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ORIGINAL ARTICLE

Effect of centre volume and high donor risk index on liver allograft survival

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Abstract

Background: A growth in the utilization of high-risk allografts is reflective of a critical national shortage and the increasing waiting list mortality. Using risk-adjusted models, the aim of the present study was to determine whether a volume–outcome relationship existed among liver transplants at high risk for allograft failure.

Methods: From 2002 to 2008, the Scientific Registry of Transplant Recipients (SRTR) database for all adult deceased donor liver transplants (n = 31 587) was queried. Transplant centres (n = 102) were categorized by volume into tertiles: low (LVC; 31 cases/year), medium (MVC: 64 cases/year) and high (HVC: 102 cases/year). Donor risk comparison groups were stratified by quartiles of the Donor Risk Index (DRI) spectrum: low risk (DRI $\leq$ 1.63), moderate risk (1.64 > DRI > 1.90), high risk (1.91 > DRI > 2.26) and very high risk (DRI $\geq$ 2.27).

Results: HVC more frequently used higher-risk livers (median DRI: LVC: 1.82, MVC: 1.90, HVC: 1.97; $P < 0.0001$) and achieved better risk adjusted allograft survival outcomes compared with LVC (HR: 0.90, 95%CI: 0.85–0.95). For high and very high risk groups, transplantation at a HVC did contribute to improved graft survival [high risk: hazard ratio (HR): 0.85, 95% confidence interval (CI): 0.76–0.96; Very High Risk: HR: 0.88, 95%CI: 0.78–0.99].

Conclusion: While DRI remains an important aspect of allograft survival prediction models, liver transplantation at a HVC appears to result in improved allograft survival with high and very high risk DRI organs compared with LVC.

Keywords

donor risk index, marginal donors, MELD, outcomes, liver transplantation, organ allocation, deceased donation

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Introduction

The volume–outcome relationship has been validated in surgery across numerous specialties and high-risk procedures by a growing body of literature over the past quarter of a century.[1–4] However, as studies continue to demonstrate that high-volume institutions deliver improved outcomes, particularly among high-risk patient populations, the implication of these findings remains controversial.[5,6] This is because many volume–outcomes studies are compromised by limited data, varying definitions of volume groups and problematic statistical methodology.[7,8] However, nowhere is this debate more complex than in the field of liver transplantation, where procedures are influenced not only by recipient and transplantation centre factors, but also by a number of donor variables.[9–13]

Unique to orthotopic liver transplantation, the ideal or reference donor is defined as less than 40 years of age, without significant steatosis, chronic liver lesions or other transmissible diseases, who deceased as a result of traumatic brain injury, is donating after brain death and prior to haemodynamic instability.[14] In the

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past, transplant surgeons were confronted with the challenge of evaluating the donor by qualitatively comparing multiple risk factors such as donor age, race, weight, cause of death, donations after cardiac death (DCD), length of hospital stay before death, use of vasopressors, cold ischaemia time and degree of steatosis.[15] Feng *et al*. clarified the significance of donor variables by creating the Donor Risk Index (DRI), which identified the following risk factors for allograft failure: age (≥40 years old), split/partial grafts, DCD, ethnicity (African-American), cause of death as a result of a cerebrovascular accident (CVA), 'other' causes of death and short stature.[16]

As annual procedure volume appears to positively impact transplant outcomes, we aimed to determine whether this volume–outcomes relationship existed among liver transplants at high risk for allograft failure, as defined by DRI scores. Therefore, using a risk-adjusted model accounting for donor, recipient, regional and centre characteristics, we evaluated the combined effect of annual procedure volume and DRI on allograft survival.

