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Original article

Risk Factors for No Valid Liver Graft. Multivariate Study Based on the Variables Included in the Donation Protocol of the National Trasplant Organisation☆

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ABSTRACT

Introduction: Among the strategies designed to optimize the number of existing liver grafts for transplantation, the implementation of the graft assessment process is one of the least explored. The main objective is to identify the risk factors presented by liver donors for "NO validity". Secondly, we analyzed the coincidence between the surgeon's assessment and that of the anatomo-pathologist in the invalid donors.

Material and method: Retrospective study conducted from a prospective database that analyzes 190 liver donors, 95 valid and 95 NOT valid. The variables of each of them corresponding to the donation protocol of the National Transplant Organization are studied. Through a multivariate study we determine the independent risk factors of NO validity. We checked the causes of NO validity argued with the histopathological findings of these grafts.

Results: The independent risk factors of non-validity in the multivariate study ($p < 0.05$) were: Dyslipidemia, personal medical history other than cardiovascular and abdominal surgical risk factors, GGT, BrT, and the result of previous liver ultrasound. The 3 most frequent causes of NO validity were: steatosis, fibrosis and macroscopic appearance of the organ. 78% of the biopsies confirmed the NO validity of the graft (In 57.9% of the cases the histological findings coincided with those described by the Surgeon). The 22.1% of the biopsies hadńt pathological findings.

Conclusions: The determination of the risk factors of NO validity will contribute to the design of future assessment scores that are useful tools in the process of liver graft assessment.

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Factores de riesgo para injertos hepáticos no válidos. Estudio multivariante a partir de las variables recogidas en el protocolo de donación de la Organización Nacional de Trasplantes

RESUMEN

Introducción: Entre las estrategias diseñadas para optimizar el numero de injertos hepáticos existentes para trasplante, la implementación del proceso de valoración de injertos constituye una de las menos exploradas. El objetivo principal es identificar los factores de riesgo que presentan los donantes hepáticos para la ''NO validez''. Secundariamente analizamos la coincidencia entre valoración del cirujano y la del anátomo-patólogo en los donantes NO válidos.

Material y método: Estudio retrospectivo realizado a partir de una base de datos prospectiva que analiza 190 donantes hepáticos, 95 válidos y 95 NO válidos. Se estudian las variables de cada uno de ellos correspondientes al protocolo de donación de la Organización Nacional de Trasplantes. Mediante estudio multivariante determinamos los factores de riesgo independientes de NO validez. Cotejamos las causas de NO validez argumentadas con los hallazgos histopatológico de dichos injertos.

Resultados: Los factores de riesgo independientes de NO validez en el estudio multivariante ($p < 0,05$) fueron: Dislipemia, antecedentes personales médicos distintos a factores de riesgo cardiovascular y quirúrgicos abdominales, GGT, BrT, y el resultado de la ecografía hepática previa. Las dos causas más frecuentes de NO validez fueron: esteatosis y fibrosis. El 78% de las biopsias confirmaron la NO validez del injerto(El 57,9% del total coincidían los hallazgos histológicos con los descritos por el Cirujano). El 22% restante de las biopsias no presentaban hallazgos patologicos.

Conclusiones: La determinación de los factores de riesgo de NO validez contribuirá al diseño de futuros escores de valoración que constituyan herramientas útiles en el proceso de valoración de injertos hepáticos.

Introduction

Expanded criteria donors[1] (ECD) have a higher probability of transplant failure or primary graft dysfunction, and transplantees have a lower survival rate when grafted with these organs compared to those from ideal donors.[2–4] However, ECD donors represent a significant proportion of the donors offered. In these cases, in situ evaluation of the liver graft can be a very complex process. This assessment has a subjective component based on the experience of the liver transplant (LT) surgeon. When in doubt, cold liver biopsy is indicated. Unfortunately, this procedure is not routinely available during donation at every centre, for various reasons. According to the Spanish National Transplant Organization (ONT in its Spanish acronym), the rate of implanted liver grafts from donation after brain death (BD) has dropped from 70% to 62% over the last 9 years,[5] which has resulted in a 3% increase in waiting-list mortality and a drop-out rate of 9%.[6]

Given that the decision about graft validity/invalidity is complex and is based on subjective criteria such as appearance and palpation, we set out to identify the risk factors for BD liver donor invalidation using the variables collected in the ONT donation protocol. Secondly, we analysed the pathological anatomy and surgeon's success rate during the in situ assessment process.

