Predicting outcome after liver transplantation

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Chapter 8

The center effect in liver transplantation in the Eurotransplant region – a retrospective database analysis

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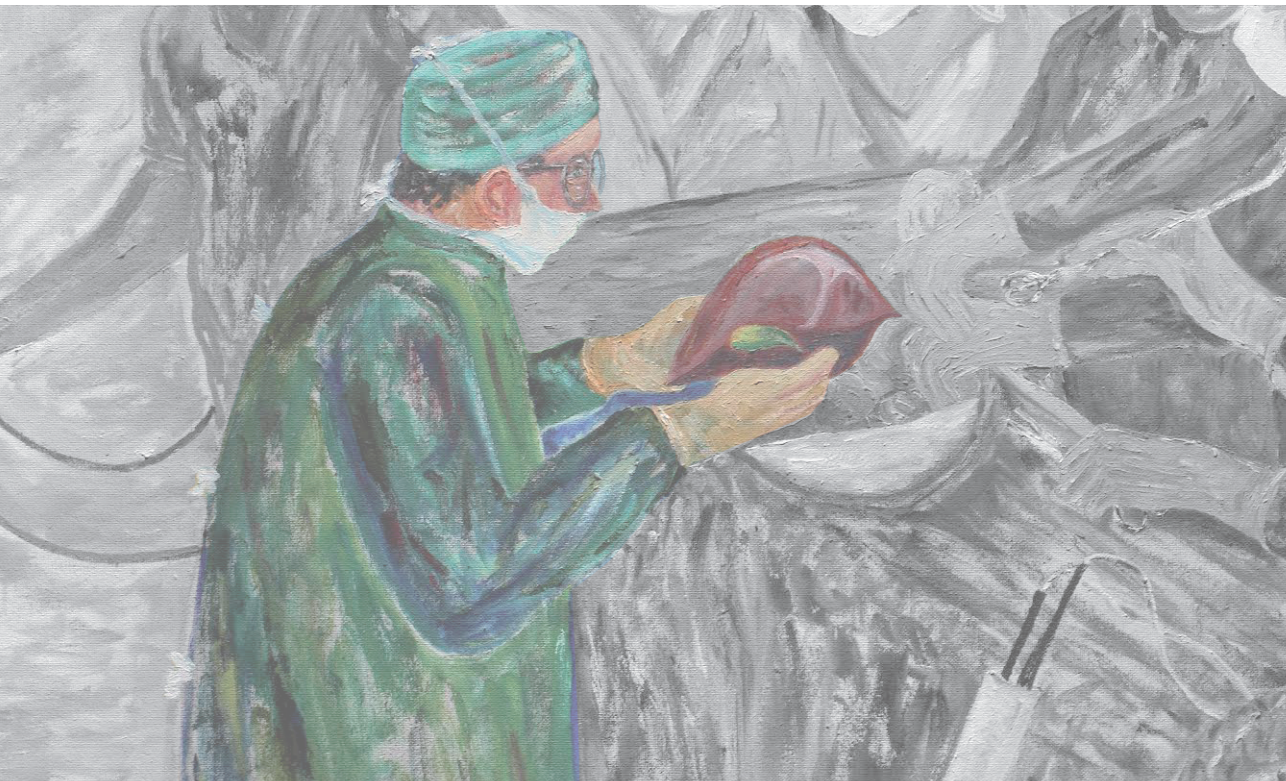

ABSTRACT

Introduction

Apart from donor and recipient risk factors, the effect of center-related factors has significant impact on graft survival after liver transplantation (LT).

Methods

In order to investigate this effect in Eurotransplant, a retrospective database analysis was performed, including all LT's in adult recipients (≥18 years) in the Eurotransplant region from 1.1.2007 until 31.12.2013. Additionally, a survey was sent out to all transplant centers requesting information on surgeons' experience and exposure.

Results

In total 10,265 LT's were included (median follow-up 3.3 years), performed in 39 transplant centers. Funnel plots showed significant differences in graft survival between the transplant centers. After correction for donor and recipient risk, with the Eurotransplant donor risk index [ET-DRI] and the simplified recipient risk index [sRRI]) and random effects, these differences diminished. Mean historical volume (in the preceding five years) was a significant ($p<0.001$), non-linear marker for graft survival in the multivariate analysis.

Conclusion

This study demonstrates that funnel plots can be used for benchmarking purposes in LT. Case-mix correction can be performed with the use of the ET-DRI and sRRI. The center effect encompasses the entire complex process of preoperative work-up, operation to follow-up.