Methods

Database

Observations were queried from the Scientific Registry of Transplant Recipients (SRTR), a nation-wide database that draws from of the Organ Procurement and Transplantation Network (OPTN). All adult recipients (≥18 years of age) of deceased donor liver transplants between 1 January 2002 and 31 December 2008 were compiled. Procedures involving partial liver transplants (reduced-liver, living donor and split-liver transplants) were excluded from the analysis of differences in organ allocation between these groups and the majority of patients with chronic liver disease awaiting liver transplantation as previously described.[17]

Volume groups

All observations were identified based on year and centre of transplantation. Each institution was coded with encrypted hospital identifiers, used to calculate centre-specific annual procedure volumes. Centres were then ranked based on annual prolificacy. Transplant centres with five or fewer cases in a year were excluded to reduce confounding variables in our analysis. Based on this order, centres were categorized into tertiles groups containing even fractions of the dataset: low volume centres (LVC), middle volume centres (MVC) and high volume centres (HVC). Because centre-specific procedure volumes varied from year to year, centre rank was re-calculated for each year studied as previously described.[3,18]

DRI groups

Donor risk comparison groups were similarly stratified by quartiles of the DRI spectrum, each containing an equal number of observations: low risk (DRI ≤ 1.63), moderate risk (DRI = 1.64–1.90), high risk (DRI = 1.91–2.26) and very high risk (DRI ≥ 2.27).

Demographics and variables

Donor demographics included age, gender, ethnicity (Caucasian, African American and all other minorities), cause of death (anoxia, CVA, head trauma or other), DCD, cold ischaemia time (in hours) and DRI. Recipient demographics included age, gender, ethnicity, time spent on the waiting list, region, year of transplantation and model for end-stage liver disease (MELD) score. Nominal variables included gender, ethnicity, cause of death and DCD status. Ordinal variables included year and region of transplantation. Continuous variables included age, time spent on the waitlist, cold ischaemia time, recipient MELD score and DRI. MELD scores were calculated for each recipient based on the United Network of Organ Sharing (UNOS) modification to the formulary described in.[19] DRI was calculated for each donor as previously described.[16]

Analysis

Nominal and ordinal categorical variables were tested for statistical significance ($P < 0.05$) with Pearson's χ^2-tests and the Mantel–Haenszel χ^2-tests, respectively. Variation in central tendencies of continuous variables between centre volume groups was evaluated using Kruskal–Wallis non-parametric ANOVA, because of non-normal distribution. Univariate analysis of all categorical variables was performed using the Log-Rank test of equality to evaluate for significance as predictors of endpoints, defined as allograft failure. Assessment results were visualized using Kaplan–Meier curves. Variables included in the calculations of DRI[16] and MELD,[19] which have already been shown to be significant, were excluded from univariate analysis.

Four separate multivariate Cox proportional hazards regression modelling were generated for each quartile of the DRI spectrum.[20] These risk-adjusted models accounted for donor characteristics (DRI), recipient characteristics (age, ethnicity and MELD), centre volume groups (LVC, MVC and HVC) and location (Regions 1–11) shown to be significant on univariate analysis. Components of the DRI and MELD score were omitted from the Cox regression model to avoid over-adjustment. Each covariate was evaluated as a predictor for allograft failure by maximum likelihood estimates of hazard ratios (HR) and 95% confidence intervals (95% CI).

SAS version 9.2 (SAS Institute, Cary, NC) was used for all statistical analysis. The present study was reviewed by the University of Massachusetts Medical School Institutional Review Board (IRB) and deemed appropriate for exemption from IRB oversight as no personal identifiers were used among datasets.

Results

Cohort description

In all, 31 587 OLT were queried. Between 92 and 102 transplant centres actively contributed data to OPTN during the time period

Table 1 Number of transplant centres per year and number of transplant cases per region per tertile group for all observations (n = 31 587)

