Utilization of Declined Liver Grafts Yields Comparable Transplant Outcomes and Previous Decline Should Not Be a Deterrent to Graft Use

Francesca Marcon, MD,[1] Andrea Schlegel, MD,[1] David C. Bartlett, PhD, FRCS,[1] Marit Kalisvaart, MD,[1] Dawn Bishop, RGN,[1] Hynek Mergental, MD, PhD,[1] Keith J. Roberts, PhD, FRCS,[1] Darius F. Mirza, MD,[1] John Isaac, FRCS,[1] Paolo Muiesan, MD, FRCS,[1] and M. Thamara Perera, MD, FRCS[1]

Background. In the United Kingdom, up to 20% of liver graft offers are not used for transplantation, and the reasons for graft refusal are multifactorial and not consistent among transplant units. **Methods.** Liver grafts previously declined by other transplant centers in the United Kingdom but transplanted in our unit in Birmingham between 2011 and 2015 were analyzed. According to the indicated reason for previous declines, liver grafts were categorized into 3 refusal groups: "quality," "logistics," and "other reasons." Results were compared with a matched, low-risk cohort of livers primarily accepted and transplanted at our center. **Results.** During the study period, 206 livers (donation after brain death: n = 141 (68.4%); donation after circulatory arrest: n = 65 (31.6%) were transplanted, which were previously discarded by a median of 4 other UK centers. The majority of declines were donor *quality* (n = 102; 49.5%), refusals followed by *logistic*s (n = 45; 21.8%), and *other reasons* (n = 59; 28.6%). Transplantation from both graft types (donation after brain death and donation after circulatory arrest) and all 3 refusal groups achieved equally good outcomes with an overall low complication rate. The incidence of primary nonfunction (2.4% vs 1.7%; *P = 0.5483*), in-hospital mortality (6.3% vs 4.1%; *P* = 0.2293) and 3-year graft (82.5% vs 84.1%; *P* = 0.6872) and patient (85.4% vs 87.6%; *P* = 0.8623) survival was comparable between livers previously declined and livers primarily accepted and transplanted at our center. **Conclusions.** Transplantation of declined livers can achieve comparable outcomes to primary liver low-risk graft offers. Previous refusal should not be taken as a barrier to use the graft, and with appropriate recipient selection, more lives could be saved.

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It is well established that marginal liver grafts or so called extended criteria donor (ECD) liver grafts substantially contribute to the organ pool in the era of severe organ shortage.[1,2] In the absence of universally accepted clear definition of what an ECD graft entails, most of the assumptions of graft quality are based on predonation donor history, such as advanced age and obesity, combined with other findings, such as steatosis and logistical parameters, that would render even a good quality graft marginal by way of extending preservation times. None of the strategies, namely, reduced-size LT, live-donor LT, splitting a cadaveric liver for 2 recipients, domino transplantation, and wider use of ECD grafts have been able to meet the demand for organs, and there is a persistent liver shortage.

Marginal or ECD liver grafts, however, expose recipients to an increased risk for reperfusion injury and impaired early graft function potentially triggering graft loss and even patient death.[3] How to best select an appropriate recipient in safe risk balanced manner is therefore repeatedly discussed among transplant professionals, and prediction scores have been recently developed.[2-7] In addition, graft acceptance and recipient selection strongly depend on the allocation system in a country, the transplant activity and center policy.[8] Allocation of a very extended donor liver may become difficult in countries with a Model of End-Stage Liver Disease (MELD)-based sickest first allocation, unless exception rules are defined to step out of the regular allocation pathway and to choose a particular recipient.[7,9]

In the United Kingdom, average liver organ discard rate approaches nearly 200 grafts each year, despite a center-oriented

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[1] *The Liver Unit, Queen Elizabeth University Hospital, Birmingham, United Kingdom.*

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Correspondence: Thamara Perera, The Liver Unit, Queen Elizabeth hospital Birmingham, Edgbaston, Birmingham, B15 2TH, United Kingdom. (Thamara.Perera@uhb.nhs.uk).

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allocation model,[10] and this reached nearly 15% to 20% of all consented liver graft donors. Although the majority of reasons for organ refusal or discard are obvious, a proportion of these grafts may be used with caution and appropriate graft/recipient matching. The liver unit of the Queen Elizabeth University Hospital in Birmingham is a very active transplant center, performing more than 200 adult liver transplants per year with an established track record of using marginal organs.[11] In this context, we reviewed our transplant cohort and became aware that almost a quarter of our transplanted livers were previously declined by other centers. The aim of this study is therefore to report our experience in Birmingham transplanting livers, which were previously declined by other UK centers, outlining short- and long-term outcomes along with pitfalls in decision making for wider benefit of the transplant community.