INTRODUCTION

Apart from known donor risk and recipient risk factors (1-6), several studies have found that liver transplantation (LT) center factors represent significant predictors of graft failure, independent of region, donor service area or donor and recipient factors (7). The hypothesis of center volume being the main 'center related' risk factor for post-LT survival were confirmed by several studies from Europe (8) and the USA (9,10), however, these studies did not correct for donor and/or recipient risk. Northup et al. showed that transplant center volume was not a significant predictor for post-transplant survival after correcting for disease severity and multiple donor and recipient factors in the model for end-stage liver disease (MELD) era. (11) In the Eurotransplant region 1,632 deceased donor LT's were performed in 2015 by 39 individual centers, leading to a mean of 42 LTs per center (12). Consequently, this broad range of low- and high-volume centers is likely to lead to a difference in experience. For pancreas transplantations in the Eurotransplant region it was recently demonstrated that high volume is associated with a reduction of graft failure rates. (13)

Besides center volume, there may be other factors influencing differences in outcome between transplant centers or a so-called 'center effect'. Regulatory bodies in many disciplines require analysis of outcome data. In the Netherlands, the Dutch Surgical Colorectal Audit (DSCA) was initiated in 2009 to monitor, evaluate and improve colorectal cancer care, coordinated by the Dutch Institute for Clinical Auditing (DICA) is an example of such an institute. (14) The collected data are used as a quality measure and performance indicator that make it possible for hospitals to benchmark their own results. (15) Consequences of these types of registries are improvements of quality and performance. Within the Eurotransplant region results are currently not evaluated in this way.

The objective of this study was to investigate the effect of transplant center characteristics on outcome after LT in the Eurotransplant region in addition to the impact of donor risk (ET-DRI) (5) and recipient risk (sRRI) (6) in an attempt to provide data that can be used to comparatively evaluate the outcome of liver transplant centers, corrected for donor and recipient case-mix (quality and performance benchmarking), in a balanced, adjusted way.

PATIENTS AND METHODS

Data selection

All deceased donor LT's performed in adult recipients (≥18 years) from January 1, 2007 till December 31, 2013 in the Eurotransplant region were included to perform a retrospective

database analysis. Eurotransplant is a non-profit organization that facilitates patient-oriented allocation and cross-border exchange of deceased donor organs and consists of eight countries (member states): Austria, Belgium, Croatia, Germany, Hungary, Luxembourg (has no LT center), the Netherlands and Slovenia. Liver allocation in the Eurotransplant region is discussed in detail by Jochmans et al. (16) All basic donor, recipient and center characteristics (Tables 1 and 2) and follow-up data were obtained from the Eurotransplant Network Information System and the Eurotransplant Liver Registry. Follow-up data from the Eurotransplant centers are uploaded individually to the Eurotransplant database and Eurotransplant delivers these follow-up data to the ELTR database. So, every center in Eurotransplant indirectly delivers data to the European Liver Transplant Registry (ELTR). A detailed survey on individual experience of LT surgeons was sent to each individual Eurotransplant transplant center (Supporting Document). The Eurotransplant Liver Intestine Advisory Committee and Eurotransplant Board approved the study protocol for this study. All data were anonymized for country and transplant center.

The center specific data were obtained by a specifically designed survey that was sent to all Eurotransplant LT centers (Supporting Document). Here we specifically focused on the effect on center experience by transplant volume, which can be defined in many ways. In this study the following four potential surrogate measures were analyzed: annual volume (the total number of transplants performed in that same year), historical volume (the mean of transplants performed in the five directly preceding years), surgical exposure (the sum of the number of transplants divided by the sum of active years of all transplant surgeons from that center both in the study period) and surgical experience (the sum of the years of experience in LT of all surgeons divided by the number of surgeons in the center). In order to categorize and compare center volume, the volume limits from Burroughs et al. (17) were used (Table 3): low (<36 transplants), median (36–69 transplants) and high (>70 transplants).

Statistical analysis

Primary outcome used in the analyses was graft survival, defined as the period between the date of transplantation and date of retransplantation or date of recipient death, which ever occurred first (death un-censored graft survival). Follow-up data until May 2016 were used in the analyses. In case of missing follow-up data, transplants were not included in the multivariate analyses. For all donors the Eurotransplant donor risk index (ET-DRI) (5) (factors: donor age, cause of death, latest gamma glutamyl-transferase, donation after circulatory determination of death [DCD], split LT, allocation, cold ischemia time and rescue allocation [definition described in Eurotransplant Manual (18) and by Jochmans et al. (16)) was calculated and for all recipients the simplified recipient risk index (sRRI) (factors: recipient age, sex, etiology of disease, laboratory MELD score and repeated transplant). In case of missing values for donor gamma glutamyl-transferase median values were used (28 U/L, 1.7% missing) and in

case of missing cold ischemia times (43.8% missing) values were imputed 5 times based on a normal distribution according to the factor allocation (cold ischemia times used were: local 7.41 hours, regional 8.55 hours, extra-regional 9.80 hours) in a 5-fold database, in order to calculate the ET-DRI. Rubin's rules were used to pool estimates obtained from different imputed datasets. If patients received renal replacement therapy, the creatinine value was set at 4 (as of 16.12.2006, implementation of MELD for liver allocation). The MELD score was rounded to the nearest whole value (range 6-40). Two centers were excluded from the analysis due to less than 10 transplantations in the total study period, and one center was excluded based on potential data manipulation in the past (19,20).