Variables	LVC (n = 10 621)	MVC (n = 10 713)	HVC (n = 10 242)	Total (n = 31 587)
2002	67 centres	18 centres	7 centres	92 centres
2003	39 centres	35 centres	20 centres	94 centres
2004	39 centres	32 centres	24 centres	95 centres
2005	41 centres	32 centres	24 centres	97 centres
2006	39 centres	33 centres	24 centres	96 centres
2007	40 centres	33 centres	24 centres	97 centres
2008	45 centres	33 centres	24 centres	102 centres
Region 1	880 cases	0 cases	0 cases	880 cases
Region 2	1837 cases	286 cases	1698 cases	3821 cases
Region 3	613 cases	1599 cases	2977 cases	5189 cases
Region 4	1284 cases	996 cases	849 cases	3129 cases
Region 5	2151 cases	575 cases	1598 cases	4324 cases
Region 6	403 cases	668 cases	0 cases	1071 cases
Region 7	905 cases	1565 cases	230 cases	2700 cases
Region 8	417 cases	1543 cases	0 cases	1960 cases
Region 9	0 cases	1971 cases	554 cases	2525 cases
Region 10	559 cases	458 cases	1954 cases	2971 cases
Region 11	1572 cases	1052 cases	382 cases	3006 cases
% of All Centers	46.06%	32.10%	21.84%	100%
% of All Cases	33.64%	33.93%	32.44%	100%
Median# Cases (SD)	31 cases (10.86)	64 cases (9.76)	102 cases (26.00)	197 cases

LVC, low volume centers; MVC, middle volume centres; HVC, high volume centres; %, per cent; #, number; SD, standard deviation.

studied. Transplant centres were sorted into tertiles: LVC (33.64% of cases; 46.06% of centres), MVC (33.93% of cases; 32.10% of centres) and HVC (32.44% of cases; 21.84% of centres; $P < 0.0001$). Donor-risk comparison groups were stratified into quartiles: low risk (DRI $\leq$ 1.63; n = 7922), moderate risk (1.63 < DRI $\leq$ 1.90; n = 7918), high risk (1.90 $\leq$ DRI < 2.26; n = 7925) and very high risk (DRI > 2.26; n = 7924). Regional trends suggest that the largest contributions came from Region 3 (16.43% of cases), whereas the smallest contributions came from Region 1 (2.79% of cases), as described in Table 1.

Demographics

The majority of donors were male (59.54%) and Caucasians (69.42%; $P < 0.0001$). The median donor age was 43 years and 15.72% were $\geq$60 years of age. The primary cause of death was CVA (44.50%) and a minority were DCD donors (4.32%; $P < 0.0001$). The majority of recipients were also male (68.20%) and Caucasian (73.45%). The median recipient age was 54 years with a MELD score of 18.

Table 2 outlines the demographics of each tertile. The following donor characteristics had statistically significant ($P < 0.05$) differences between tertiles: age, ethnicity, cause of death, DCD status and DRI. The following recipient characteristics were also found to be different: age, ethnicity, MELD score, time spent on the waiting list and region. Evaluation of DRI groups showed that higher volume groups utilizing higher median DRI allografts (LVC: 1.82, MVC: 1.90, HVC: 1.97; $P < 0.05$), as depicted in Fig. 1. In contrast, median MELD scores (LVC: 19.0, MVC: 19.0, HVC: 17.0; $P < 0.05$) and median time spent on the waiting list (LVC: 92 days, MVC: 79 days, HVC: 55 days; $P < 0.05$) were inversely proportional to procedure volume.

Multivariate allograft survival outcomes

HVC achieved better overall risk-adjusted allograft survival outcomes compared with LVC (HR: 0.90, 95%CI: 0.85–0.95) for all patients who underwent liver transplantation. However, risk-adjusted models showed that for low- and moderate-risk groups, HVC did not confer significant graft survival benefits, as described in Table 3, and shown in Fig. 2a–b, respectively. However, for high and very high risk groups, HVC did significantly contribute to graft survival (high risk: HR: 0.85, 95%CI: 0.76–0.96; very high risk: HR: 0.88, 95%CI: 0.78–0.99), as described in Table 3, and shown in Fig. 2c–d, respectively.

