURE 3 Graphical abstract summarizes this study which uses the UNOS database heart transplant population to reveal a 3 h donor heart preservation threshold for determining heart transplant survival.

contrast to IT < 3 h showing relatively little change with HR = 1.11, HR = 1.00, and HR = 1.04, respectively.

This early mortality likely reflects the impact of PGD where Young et al. documented that mortality after heart transplant was 7%–8% with PGD accounting for 39%–43% of these deaths.[19,20] Indeed the ≥3 h IT group had a significantly higher rate of death from PGD (1.2% vs. 1.8%, $p < .001$). Poorer survival with longer IT was likely contributed by a higher incidence of postoperative complications such as stroke, dialysis, arrhythmia requiring pacemaker implant, as well as death from PGD and acute rejection.

Interestingly, for the ≥3 h IT blood type O group, a significantly increased hourly IT mortality risk was demonstrated at all three aforementioned time strata at HR = 1.27, HR = 1.22, and HR = 1.05, respectively. For blood groups A, B, and AB, hourly increase in mortality risk was only increased at 90 days and/or 90 days to 1 year but not at longer time points. Kaplan–Meier analysis (Figure 2) also confirms the lower survival of transplants utilizing O blood type donor hearts compared to A, B, and AB donor blood types which is congruent with our previous study using propensity matching.[9] This finding may be due to heightened tissue inflammatory responses in persons with O blood type as we previously discussed.[9]

Our study identifies a distinct IT threshold of 3 h whereby longer preservation times confers a progressively heightened risk for mortality. Our study advances the scientific literature by identifying a distinct IT threshold of 3 h whereby longer preservation times confers a progressively heightened risk for mortality. O blood type donor hearts in particular were more susceptible to the mortality risks of prolonged IT. While IT is an important factor that determines heart transplant outcomes, this needs to be assessed in the context of other risk factors (e.g., donor age and recipient acuity). A multifaceted judgment process needs to be exercised by the transplant program as to what constitutes reasonable mortality risk for the individual patient. Our current study offers an in-depth analysis of the contribution of IT to heart transplant outcomes. Compared with our prior report that noted a heightened mortality risk associated with transplanting O blood type donor hearts exposed to extended IT, the novel application of unbiased statistical techniques has identified a 3-hour IT hinge-point for transplant mortality to inform future research and quality improvement interventions for human donor hearts. However, it is critical to stress that the selection of an acceptable IT as a component of mortality risk needs to be individualized to the acuity and urgency of transplant for the individual recipient. A graphical summary of our study is shown in Figure 3.

4.1 | Limitations

Limitations of this study include its nature as a retrospective cohort study of prospectively collected data. Multivariable Cox regression survival analysis can only adjust for recognized confounding factors and does not consider unknown variables. For example, technical issues during recipient heart explant can prolong donor heart IT. Furthermore, information on other confounding factors that may influence graft function and outcomes such as the number of redo-sternotomies and cardiopulmonary bypass. duration and blood transfusion volume are not available in the database. Importantly, the accuracy of this retrospective multicenter study is dependent on the accuracy and quality of the variables in the database. While study power is high given the large size of the national database, its granularity is limited compared to single or multi-institutional studies. However, given our study represents a very large national experience in heart transplantation and we have intensively interrogated our results using multiple statistical strategies, we are confident in our conclusions. We recognize that higher volume transplant

centers with greater resources may have a tendency to utilize donor hearts exposed to longer ITs which may limit the generalizability of our results.

5 | CONCLUSION

Unsupervised statistical analysis identifies an IT time threshold of approximately 3 h for survival outcomes following heart transplantation. Spline modeling determined that the majority of the mortality risk from increased IT is imposed in the first year after transplantation. Transplantation using O blood type donor hearts is particularly sensitive to the mortality risk of prolonged preservation.

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CONFLICTS OF INTEREST

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ETHICS STATEMENT

Institutional Review Board Approval and waiver of informed consent: IRB#HUM00182225, approved 5/14/2020.

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SUPPORTING INFORMATION

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

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