Clinical characteristics were summarized by median and 25th–75th percentile or number and percentage for categorical factors. Comparison between groups was done by using Chi-square (categorical factors) or a Kruskall-Wallis test (numerical factors). Survival analyses were performed using Kaplan-Meier survival models and multivariate analyses were performed using Cox regression models. Uncorrected / corrected funnel plots were obtained by fitting Cox proportional hazards models with fixed effects for center, unadjusted / adjusted by ET-DRI and sRRI (both log-transformed). Unadjusted and adjusted center effects (log hazard ratios) were then centered and plotted against the precision (1 over variance) of the centered estimates, calculated under the null hypothesis of no difference between centers. Confidence limits are plotted as exp(+/-1.96 / sqrt(precision)) for 95% confidence limits and exp(+/-2.58 / sqrt(precision)) for 99% confidence limits. The funnel plot was used to demonstrate transplant centers with graft survival rates that were significantly higher or lower than the mean within Eurotransplant (high and low outliers, transplant centers that are outside the 95% or 99% confidence limits). Two ways of correcting for possible correlation of outcomes were considered. The first was by adjusting standard errors using sandwich estimators, the second was using random effects models. Analysis of volume-outcome relations was performed by considering the mean volume in the center over the five years preceding each transplantation. This "historical" volume was used to guard against reverse causation, the possibility that bad/good performance of a center leads to lower/higher volume afterwards. (21) In Figure 3, that shows the analysis of the relationship between volume and transplantation, P-splines with four degrees of freedom were used to test for and model non-linear relations between volume and outcome. The mean historical volume may vary every following year. For all analyses, a p-value of <0.05 was considered significant. All analyses were performed with SPSS (version 22.0) and R (version 3.3.2).

RESULTS

The total number of included transplants was 10,265 performed in thirty-nine transplant centers (range of 21–768 LTs per center in the whole study period) during the 7 years study period (median follow-up time 3.3 years, maximum follow-up time 9.2 years). Follow-up data were missing in 387 cases (96% completeness). Demographics of donor and transplant characteristics are shown in Table 1. Median donor age was 53 years, 4.4% of all transplants were with DCD allografts, 25% with a rescue allograft and median ET-DRI was 1.89. Twenty-five

Table 1. donor and transplant characteristics (N = 10,265)

	n (%) / median (25^{th}-75^{th} percentile)
Donor factor	
Age (years)	53 (42 – 65)
Height (cm)	173 (165 – 180)
Weight (kg)	75 (68 – 85)
BMI	25 (23 – 28)
Last GGT (U/L)	38 (20 – 86)
Sex	
Male	5,444 (53%)
Female	4,821 (47%)
Cause of death	
Trauma	2,178 (21%)
CVA	6,286 (61%)
Anoxia	1,014 (9.9%)
Other/unknown	787 (7.7%)
DCD	454 (4.4%)
Split liver	308 (3.0%)
Transplant factor	
Allocation	
Local	2,565 (25%)
Regional	2,558 (25%)
Extra-regional	5,142 (50%)
Rescue allocation	2,540 (25%)
Cold ischemia time (hours)	8.82 (6.98 – 10.72)
ET-DRI	1.89 (1.53 – 2.22)
Number of transplants according to center volume (according to Burroughs *et al.*)	
Low (£36 transplants)	2,602 (25)
Median (36 – 69 transplants)	5,084 (50)
High (≥70 transplants)	2,579 (25)

BMI, body mass index; GGT, gamma glutamyl-transferase; CVA, cerebral vascular accident; DCD, donation after circulatory determination of death; Eurotransplant donor risk index (ET-DRI)

percent of all transplants were performed in a low volume center, 50% in an intermediate volume and 25% in a large volume center according to the 'Burroughs volume categories', which were used as a practical example for center volume in this study. (17) A total of 30 centers (out of the included 39 centers) returned a filled-out survey (75% response rate), equally divided amongst the small (80% response), medium (80%% response) and large center size categories (75% response). Demographics of recipient characteristics are shown in Table 2. Median recipient age was 55 years, with a median lab-MELD at transplant of 18. The most frequently transplanted primary liver disease was alcoholic cirrhosis (23%) followed by patients with a malignant etiology of liver disease (21%). The number of repeated LT was 13%.

Table 2. recipient characteristics (N = 10,265)

	n (%) / median (25^{th}-75^{th} percentile)
Recipient factor	
Age (years)	55 (48 – 61)
Height (cm)	173 (167 – 180)
Weight (kg)	78 (67 – 89)
BMI	25.7 (22.9 – 29.0)
Lab-MELD	18 (12 – 30)
Sex	
Male	6,881 (67%)
Female	3,384 (33%)
Primary disease on WL	
Metabolic	302 (3%)
Acute	966 (9%)
Cholestatic	1,229 (12%)
Alcoholic	2,335 (23%)
Malignant	2,164 (21%)
HBV	327 (3%)
HCV	1,042 (10%)
Other cirrhosis	1,267 (12%)
Other/unknown	633 (6.2%)
Repeat transplant	1,299 (13%)
Lab-MELD category	
<15	3,830 (37%)
15 – 25	2,947 (29%)
26 – 34	1,751 (17%)
≥35	1,686 (16%)
missing values	51 (1%)
sRRI	1.96 (1.59-2.63)