Discussion

The volume–outcome relationship in liver transplantation continues to be defined and its significance studied as a result of the

Table 2 Donor and recipient demographics for all observations (n = 31 587)

Demographics	LVC (n = 10 621)	MVC (n = 10 713)	HVC (n = 10 242)	P-value
Recipient female	31.17%	32.19%	32.07%	0.223
Donor female	40.17%	40.38%	40.87%	0.569
Recipient ethnicity				0.003
Caucasian	72.31%	74.60%	73.50%	
African American	9.18%	8.38%	8.41%	
Other ethnicities	18.51%	17.02%	18.09%	
Donor ethnicity				<0.0001
Caucasian	69.03%	70.97%	68.28%	
African American	14.62%	15.46%	15.51%	
Other ethnicities	16.34%	13.57%	16.21%	
Recipient age (≥18 years), Median	53 years	54 years	54 years	<0.05
Donor age, median	41 years	43 years	45 years	<0.05
≥40 years of age	51.29%	55.03%	58.37%	<0.0001
≥60 years of age	12.39%	16.85%	18.02%	<0.0001
Cold ischaemia time, median	7.0 h	7.0 h	7.0 h	NA
Recipient wait time, median	92 days	79 days	55 days	<0.05
Donor cause of death				<0.0001
Anoxia	13.15%	14.22%	15.35%	
CVA	43.36%	3.71%	46.53%	
Head trauma	41.14%	38.72%	35.79%	
Other	2.35%	3.35%	2.31%	
DCD	3.51%	4.45%	5.04%	<0.0001
Recipient MELD, Median (SD)	19.0 (9.10)	19.0 (8.84)	17.0 (8.65)	<0.05
DRI, Median (SD)	1.82 (0.41)	1.90 (0.48)	1.97 (0.49)	<0.05

HVC, high volume centres; MVC, middle volume centres; LVC, low volume centres; %, per cent; other ethnicities, Hispanics, Asians and 'others'; CVA, cerebrovascular accident or stroke; DCD, donation after cardiac death; DRI, donor risk index; SD, standard deviation; MELD, model for end-stage liver disease; NA, not applicable.

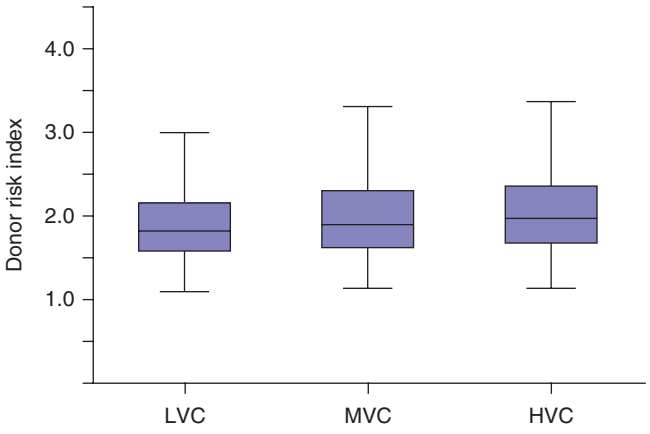

Figure 1 Box and whisker* plot of donor risk index (DRI) by transplant centre volume, $P < 0.0001$. *Whiskers calculated as data ≤1.5 inter-quartile range

current era of quality, cost containment and health care reform. In the present study, we have found that a centre volume benefit exists at HVC and in a risk-stratified model, the largest benefit appears to exist in the transplantation of the highest risk organs. The current results are present in spite of minimal differences in donor and recipient demographics. Risk-adjusted models showed that for low- and moderate-risk groups, HVC did not confer significant graft survival benefits. However, for high and very high risk groups, HVC did contribute to improved graft survival of 12–15% compared with transplantation at LVC. While DRI remains an important aspect of allograft survival prediction models, further understanding in its use as a predictor for graft failure is necessary.