MATERIALS AND METHODS

Study Design and Patients

This retrospective study base on a prospectively maintained database of all adult liver transplantations (LTs) performed at our institution at Queen Elizabeth University Hospital in Birmingham. Between 2011 and 2015, liver grafts previously declined by other transplant centers in the United Kingdom, and subsequently accepted and transplanted at our center in Birmingham, were identified. Data analysis included donor and recipient demographics, intraoperative parameters, posttransplant complications, and survival.

Identification of Donor Offering Pattern

Potential organ donors in the United Kingdom are registered in an electronic secure web site (Electronic Offering System [EOS]) at the time of donor identification. This website is administered by the National Health Service Blood and Transplant, and all healthcare professionals involved in solid organ transplantation have access on demand. Each organ donor has a core donor dataset completed after performance of essential investigations, required for organ donation. Such detailed information's include a comprehensive past medical donor history of the predonation medical conditions. The responsibility of completing core data is conferred to the specialist nurse in organ donation involved in the donation process. Once an organ is identified for donation, it is offered first to the transplant center that has been selected based on the organ allocation rules. If there are no "super urgent" (category I) patients requiring emergency transplants, the liver is generally offered to the geographically closest center (zonal allocation). When a liver is declined by the zonal allocation center, the graft is offered to the remaining 6 transplant centers in a sequence, determined by the transplant activity within the immediate preceding 4 weeks. Importantly, the center that has performed the least liver transplants gets the first priority and the subsequent order of centers based on the number of transplants in each unit. If centers decline a particular offer, a clear reason is recorded on EOS at the time of decision including the date.

Reasons for Organ Refusal

For all LTs performed at our center in the study period, the donor organ offering pattern on EOS was studied. We documented how often a liver has been refused before acceptance by our center, and the reasons cited by the declining centers were recorded. Based on this, liver graft offers were allocated to 3 different refusal groups: (a) "quality," (b) "logistics," and (c) "other reasons" Table 1). The "quality" group included donor livers, refused due to deemed poor quality or "nontransplantability" of the organ, and the cited reasons comprised donor age, functional donor warm ischemia time (fDWIT) or graft steatosis. When "poor function" was selected as a cause used for refusal, donors presented either with elevated liver enzymes or lactate or International Normalized Ratio. In selected cases, the reason given was "center criteria are not met," because some transplant centers have an arbitrary upper age cutoff limit in accepting donation after circulatory arrest (DCD) grafts and this also symbolized the marginality/"nontransplantability" of the organ by this particular transplant center.

Donor medical history (MH) was thoroughly reviewed in all cases to recognize the most valid reasons to decline the offer. Majority of the predonation MH involved conditions that would categorize the donor under the *quality group* (drugs/alcohol abuse, severe donor infections). However, donors with a medical disorder related to neoplastic or to controversial benign disorders (including brain tumors) were classified as *other reasons* (donor MH: tumor/other benign). Although the quality of such donor organs may be excellent, the high risk of donor disease transmission was deemed to be the reason for graft refusal. The parameter "no suitable recipient available" involves cases, where in a particular blood group, no appropriate recipient was identified on the center-specific waiting list. The term "other logistics" includes a lack of transplant capacity at the intensive care unit (ICU) or operation theater in a corresponding transplant center.

Data Analysis, Matching of Control Group, and Statistics

Graft and recipient parameters were collected from our institutional recipient database for LT. Multiple outcome measures, including intraoperative values, posttransplant complications, and graft and patient survivals, were analyzed. Complications were classified according to the Clavien-Dindo Classification.

Next, we performed a multivariate regression analysis and applied different risk factors (donor age, graft type DCD, cold ischemia time [CIT], number of declined centers, cause of graft refusal, recipient age, and recipient United Kingdom Model of End-Stage Liver Disease [UKELD]) for best stratification of worse outcome in our cohort of declined livers.

To better assess the impact of donor quality on outcome, the results of LT from previously declined liver grafts were compared with a liver transplant cohort, where the graft was primarily accepted. Importantly, this matching cohort included low-risk, primary transplantations, performed at our center within the study period. With the baseline division of liver transplant recipients into 2 groups (previously declined vs primarily accepted without previous decline), a case-control matching analysis was done to correct for potential differences in baseline donor, graft and recipient characteristics among the 2 groups, separately for the donation after brain death (DBD) and DCD liver cohort. Based on the overall number of LTs performed at our centers between 2011 and 2015, a 1:2 matching for DBD livers and a 1:1 matching for

TABLE 1.