BMI, body mass index; labMELD, laboratory model for end-stage liver disease score; WL, waiting list; HBV, hepatitis B virus; HCV, hepatitis C virus; sRRI, simplified recipient risk index

Table 3. center characteristics according to low/median/high categories (N = 10,265 transplants, n = 39 transplant centers)

Factor	Center volume			p-value
	Low (n = 20 centers) n = 2,602 transplants	Medium (n = 15 centers) n = 5,084 transplants	High (n = 4 centers) n = 2,579 transplants	
Donor age (y), median (25^{th}-75^{th} %)	52 (41 – 63)	52 (41 – 63)	56 (45 – 69)	<0.001
Donor BMI, median (25^{th}-75^{th} %)	25 (23 – 28)	25 (23 – 28)	26 (24 – 28)	<0.001
Donor, male sex, n (%)	1,405 (54)	2,694 (53)	1,345 (52)	0.411
Donor DCD, n (%)	196 (7.5)	258 (5.1)	n/a	<0.001
Split liver, n (%)	58 (2.2)	185 (3.6)	65 (2.5)	0.001
Allocation, n (%)				<0.001
Local	573 (22)	1,217 (24)	775 (30)	
Regional	796 (31)	1,384 (27)	378 (15)	
Extra-regional	1,233 (47)	2,483 (49)	1,426 (55)	
Rescue allocation, n (%)	618 (24)	1,008 (20)	914 (35)	<0.001
ET-DRI, median (25^{th}-75^{th} %)	1.88 (1.53-2.20)	1.86 (1.51-2.18)	1.92 (1.63-2.31)	
Recipient age (y), median (25^{th}-75^{th} %)	55 (48 – 62)	55 (47 – 61)	54 (48 – 60)	<0.001
Recipient BMI, median (25^{th}-75^{th} %)	26 (23 – 29)	26 (23 – 29)	26 (23 – 29)	0.258
Recipient lab-MELD, median (25^{th}-75^{th} %)	18 (11-31)	18 (11-30)	17 (12-28)	0.687
Recipient, male sex, n (%)	1,791 (69)	3,399 (67)	1,691 (66)	0.041
Recipient primary disease, n (%)				0.179
Acute	247 (10)	560 (11)	152 (5.9)	
Cholestatic	240 (9)	660 (13)	329 (13)	
HCV	218 (8)	464 (9)	360 (14)	
sRRI	1.91 (1.59 -2.63)	1.98 (1.63 – 2.64)	1.91 (1.59-2.60)	

BMI, body mass index; DCD, donation after circulatory determination of death; Eurotransplant donor risk index (ET-DRI); labMELD, laboratory model for end-stage liver disease score; HCV, hepatitis C virus; sRRI, simplified recipient risk index

Center effect analyses

Demographics categorized according to low, intermediate or large center size are shown in Table 3. Median donor age was the highest in the high-volume centers (56 vs. 52 years p=<0.001) and a higher percentage of extra-regional (55% vs. 47% and 49%, p<0.001) and rescue allocated liver allografts (35% vs. 24% and 20%, p<0.001) were transplanted in high-volume centers. No DCD donors were transplanted in the high-volume centers, the percentage of DCD transplantation was the highest in low-volume centers (7.5% vs. 5.1%, p<0.001). Split liver transplantation was the highest in intermediate volume category (p=0.001).

The first step was to analyze graft survival per transplant center, shown in Figure 1a (uncorrected graft survival), in a funnel plot. Next, a funnel plot corrected for donor-recipient case-

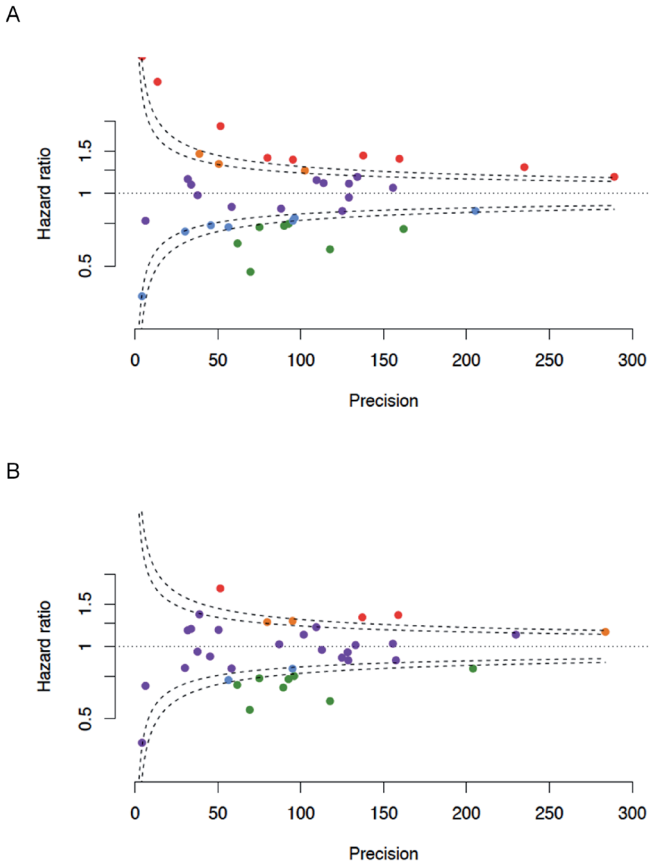

Figure 1. funnel plots with uncorrected (1a) and corrected for ET-DRI and sRRI (1b) graft survival rates plotted for every liver transplant center in Eurotransplant