Materials and Methods

This was a retrospective, single-centre cohort study conducted using a prospective database. Between 2012 and 2016 we analysed 190 liver graft cases from BD donors (95 invalidated cases, consecutively followed by valid cases). All the donors who met the ONT criteria and were evaluated in situ by the same LT surgeons, who had more than 5 years' experience in liver donation case management at a national high-volume centre.

We studied all the variables included in the ONT donation protocol, an official document that the coordinators must comply with to generate the offer and which the surgical team uses to assess the suitability of the graft.[7] We understood a valid graft as one that was assessed in situ following the criteria recorded in the 'Guide to Quality and Safety of Transplantation Organs' document.[8] If there was any doubt, we performed a liver biopsy. Grafts that did not pass the in situ evaluation were considered 'invalidated'. The causes of invalidity (steatosis, cholestasis, fibrosis, cirrhosis, atheromatosis, ischemia, and other considerations related to the macroscopic appearance) are included in the ONT donation protocol.[9] The item 'macroscopic appearance' is subjective and did not correspond to any of the other six causes of invalidity. We considered the ultrasound to be pathological if

it presented findings compatible with hepatic steatosis, cirrhosis, fibrosis, or any other morphological abnormality.[10]

We divided our series into two groups:

- Invalidated liver grafts (n = 95): Assessed in situ and not considered valid. We compiled the causes of invalidation given by the LT surgeon. We only included deferred cases with a liver biopsy to confirm the non-validity because, for different reasons, the donor hospital did not have a pathologist. They were examined by the Pathological Anatomy Service at the Virgen del Rocío Teaching Hospital (Seville) by a pathologist expert in liver histopathology.
- Valid liver grafts (n = 95): consecutive valid grafts were included to the 95 invalidated grafts. All underwent post-reperfusion biopsy.

We compared the variables of the donors of both groups and performed a univariate study to examine whether there were statistically significant differences between them. Variables that were statistically significant ($P < .05$) were included in the multivariate study to determine the independent factors that predicted inalidity. We assessed age (years), sex (male/female), body mass index (Kg/m^2), arterial hypertension (yes/no), diabetes mellitus (yes/no), dyslipidemia (DLP; hypercholesterolemia and/or hypertriglyceridemia; yes/no), personal medical history other than cardiovascular risk factors (donor medical history other than hypertension, diabetes, or DLP), personal surgical history (previous abdominal surgeries), ultrasound ('Not performed' if no report was available, 'Pathological' if the findings deviated from normal, and 'Normal' if there was no evidence of any pathological findings), anti-hepatitis B virus antibodies (yes/no), hepatitis C virus antibodies (yes/no), aspartate aminotransferase (IU/mL), alanine aminotransferase (IU/mL), gamma-glutamyl transpeptidase (IU/mL), total bilirubin (TBr; mg/nL), sodium (mg/mL), use of amines (yes/no), and amines dose (mcg/Kg/min). In relation to steatosis, it should be noted that in our centre and during the study period considered in this article, we considered grafts with steatosis exceeding 30% as invalidated.

Subsequently, we analysed the group of invalidated grafts. We listed the macroscopic causes of invalidity (LT surgeon's judgment) and the biopsy results (anatomical pathologist's diagnosis). We also estimated the success rate of the LT Surgeon (number of LT surgeon assessments that coincided with the anatomical pathologist's diagnosis/total number of biopsies). In addition, we performed univariate analysis to study if there were differences between the invalidated graft subgroups with and without a pathological biopsy result. Lastly, we quantified the success rate related to the specific macroscopic cause of the invalidity (number of specific LT surgeon assessments that coincided with the anatomical pathologist's diagnosis/total number of anatomical pathology diagnoses).