Differences in centre volume were evident by groups, region as well as year. Certain regions do have HVC in our cohort based on tertiles for creating volume groups. Minor differences were seen in donor and recipient demographics between volume groups. HVC for instance, used organs with a higher DRI, but yet the median MELD score of the recipient was lower. Further understanding in

Table 3 Risk-adjusted analysis of allograft failure risk among DRI quartiles

Centre volume groups	Donor risk groups	HR	95% CI	*P*-value
LVC	Low risk	Reference	–	–
MVC		1.06	0.93, 1.20	0.41
HVC		0.99	0.86, 1.14	0.90
LVC	Moderate risk	Reference	–	–
MVC		1.04	0.92, 1.19	0.50
HVC		0.91	0.80, 1.04	0.16
LVC	High risk	Reference	–	–
MVC		0.90	0.80, 1.02	0.10
HVC		0.85	0.76, 0.96	0.007
LVC	Very high risk	Reference	–	–
MVC		1.01	0.89, 1.14	0.92
HVC		0.88	0.78, 0.99	0.03

LVC, low volume centres; MVC, middle volume centre; HVC, high volume centre; MELD, model for end-stage liver disease; DRI, donor risk index; HR, hazard ratio; %, per cent; CI, confidence interval.

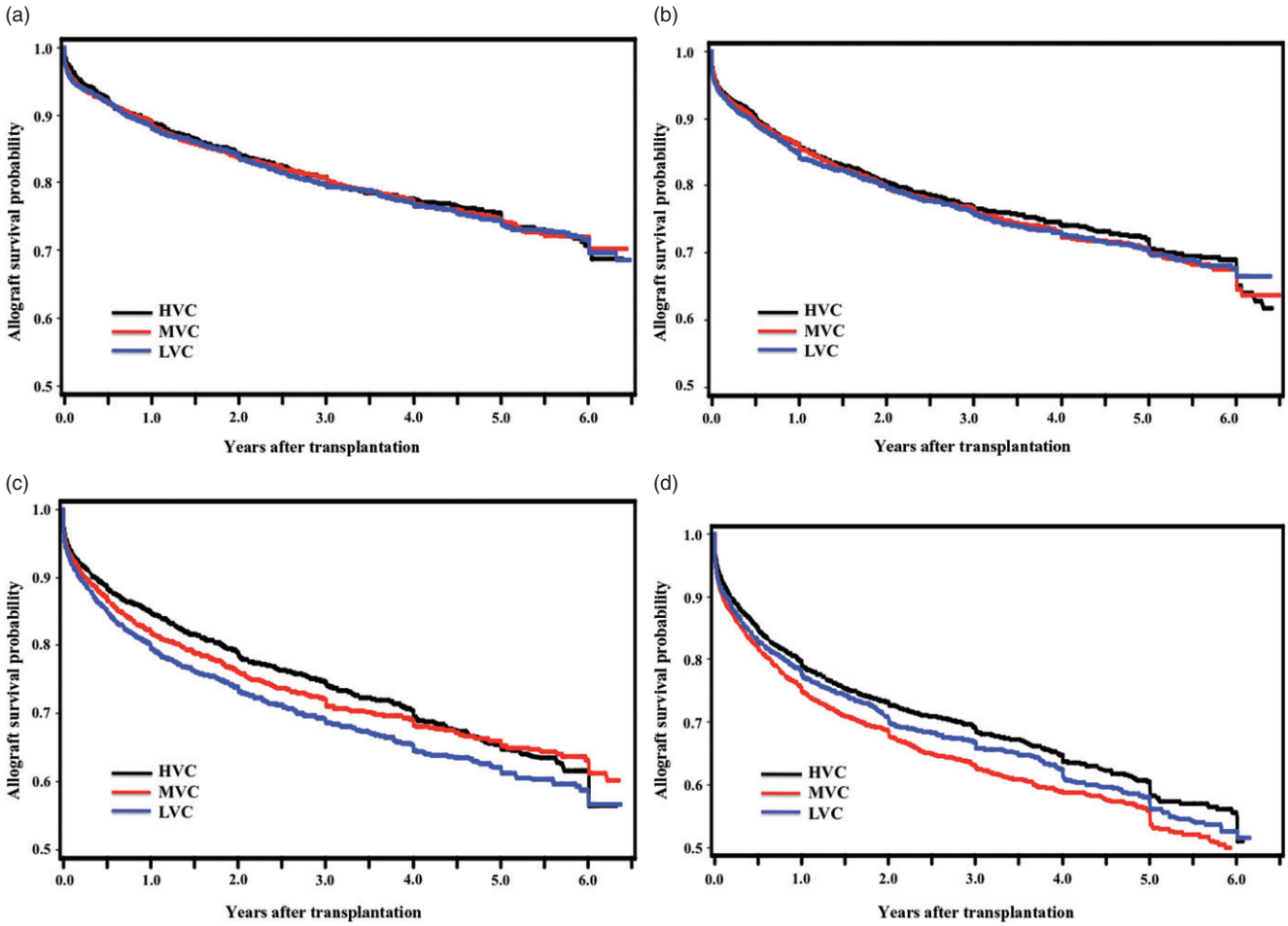

Figure 2 (a) Allograft survival by transplant Centre volume for low donor risk (DRI ≤ 1.63, n = 7922; P = 0.865). (b) Allograft survival by transplant centre volume for moderate donor risk (1.63 < DRI ≤ 1.90, n = 7918; P = 0.718). (c) Allograft survival by transplant centre volume for high donor risk (1.90 < DRI ≤ 2.26, n = 7925; P = 0.0006). (d) Allograft survival by transplant centre volume for very high donor risk (DRI > 2.26, n = 7924; P = 0.0002)

these practices is needed. Should centre volume be a component in determining the true 'risk index' of use of an allograft?

In spite of its benefit as an addition to the donor pool, the use of high-risk or marginal donor livers have brought about much attention because of the potential for inferior outcomes. As no defined criteria exists for expanded donor liver allografts, the DRI as described by Feng, has gained acceptance in the liver transplant community for quantification of donor risk and potential for allograft failure.[16,21,22] Use of these organs requires experience and expertise and appropriate allocation for optimal use. Studies have described its utility as well as its drawbacks with a comprehensive risk assessment for all organs.[21,23,24] Bashes *et al*. described acceptable results with these high-risk organs by documenting reduced mortality on the waiting list.[25] We used the DRI to create quartile gradients to assess if there is a volume impact on not only the use of these organs, but also in the results after transplantation. In these cohorts that were created based on quartiles of DRI, there was no volume benefit at low- and medium-risk organs while a significant advantage was noted in the higher risk organs. This is the first report to describe a volume relationship with gradients of DRI liver allografts.