mix (donor risk measured by ET-DRI and recipient risk by sRRI) was constructed (Figure 1b). In this figure with 'risk-adjusted' graft survival rates, there were eight centers with an outcome below average (orange and red dots, hazard ratio [HR] above the 95% confidence interval), ten centers with an outcome above average (blue and green dots, HR below the 95% confidence interval) and the remaining twenty-one centers were within the 95% confidence limits (the average/majority cohort, purple dots). Differences in donor, transplant and recipient characteristics for the centers are shown in Table 4 according to their outcome/performance. Median donor age was highest in the below-average centers (55 years vs. 52 years and 53 years, $p<0.001$) as well as the donor BMI (26 vs. 25, $p<0.001$). There were no DCD transplants performed in the below-average centers, whereas the highest percentage of DCD donors was used in the above-average centers (11% vs. 2%, $p<0.001$). The below-average centers transplanted the most extra-regional (62% vs. 36% and 54%, $p<0.001$) and rescue allocated (39% vs. 22%

Table 4. Center characteristics according to outcome in a corrected funnel plot outcome. Average outcome is defined as within the 95% confidence interval, poor above and good below the 95% confidence interval (N = 10,265 transplants, n = 39 transplant centers).

Factor	Outcome			p-value
	Poor performance (n=8 centers, 2091 transplants)	Average performance (n=21 centers, 5000 transplants)	Good performance (n=10 centers, 3174 transplants)	
Donor age (y), median (25^{th}-75^{th} %)	55 (45 - 67)	52 (41 - 64)	53 (42 - 63)	<0.001
Donor BMI, median (25^{th}-75^{th} %)	26 (24 - 28)	25 (23 - 28)	25 (23 - 28)	<0.001
Donor, male sex, n (%)	1,048 (50)	2,679 (54%)	1,717 (54%)	0.010
Donor DCD, n (%)	n/a	95 (2%)	359 (11%)	<0.001
Split liver, n (%)	36 (2%)	197 (4%)	75 (2%)	<0.001
Allocation, n (%)				<0.001
Local	348 (17%)	1,210 (24%)	1,007 (32%)	
Regional	458 (22%)	1,085 (22%)	1,015 (32%)	
Extra-regional	1,258 (62%)	2,705 (54%)	1,152 (36%)	
Rescue allocation, n (%	805 (39%)	1,119 (22%)	616 (19%)	<0.001
ET-DRI, median (25^{th}-75^{th} %)	1.98 (1.69- 2.32)	1.86 (1.51-2.20)	1.83 (1.51-2.14)	<0.001
Recipient age (y), median (25^{th}-75^{th} %)	55 (48-60)	55 (47-61)	56 (48-62)	<0.001
Recipient BMI, median (25^{th}-75^{th} %)	26 (23-29)	26 (23 -29)	26 (23-29)	<0.001
Recipient, male sex, n (%)	1349 (65%)	3389 (68%)	2143 (68%)	0.022
Recipient lab-MELD, median (25^{th}-75^{th} %)	18 (11-32)	18 (12-31)	16 (10-27)	<0.001
Recipient primary disease, n (%)				<0.001
Acute	200 (10%)	509 (10%)	257 (8%)	
Cholestatic	212 (10%)	647 (13%)	370 (12%)	
HCV	220 (11%)	575 (12%)	247 (8%)	
sRRI	1.97 (1.59 – 2.63)	1.97 (1.59-2.64)	1.87 (1.59-2.51)	<0.001

BMI, body mass index; DCD, donation after circulatory determination of death; Eurotransplant donor risk index (ET-DRI); labMELD, laboratory model for end-stage liver disease score; HCV, hepatitis C virus; sRRI, simplified recipient risk index

and 19%, p<0.001) allografts. The above-average centers transplanted patients with the lowest median MELD score (16 vs. 18, p<0.001).

Figure 2 shows a ranking of all thirty-nine transplant centers, ranked by the HR for decreased graft survival. Figure 2a and 2b show the unadjusted and (case-mix) adjusted HRs, respectively. Figure 2c shows the HR for decreased graft survival, adjusted for case-mix and random effect. This analysis shows that after using a random-effects model, there were still six centers with a significant below average outcome than the mean and ten centers with a significant outcome above average.