Cause of initial graft refusal by other centers for each liver accepted and transplanted at our center

	Declined grafts		
Main reason for graft refusal	Overall (n = 206)	DBD (n = 141)	DCD (n = 65)
(1) Quality	102 (49.5%)	65 (46.1%)	37 (56.9%)
Donor MH:	17 (8.3%)	11 (7.8%)	6 (9.2%)
Drugs/alcohol	12 (5.8%)	6 (4.3%)	6 (9.2%)
Infection[a]	5 (2.4%)	5 (3.5%)	0
Liver size	25 (12.1%)	25 (17.7%)	0
Donor age	18 (8.7%)	6 (4.3%)	12 (18.5%)
Poor function	17 (8.3%)	13 (9.2%)	4 (6.2%)
Center criteria not met	11 (5.3%)	1 (0.7%)	10 (15.4%)
CIT	6 (2.9%)	4 (2.8%)	2 (3.1%)
Graft steatosis	6 (2.9%)	5 (3.5%)	1 (1.5%)
Duration of fDWIT	2 (1%)	-	2 (3.1%)
(2) Logistics	45 (21.8%)	32 (22.7%)	13 (20%)
No "suitable" recipient	26 (12.6%)	20 (14.2%)	6 (9.2%)
Other logistics	19 (9.2%)	12 (8.5%)	7 (10.8%)
(3) Other	59 (28.6%)	44 (31.2%)	15 (23.1%)
Donor MH:	41 (19.9%)	28 (19.9%)	13 (20%)
Tumor/other benign[b]	8 (3.9%)	5 (3.5%)	3 (4.6%)
Unknown	33 (16%)	23 (16.3%)	10 (18.4%)
Virology (HCV+; HBV+)	4 (1.9%)	3 (2.1%)	1 (1.5%)
Anatomy	3 (1.5%)	3 (2.1%)	0
Other	9 (4.4%)	8 (5.7%)	1 (1.5%)
Unknown	2 (1%)	2 (1.4%)	0

Data presented as frequency in n/%.
[a] MH infections: bacterial endocarditis, other severe sepsis.
[b] Benign/others: brain tumor, treated, amyloid angiopathy, dilated CBD, cyst in right liver, pulmonary fibrosis, diabetes and hypertension, donor sister fam. Hemochromatosis, popliteal thrombosis, Danon disease; unknown: not identifiable on EOS, MH without further specification.

DCD grafts without replacement was performed. The matching process corrected for potential key confounders, that is, comparable donor age, CIT, recipient age, and UKELD score. In this context, case-control matching was performed according to the following donor, graft, and recipient criteria: donor age (±4 years), CIT (±1.5 hrs), recipient age (±1 year), and UKELD score (±2 points). For each declined DBD liver used for transplantation at our center, 2 appropriate DBD livers were matched according to previously defined parameters. To correctly match the control group in the setting of declined DCD livers, fDWIT (±1 minute) was used in addition to the 4 other donor/recipient parameters. Cases were selected to keep the risk in the "primarily accepted cohort" as low as possible, and our aim was to compare the outcomes of previously declined grafts with outcomes from a best-selected, low-risk cohort (labeled as: primarily accepted DBD and DCD cohort) (Table 2). Our center policy regarding transplant technique, bench practice, and organ flush can be found elsewhere.[11]

Data are presented using the median and interquartile range (IQR) for continuous variables. The nonparametric Mann-Whitney *U* test was used to determine whether significant differences existed between groups. Differences in nominal data were compared by Fisher's exact test. A *P* value less than 0.05 was deemed statistically significant. Clinical outcomes analysis was performed through Kaplan-Meier survivor plots, and significant differences between groups were assessed by Log-rank/Mantel-Cox testing. Additionally, Logistic regression models were fit to assess the impact of individual covariates on the rate of respective events (majority are continuous parameters and a few binary). All data were analyzed using IBM SPSS v.23.0 and prism v.5.

Ethical Approval and Quality Control

Completeness, plausibility, and validity of the data were independently verified (by F.M., A.S., M.K., and M.T.P.R.P.), including objective review of all historical medical charts. The local regulatory board approval was obtained before study initiation and database/chart review (CARMS-12498, CARMS-02246).