The results of the present study are important because they suggest a volume advantage with these high-risk allografts. While further research is necessary to understand the implications of the results, use of these organs clearly requires experience for optimal results. Previous studies have shown conflicting data regarding the role of volume with improved transplant outcomes.[9,12,17] Based on the data, it is unclear whether this is as a result of organ allocation, recipient selection or post-transplant care. Identifying this level of care and determining where the difference lies, if any, is imperative to determine how we can improve outcomes overall and consider the use of other high-risk organs such as hepatitis C positive livers, older organs or donors with malignancy. As a result of the retrospective nature, large database used and inherent biases present in the use of these organs, it is not possible to determine if there was a reduction in waiting list mortality with the use of these organs at HVC.

Several limitations must be considered. As this was a retrospective study, it has the associated constraints specific to the variables collected in the SRTR database. While the database is comprehensive and inclusive, it does not include significant clinical variables that may be important for organ selection. For example, data on steatosis or causes of allografts failure were not available and thus could not be included in our analysis. Furthermore, such standards may vary significantly from centre to centre or between regions. We tried to control for this by examining the results within regions. All centres that performed deceased donor liver transplantations and contributed data to the SRTR database during the evaluated time period were utilized in the present study. We excluded all centres that performed less than five liver transplants per year to reduce statistical variability and ensure the volume groups were appropriately represented.

A centre volume advantage exists in the use of increasingly higher risk donor allografts. Based on these results, we have shown that the potential for optimization for these high-risk organs may exist in organ allocation, recipient selection or regional variability. Further research and comparison in specific practices is imperative to understand how best to optimize results and the use of these allografts.

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Conflicts of interest

None declared.

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