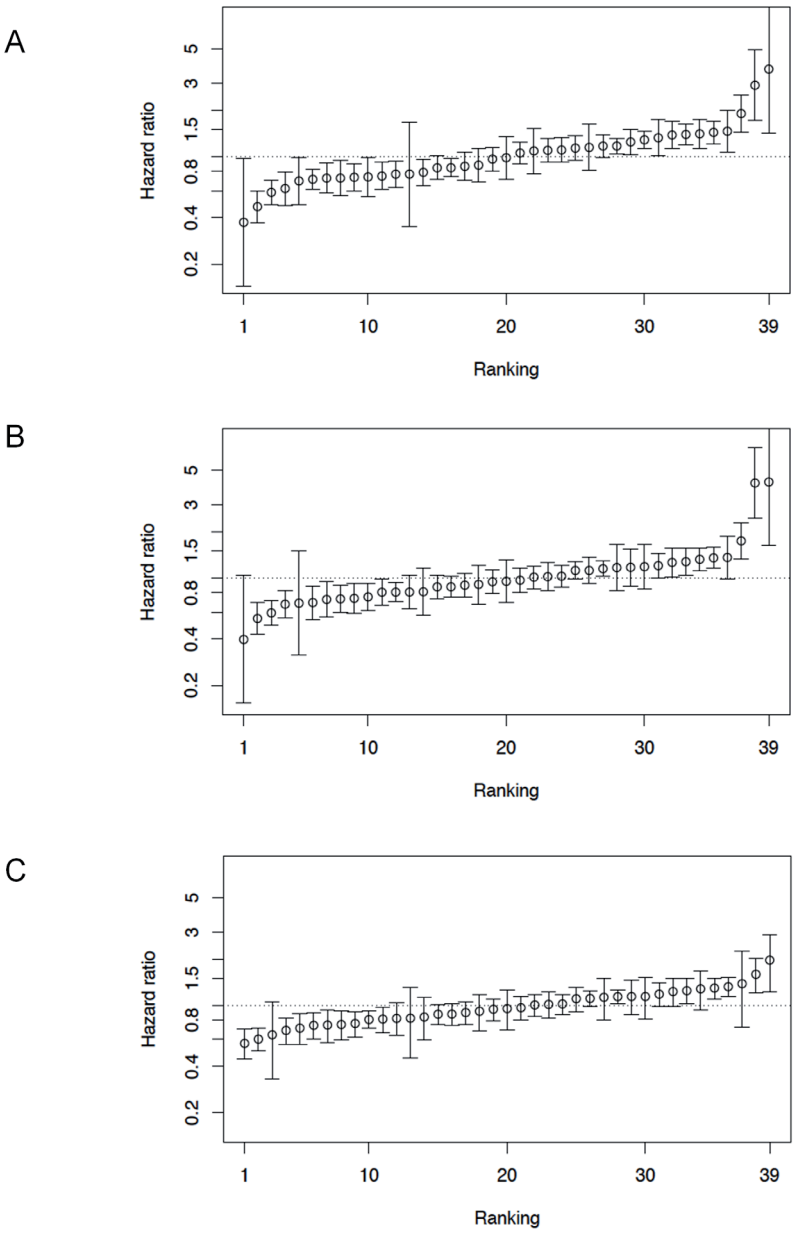

Figure 2. ranking of all liver transplant centers in Eurotransplant according to hazard ratio (ranked from low to average to high risk); uncorrected (2a), corrected for donor and recipient risk (2b) and corrected for donor risk, recipient risk and random effect (2c)

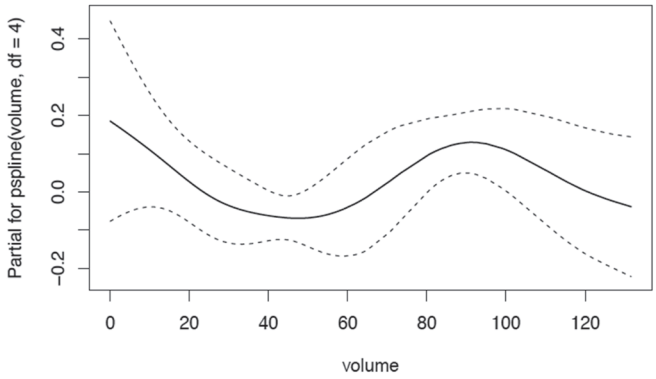

Figure 3. effect of center historical volume (the average number of transplants performed in the five directly preceding years) on the risk (hazard ratio) for decreased graft survival after liver transplantation (non-linear relation)

Measures for center related effects

The next step was to analyze which of the center-related factors (annual volume, historical volume, surgical experience and surgical expertise) was associated with graft survival. The following results were found: annual volume $p<0.001$, historical volume $p=0.015$ (non-linearity test $p<0.001$), surgical experience $p<0.001$ (non-linearity test $p<0.001$) and surgical exposure $p=0.029$ (non-linearity test $p<0.001$). For further analysis we chose to use the historical volume as a marker for center experience, as it has a significant relation with graft survival and historical volume is a reliable way of analyzing this factor in a longitudinal way according to the literature (21). Figure 3 shows the results of the multivariate analysis of historical volume and the relation with the risk (HR) for decreased graft survival. The relation is non-linear. The precise form of the curve has to be interpreted with caution, but a decreasing relative risk can be seen until the center volume reaches approximately 50 transplants (historical volume). The relative risk subsequently increases until around 100 transplants and finally decreases again.