RESULTS

Pattern of Graft Refusal and Reasons

A total number of 901 (n = 901) adult cadaveric LTs were performed during the study period and in more than 20% (n = 206/901; 22.7%) grafts previously declined by other UK transplant centers were used (Figure 1A, B). The majority (n = 141; 68.4%) were organs donated after brain death (DBD), and 13 livers were right lobe (RL) split DBD grafts. The DCD cohort involved 65 grafts (31.6%) (Table 1). A steady increase in utilization of liver grafts previously declined was noted over the years. The peak activity was recorded in the most recent year of the study, contributing to 28% of transplants (Figure 1A).

Table 1 outlines the reasons for graft refusal, documented in EOS by the transplant centers at the time of organ offer. According to the main reason for graft refusal, cited by the majority of declining centers, liver grafts were allocated to the following 3 categories: *organ quality* (n = 102; 49.5%), *logistics* (n = 45; 21.8%), and *other reasons* (n = 59, 28.6%) (Table 1). The most common reason for refusal was MH (n = 58, 28%), followed by "no suitable recipient" (n = 26, 12.6%), liver size (n = 25, 12.1%), donor age (n = 18, 8.7%), poor function (n = 17, 8.7%), and other logistical reasons (n = 19, 9.2%) (Table 1). The MH of 18 donors involved cancer. Sites of malignancy included: brain (n = 9), prostate (n = 2), breast (n = 2), and 1 in each of the following: cervix, testis, melanoma, and thyroid. Brain tumor–induced bleeding was the cause of death in 6 donors; however, all other donors have been clear from the disease for at least 5 years before donation.[12] In 2 donors, such history of cancer was the main reason to decline this liver, 1 melanoma (Breslow index, 0.8; >5 years before donation)[12] and 1 breast cancer (T1N0M0, 7 years before donation, classified under the "other reasons" group: MH tumor/other benign; Table 1). Although liver enzymes were deranged in 38.3% of the donors, in only 17 (8.3%) cases "poor function" was indicated as cause of graft refusal.

Within our cohort, DCD liver grafts were more frequently declined for "quality" reasons (56.9% vs 46.1%), whereas DBD grafts are more often refused for "other" reasons 11.3% vs 3.1%). Majority of liver grafts were declined by more than 1 center (n = 128, 62.1%). The median refusal rate was 4 centers per liver (IQR, 1–6), with higher decline rate for DCD grafts compared with DBD livers (Table 2). In addition, 41% of DBD livers and 60% of DCD grafts were refused by more than 4 transplant centers in the United Kingdom (Figure 1B).

TABLE 2.

Donor, graft, and recipient characteristics

Characteristics	Overall declined livers, n = 206	Declined DBD, n = 141	Primarily accepted DBD cohort, n = 282	Declined DCD, n = 65	Primarily accepted DCD cohort, n = 65	*P* (declined DBD vs primarily accepted DBD)	*P* (declined DCD vs primarily accepted DCD)
Donor age, y	51 (39-66)	52 (42-64)	54 (43-63)	61 (47-69)	45 (33-54)	0.176	0.005
Donor BMI, kg/m^2	24.6 (22.1-28.1)	24.8 (22.1-28.4)	24.5 (22.5-27.8)	24.5 (22-27)	24.2 (22.6-26.6)	0.602	0.726
Donor ICU stay, d	1.5 (1-3)	1 (1-3)	2 (1-4)	2 (1-4)	3 (1-6)	0.401	0.311
Total warm ischemia time, min	—	—	—	29 (21-34)	25 (22.5-30)	—	0.049
Functional warm ischemia time, min	—	—	—	17 (14-22)	18 (15-22)	—	0.473
Asystolic warm ischemia time, min	—	—	—	11 (10-13)	12 (10-13.5)	—	0.372
Cold storage, h	8.1 (6.9-9.7)	8.6 (7.4-10.3)	8 (7-10)	7.46 (6.5-8.2)	5.7 (4.6-6.4)	0.019	0.001
Recipient age, y	54 (46-61)	54 (44-61)	54 (45-61)	56 (52-62)	56 (48-62.5)	0.849	0.861
Recipient UKELD (points)	53 (49-57)	54 (50-58)	53 (48-57)	52 (49-56)	54 (48.5-57)	0.151	0.112
Recipient underlying disease (n/%)							
HCV	39 (18.9%)	26 (18.4%)	57 (20.2%)	13 (20%)	17 (26.2%)	0.6988	0.5328
HBV	11 (5.3%)	6 (4.3%)	10 (3.5%)	5 (7.7%)	2 (3.1%)	0.7884	0.4401
PSC	23 (11.2%)	14 (9.9%)	36 (12.8%)	9 (13.8%)	8 (12,3%)	0.4289	1.000
PBC	23 (11.2%)	13 (9.2%)	34 (12.1%)	10 (15.4%)	12 (18.5%)	0.4166	0.8155
ALD	55 (26.7%)	35 (24.8%)	80 (28.4%)	20 (30.8%)	16 (24.6%)	0.4875	0.5569
NASH	15 (7.3%)	13 (9.2%)	16 (5.7%)	2 (3.1%)	5 (7.7%)	0.2199	0.4401
AIH	4 (1.9%)	3 (2.1%)	11 (3.9%)	1 (1.5%)	1 (1.5%)	0.4027	1.000
Polycystic liver disease	3 (1.5%)	2 (1.4%)	5 (1.8%)	1 (1,5%)	0	1.000	1.000
Other	25 (12.1%)	22 (15.6%)	30 (10.6%)	3 (4.6%)	4 (6.2%)	0.1584	1.000
HCC alone	3 (1.5%)	2 (1.4%)	3 (1.1%)	1 (1.5%)	0	1.000	1.000
Re-OLT for PNF/HAT/chron. Reject.	5 (2.4%)	5 (3.5%)	0	0	0	0.0039	1.000
HCC (n/%)	39 (18.9%)	25 (17.7%)	48 (17%)	17 (26%)	13 (20%)	0.8917	0.5328
No. times declined by centers (n)	4 (1-6)	2 (1-6)	—	5 (2-6)	—	—	—

Data presented as median and IQR or frequency in n/%.

HCV, hepatitis C virus; HBV, hepatitis B virus; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; ALD, alcoholic liver disease; NASH, nonalcoholic steatohepatitis; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; re-OLT, reorthotopic liver transplantation.

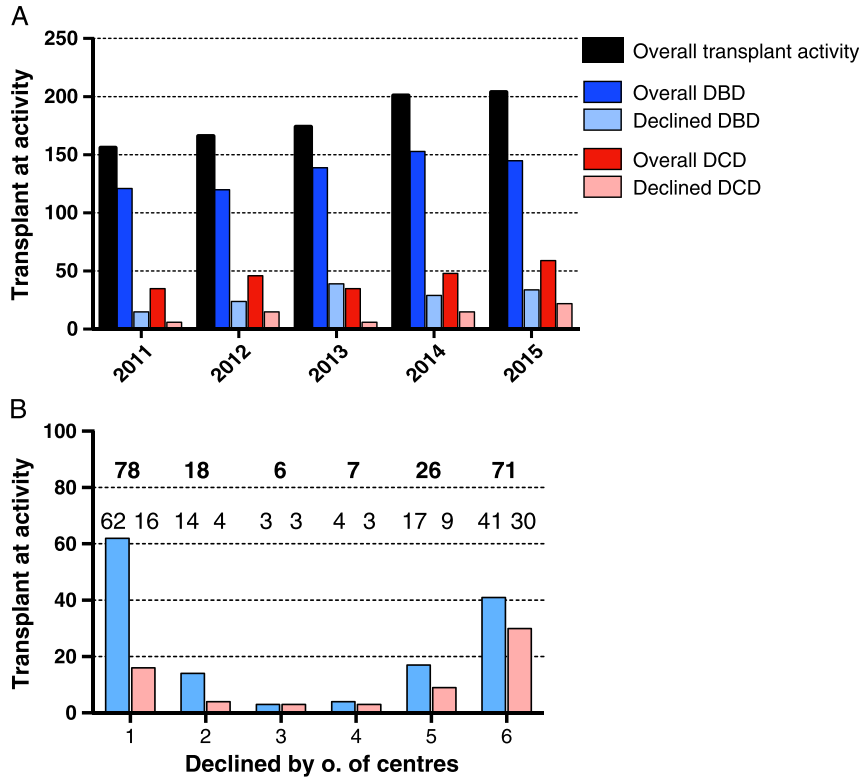

FIGURE 1. Transplant activity between 2011 and 2015. (A) Overall frequency of DBD and DCD LTs at Queen Elizabeth University Hospital Birmingham, UK, between 2011 and 2015, comparing declined and primarily transplanted liver grafts. (B) The number of declining centers is shown for the entire cohort of DBD livers and DCD grafts.