DISCUSSION

This study, performed with data from the Eurotransplant database covering 7 years from 2007 till 2013, confirms that outcome (death-uncensored graft survival) differs between transplant centers in the Eurotransplant region, demonstrated with the use of funnel plots. When correcting these funnel plots of center-related risks for donor and recipient risks, with the ET-DRI and sRRI respectively, four (poor performing) centers came within the confidence intervals for graft survival. When the centers were ranked according to HR, the risk was more clearly delineated. This shows the possibility to demonstrate graft survival, corrected for donor-recipient case-mix. In light of quality control and transparency, openly sharing of

outcome data is very important and requires centers to be willing to share their data. It is clear that the 'best' organs in the 'best' recipients risk have the best results. Hesitation or reluctance to transplant high-risk organs into high-risk recipients or to share outcome data when results seem suboptimal as compared to other centers, should be overcome. Correction for case-mix is essential and will promote sharing of outcome data amongst transplant centers. In the future, it would be interesting if centers could access their own individual center performance within the international allocation organization with correction for case-mix, similarly as shown in this this study. This would likely improve awareness of performance based on comparisons with other centers and longitudinal developments and may thus contribute to improving quality of care and transparency for the whole transplant community.

The persisting differences between the transplant centers can be explained best by a "center effect". This center effect can be defined as all the factors that influence outcome after LT, beyond typical factors such as donor quality and recipient risk. In view of the large variation of the practice of LT in the Eurotransplant region, these factors are influenced by local protocols, waitlist management, acceptance policy (driven by access to liver grafts or availability of liver donors, which varies amongst Eurotransplant-countries (12)), legal framework (i.e. regarding the possibility of DCD LT) and potentially other unknown factors. For example, DCD LT is only performed in Belgium and the Netherlands. The differences in risk taking behaviors between the low/intermediate/high risk centers and the underperforming/medium/over performing centers, as demonstrated in respectively Table 3 and Table 4, could have been partly caused by this variation between the Eurotransplant countries. Not only surgical experience (skills and quality), but also experience in the entire donor and transplant process, from donor management to the follow-up of recipients, may play a significant role. This experience could partly be determined by the expertise of the center or other contributors like logistical factors or factors that are not readily appreciable in the analysis of large databases (e.g. data that are not routinely collected). Therefore, it is important when evaluating center outcomes, to keep in mind that differences in case-mix and waitlist mortality between centers exist.

In an attempt to make this more visible we divided the centers in three volume categories (low-intermediate-high). As an example, we used the proposed categories of the European Liver Transplant Registry (ELTR) study by Burroughs et al. in 2006. (17) Half of all transplants were performed in intermediate-volume centers. High-volume centers transplanted liver allografts with the highest median donor age, with highest percentage of extra-regional allocated or rescue allocated allografts, as well as the highest percentage of patients listed with hepatitis C. These higher donor and recipient risks would potentially lead to inferior outcomes and was therefore corrected by using the ET-DRI (donor risk), sRRI (recipient risk) and by performing a random-effects analysis. Even after these random-effects analyses centers with a significantly lower/higher risk than average remained.

In order to determine the best surrogate marker for center experience, we investigated four factors potentially associated with center outcome: annual volume, historical volume (mean volume over the past five years), surgical experience and surgical exposure. The latter two factors were determined by a survey independent of the data analysis that was sent out to all Eurotransplant LT centers. The reason for choosing historical volume as the putatively best surrogate marker for center experience, was the significant association with outcome in the analyses and based on published literature. (21) However, there are many differences in surgical practice between the Eurotransplant centers, e.g. whether a LT is being performed by one or two transplant surgeons or the organization of standard operating procedures in transplantation medicine. A separate analysis, in which the specific size of the center and its association with decreased graft survival were evaluated, showed that there was no linear relation with outcome. The results showed a curve with two optimal points (low HR) with regard to graft survival; around 50 transplants per year and when performing more than 120 transplants per year (historical volume). These results differ from findings by Burroughs et al. in another European study with ELTR data, published in 2006 (17). Even though that study was performed with data of transplants performed between 1988 and 2003, it was a large dataset with 34,664 LTs, which showed that centers with ≥70 transplants per year were associated with improved patient survival at 3-months and 1-year follow-up. Based on these considerations, a limit for improved or decreased graft survival such as that a transplant center that performs 69 transplants annually, would be a worse performer than a center with 70 transplants does not appear justified. In contrast, the use of a range of the number of transplants, in which a center would have less risk for decreased graft survival, would be preferable. Another difference with the ELTR study were the outcome end points employed. We looked at medium-term (3 years) graft survival as opposed to short-term patient survival, an approach that may explain the difference in the range for the decreased risk of center volume. The improved outcomes for high-volume centers in Germany, one of the Eurotransplant countries, was recently addressed in a study by Nijboer et al. (22) and an editorial related to this study also suggested that there was no linear relation between outcome and center size (23), which was also seen in the present study. One explanation for this effect could be that when a center grows beyond the 50 transplants, there will first be a transition period from being an intermediate-volume to a high-volume center. Eventually the increased exposure will lead to better results with an optimum that surpasses 120 transplants.