Impact of Declined Livers on Early Outcome After Transplantation

Overall, 8 (3.9%) patients underwent retransplantation in the immediate posttransplant period. The main reasons for graft loss were: primary nonfunction (PNF), hepatic artery thrombosis (HAT) or dissection, hemorrhagic necrosis and ischemic cholangiopathy. All recipients survived the retransplantation. Within the first 90 days, 13 recipients died, leading to a 90-day patient survival of 94%. Main causes of death were as follows: PNF (without retransplantation), hemorrhagic necrosis, intraoperative cardiac arrest (in 2 cases before graft reperfusion), bleeding due to pseudo-aneurysm at aortic conduit, intracranial bleeding, and 1 unknown etiology. The majority of such donor livers were DBD grafts, and livers were equally distributed to all 3 groups of graft refusal, for example, quality (n = 4), logistics (n = 4), and other (n = 5) (**Table S2, SDC,** http://links.lww.com/TP/B533).

Medium- and Long-Term Outcomes of Declined Grafts Compared With Livers Primarily Accepted and Transplanted

Between 2011 and 2015 at our center, overall, 695 adult LTs were primarily performed without previous declines. After exclusion of combined liver-kidney transplantations, acute liver failures, and livers included in other trials, 423 DBD grafts and 226 livers from DCD donors were eligible for matching. Case-control matching was performed based on previously described clinical donor, graft, and recipient characteristics (Table 2).

The overall 3-year patient and graft survival was comparable to that of lowest risk cohort of primarily accepted DBD and DCD transplantations (patient survival, 85.4% vs 87.6%; graft survival, 82.5% vs 84.1%), respectively (Figure 2). In the matched control cohort: 6 PNFs and 13 HATs were recorded. Early graft loss accumulated to 19 for the DBD and 4 for the DCD cohort of primarily accepted grafts (**Table S1, SDC,** http://links.lww.com/TP/B533). There was no significant difference in posttransplant graft and patient survival comparing the quality, logistics, and other causes group (**Figure S1, SDC,** http://links.lww.com/TP/B533).

The number of declining centers had no significant impact on graft survival. Multivariate analysis confirmed previous results and none of the parameters were shown to impact on graft survival (Table 3).

Is There a Higher Risk for More Posttransplant Complications Transmitted by Declined Liver Grafts?

Compared with the low-risk matching cohort of primarily accepted liver grafts, outcomes regarding graft function and complications were equal. Livers of all cohorts showed an immediate function, and median peak alanine aminotransferase (ALT) was equally low and expectedly higher in the DCD cohort (**Table S1, SDC,** http://links.lww.com/TP/B533). Majority of recipients experienced a type of posttransplant complication. Liver retransplantation and new onset of renal replacement therapy during postoperative course significantly contributed to the amount of complications in all groups. In addition, we have performed a subgroup analysis of all RL split livers used in this cohort (n = 13, all DBD grafts). Two grafts were lost in this subgroup, although none of those was due to the development of a HAT or biliary complications. One RL recipient died due to intracranial bleeding, and another recipient was registered dead of unknown etiology with functioning graft and patent vessels.

DISCUSSION

Previously declined liver graft offers contribute to almost one quarter of our annual transplant activity. Although most other centers refuse liver grafts claiming quality issues, these data suggest that donor assessment differs significantly among transplant surgeons. In this study, we highlight several factors; we first demonstrate that most livers were refused for "quality" reasons; however, there is a significant disparity among the transplant surgeons' opinion on quality assessment at the time of organ offer; there was nearly two third of the cases where there was disagreement among opinions. Second, the recipients of declined grafts showed a comparably low complication rate and equal survival as candidates transplanted from livers primarily accepted without previous declines. Finally, we have demonstrated that the cause of graft refusal and the number of times an organ was declined by other centers did not impact the outcome.

The definition of extended criteria grafts (ECD) remains subjective and varies significantly between countries and even centers. According to the European Liver Transplant Association, the following donor and graft characteristics define liver marginality: donor age, older than 65 years, donor ICU stay with ventilation, longer than 7 days; donor body mass index (BMI), greater than 30 kg/m^2; graft steatosis, greater than 40%; donor serum sodium, greater than 165 mmol/L; elevated liver enzymes (alanine aminotransferase > 105 U/L, aspartate aminotransferase > 90 U/L); and serum bilirubin, greater than 3 mg/dL.[11,12] In accordance with the aging population, most donors are bound at least to be consisting of 1 or more of these characteristics. Despite multiple definitions and threshold, judgement and subsequent liver acceptance rate of marginal grafts is strongly correlated with the experience of transplant surgeon taking the offers.[13] Though the process of declining an organ is multifactorial, we believe that some donor livers potentially have been declined by misperception of the underlying graft quality.[13] There is a center influence on this behavior because larger transplant centers with long waitlists are more likely to accept marginal offers. However, majority of abovementioned parameters imprecisely define a subjective measure, for example, 40% steatosis, which does not include the differences between microsteatosis and macrosteatosis. The impact of donor age has also been frequently discussed, and several centers have abandoned their cutoff 65 years in DBD and also DCD grafts.[14-18]