In 2013 Asrani et al. showed that the transplant center represents a significant determinant of graft failure that could provide an explanation for the disparities in outcomes after LT, with data from the Organ Procurement and Transplantation Network. Interestingly there was no effect of center volume when donor, recipient and transplant characteristics were taken into account. The authors suggested that the differences in outcome might well be explained by differences in surgical, medical and/or nursing expertise, that may influence the quality of care

at a transplant center. (7) Unfortunately, these factors are generally not recorded in databases such as the Scientific Registry of Transplant Recipients and the Eurotransplant database. One way of looking more closely to post-transplant results on a more detailed (center) level would be with a cumulative sum (CUSUM) analysis (24,25), performed by the centers themselves. This might be a means to more rapidly implement quality improvement and performance than by means of retrospective database analyses. In light of comparing results with other centers, the risk of the center in relation to ET-DRI or sRRI might also be different.

There are several potential limitations of this study, which represents a retrospective database analysis. Eurotransplant collects many donor factors, but only basic recipient data. In order to correct for recipient risk, we used the sRRI, that includes these basic factors as described previously. Nevertheless, additional relevant factors likely exist that may play a role in determining outcome. But because these were not recorded in the database, these could therefore not be entered into the analysis. Unfortunately, the cold ischemia times were incomplete for 44% of the transplants, which we countered by multiple imputation based on the factor allocation. Altogether, this will have only a limited impact on the ET-DRI calculation, as there is a narrow range of cold ischemia times. Another potential confounder could be the fact that the criteria for listing on the liver transplant waitlist differ considerably per country (and even per transplant center). This is also true for the decision process of whom to transplant or not to transplant, which is dependent on the availability of donors and the allocation system employed (MELD vs. non-MELD countries), as well as specific legal frameworks. All these considerations might have an impact on the center effect. Currently, the best way to correct for (part of) these factors is to use the ET-DRI and sRRI. Overall, the graph in Figure 3 demonstrates that additional factors apart from the numerical performance of transplant centers plays into the probability of graft and patient survival and that these associations have to be viewed and interpreted with caution.

CONCLUSIONS

In conclusion, our study demonstrates a center effect in liver transplantation in the Eurotransplant region by specifically looking at outcome and volume on a center-specific level. There are significant differences in graft survival rates between the Eurotransplant liver transplant centers. However, by correcting for donor and recipient risks (ET-DRI and sRRI) and random effects, these differences are partially corrected, and as such, funnel plots can be used for benchmarking purposes. The center effect consists of the whole process from preoperative work-up, operation to post-operative follow-up. In this study, we also specifically analyzed center (historical) volume. Although the results have to be viewed with caution in light of the considerable differences across the countries within the Eurotransplant region, a center

effect appears to be a relevant factor influencing outcome. In general, but certainly also for the centers itself, it is important to get insight in this center effect. Correcting for case-mix, using the donor-recipient model (ET-DRI + sRRI), is an elegant tool for such benchmarking efforts.

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SUPPORTING INFORMATION

Table S1. Survey on center/surgical experience.

Procurement surgeon information

Question 1

What is the total number of surgeons that currently perform **deceased donor organ procurement procedures** in your center?

.....

Question 2

What is the experience in **deceased donor organ procurement procedures** of these surgeons?

Surgeon	Experience	(years)
Surgeon 1	.....	years
Surgeon 2	.....	years
Surgeon 3	.....	years
Surgeon 4	.....	years
Surgeon 5	.....	years
Etc.	.....	years

Question 3

What is the number of **deceased donor organ procurement procedures** these surgeons performed per year from 2007-2013?

Surgeon	2007	2008	2009	2010	2011	2012	2013
Surgeon 1	.....	.....	.....	.....	.....	.....	.....
Surgeon 2	.....	.....	.....	.....	.....	.....	.....
Surgeon 3	.....	.....	.....	.....	.....	.....	.....
Surgeon 4	.....	.....	.....	.....	.....	.....	.....
Surgeon 5	.....	.....	.....	.....	.....	.....	.....
Etc.	.....	.....	.....	.....	.....	.....	.....

Transplant surgeon information

Question 4

What is the total number of surgeons that currently perform **liver transplants** in your center (staff/consultant)?

.....

Question 5

What is the number of years of experience in **liver transplantation** per surgeon in your center?

Surgeon	Experience (years)
Surgeon 1	..... years
Surgeon 2	..... years
Surgeon 3	..... years
Surgeon 4	..... years
Surgeon 5	..... years
Etc.	..... years

Question 6

What is the number of **liver transplants** performed by these surgeons per year from 2007-2013?

Surgeon	2007	2008	2009	2010	2011	2012	2013
Surgeon 1	.....	.....	.....	.....	.....	.....	.....
Surgeon 2	.....	.....	.....	.....	.....	.....	.....
Surgeon 3	.....	.....	.....	.....	.....	.....	.....
Surgeon 4	.....	.....	.....	.....	.....	.....	.....
Surgeon 5	.....	.....	.....	.....	.....	.....	.....
Etc.	.....	.....	.....	.....	.....	.....	.....