In this study, we have demonstrated that livers precluded by only recipient- or logistic-related conditions performed equally well compared with those grafts refused primarily by liver quality. Majority of livers were discarded by more than 1 "risk factor," where we may speculate that many professionals have discarded the organs due to a cumulative effect of multiple risk factors. Unfortunately, the national record on EOS fails to provide a multiple list of clear

TABLE 3.

Multivariate analysis of potential risk factors for graft loss after utilization of previously declined livers

Parameters	OR	95% CI		P
Overall graft loss		Lower	Upper	
Donor age, y (c)	1.003	0.976	1.030	0.835
Donor BMI, kg/m^2 (c)	1.046	0.951	1.150	0.355
Graft type DCD (d)	1.611	0.714	3.635	0.251
CIT, h (c)	0.883	0.738	1.056	0.173
Recipient age, y (c)	0.967	0.927	1.008	0.114
UKELD (points) (c)	1.005	0.934	1.080	0.900
No. centers declined (c)	1.408	0.905	2.191	0.129
Cause of decline (group) (d)	1.158	0.724	1.850	0.540
Parameters	**OR**	**95% CI**		**P**
In-hospital graft loss		Lower	Upper	
Donor age, y (c)	1.011	0.979	1.044	0.518
Donor BMI, kg/m^2 (c)	1.009	0.907	1.123	0.869
Graft type DCD (d)	2.480	0.692	8.888	0.163
Cold storage, h (c)	1.042	0.818	1.327	0.738
Recipient age, y (c)	0.992	0.944	1.043	0.766
UKELD (points) (c)	1.036	0.953	1.126	0.409
No. centers declined (c)	1.139	0.689	1.882	0.613
Cause of decline (group) (d)	1.279	0.736	2.224	0.383

OR, odds ratio; 95% CI, confidence interval; c, continuous variable in logistic regression; d, dichotomous variable in logistic regression.

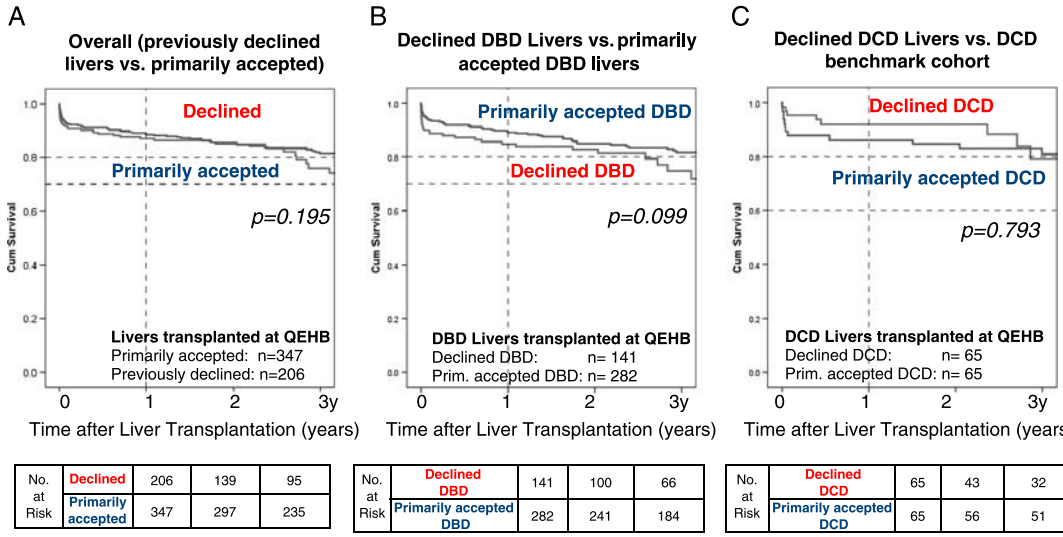

FIGURE 2. Graft survival of declined livers used for transplantation, compared with a matched, low-risk cohort of primarily accepted liver grafts (2011–2015). Declined (as indicated by red line) and matched primarily accepted liver grafts, demonstrate no difference in graft survival.

indicators why a specific liver was refused. In this context, interesting information regarding surrogate donor-related variables motivating each liver refusal are lost. For example, the term "center criteria not met" is very imprecise, and the exact donor history or the objective variable that led the center to assume a poor donor condition could not be explored, retrospectively. In addition, a "domino effect" cannot be excluded in cases where livers are refused by many centers, stating the same cause. In this study, the most frequent argument to decline a graft has been donor MH. This finding has been paralleled by the previous study by McCormack et al[19] showing a similar feature of main reason for graft refusal in Argentina. By contrast, our center policy reduced the importance of past medical donor history, whereas direct visualization of the graft by the implanting surgeon has been our practice, rather than relying on history alone. For example, elevated gamma-glutamyl transferase in combination with higher donor BMI results in graft rejection by many, despite having not inspected the graft.[17,19,20] In addition, donor history of alcohol abuse does not necessarily result in a bad liver quality. We, therefore, consider that donor history of alcohol abuse and obesity are not acceptable for graft refusal at the point of graft offer.

Our approach in these high-risk donor history scenarios is to accept the liver offer and visualize the graft upon arrival at the transplanting center. We believe additional parameters may impact even more on outcome. The donor procedure should be performed by experienced surgeons to avoid further ischemic injury of the graft. Also, recipient surgery should be carried out with a more expedited manner maximizing the effort in reducing cold and recipient warm ischemia time. Exclusively by following this strategy, we achieved results comparable with the lowest risk and matched control cohort. Optimized matching strategies to balance donor and recipient risk represent another target to further improve outcomes.

In the United Kingdom, a center-based allocation system is currently used, where different regions are covered by 7 transplant centers. Such center-oriented allocation system is a clear advantage for the utilization of higher-risk grafts which could be of particular benefit for liver recipients, who are underestimated by the MELD system, for example, due to pruritus, advanced encephalopathy, ascites and hyponatremia, or recurrent bacterial cholangitis in other countries.[21,22] In doing so, we achieved graft and patient survival rates similar to those after transplantation of higher ranked candidates transplanted with better organs. McCormack et al[19] have previously demonstrated similar outcomes in a smaller cohort in Argentina. Also, the Essen group in Germany successfully transplanted 10 livers "that nobody wanted," allocated separately and excluded from the MELD-based allocation system.[23] Other reports from Europe have indicated that busy centers are less selective in their decisions on whether or not to accept a liver compared with low-volume centers.[24] Although surgeons at our institution accept most offers, we carefully select liver recipients particularly for extended DCDs and other marginal DBD grafts. In this context, at the listing meeting our multiprofessional team discuss potential graft types for each transplant candidate. For example, liver recipients listed for retransplantation or with known portal vein thrombosis or an otherwise expected prolonged hepatectomy time are listed to exclusively receive DBD livers. We believe that such strategy helps to recognize the sometimes primarily invisible risk and to guide our team through the process of donor liver acceptance for a specific recipient. To further evaluate the imperceptible risk of a graft during cold storage, new preservation techniques are currently under evaluation to assess organ quality, which may impact on the selection of an appropriate recipient in the future.[25-28]

What is important to understand is that many donors may have not entered to actual donation process, because professionals deem certain donors to be of too low quality. In contrast, our transplant team consider that evaluation and procurement of any graft with the intent of saving a usable liver carries a high chance of retrieving a beneficial graft from an ethical point of view. Our study has several limitations. For example, the number of livers which were declined by our center during the same period were not recorded, and it may be possible that the liver grafts refused by or centers for various reasons by on-call surgeons have been successfully transplanted elsewhere. The specific cause of graft refusal of a small percentage of donors could not be obtained from the EOS database, due to the lack of such information. In addition, liver graft biopsies are not routinely available for analysis before transplantation.

In conclusion, we have underlined that utilization of previously declined livers can achieve excellent outcomes. These results perhaps answer a critique whether transplantation of declined liver grafts is associated with greater risk for life or if the long-term benefits are acceptable. Progressive and active centers may therefore want to discuss internally and set limits for donor parameters to define the acceptable criteria to reduce dropout rates from the waiting list. Regular outcome analysis and internal review of the transplant activity are of utmost importance to guarantee a certain standard of care in this field of transplantation.

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