Our statistical analyses were carried out with SPSS v22.0 software. The normality of the sample distribution was determined using the KolmogorovSmirnov test, which is why the continuous variables are reflected as the mean ± s-standard deviation, and we compared them using Student t-tests. We expressed the qualitative variables in absolute figures (n) with the percentage in parentheses (%) and compared them using Chi-squared tests. The multivariate study was carried out using logistic regression. Statistical significance was established as a P-value $< .05$ and the risk was estimated using B and EXP (B) risk coefficients.

Results

Characteristics of Valid Versus Invalidated Donors (Table 1)

There were no cases of primary graft failure among the 95 livers reported as valid once implanted. We found significant differences between the valid and invalidated grafts in terms of DLP: 18 (19%) vs. 40 (42%) respectively, $P = .001$; personal medical history other than cardiovascular risk factors (PMHCVRF): 36 (38%) vs. 65 (68%) respectively, $P = .001$; personal medical history of abdominal surgery (PMH-QXAb): 16 (17%) vs. 34 (36%) respectively, $P = .003$; GGT: 48 ± 59 vs. 77 ± 69 IU/mL respectively, $P = .003$; BrT: 0.55 ± 0.38 vs. 0.85 ± 0.53 mg/mL respectively, $P = .001$; pathological ultrasound in 8 (8%) valid donors vs. 29 (30%) invalidated donors, $P = .001$. Amines were required for the maintenance of 60 valid donors (63%) vs. 76 cases of invalidated donors (80%), $P = .04$ with a mean dose of 0.13 ± 0.18 vs. 0.21 ± 0.24 mcg/Kg/min respectively, $P = .04$. There were no statistically significant differences in the other variables.

The multivariate study confirmed the following factors as independent factors for invalidity: TBr (odds ratio [OR]: 4.963; 95% CI [1.853, 13.289]; $p = 0.04$), DLP (OR: 4.767; 95% CI [1.873, 12.134]; $p = 0.01$), pathological liver ultrasound (OR: 4.727; 95% CI [1.714, 13.035]; $p = 0.03$), PMH-QxAb (OR: 3.989; 95% CI [1.591, 10.001]; $p = 0.02$); PMHCVRF (OR: 2.734; 95% CI [1.227, 6.092]; $p = 0.01$); and GGT (OR: 1.01; 95% CI [1.004, 1.017]; $p = 0.03$).

Univariate Analysis of the Invalidated Graft Group (Pathological vs. Non-pathological Biopsy Results) (Table 2)

All 95 (100%) invalidated grafts had a biopsy with a deferred report. The LT surgeon success rate was 78% (in 74 of the 95 confirmed invalidated cases). A total of 21 (22%) grafts rated as invalidated corresponded to a biopsy report without pathological findings. There were no statistically significant differences between any of the values compared between groups.

List of Macroscopic Causes of Invalidity According to the LT Surgeon and the Anatomical Pathology Diagnosis (Table 3)

The 3 most frequent causes of invalidity cited by the LT surgeon were steatosis, n = 29 (30%); fibrosis, n = 8 (8%), and the macroscopic appearance of the organ, n = 4 (4%). From the anatomical pathology viewpoint, the most frequent microscopic diagnosis of invalidity was steatosis, n = 37 (39%); followed by fibrosis, n = 15 (16%), and cirrhosis, n = 8 (8%). The cases with the highest diagnosis success rate were fibrosis, cirrhosis, and ischemia (100% of the cases). Steatosis coincided with the pathologist's diagnosis in 86% of the cases. The most frequent causes of LT surgeon confusion were the macroscopic appearance and atheromatosis of the graft.

Table 1 – Univariate and Multivariate Study of Risk Factors for Liver Graft Invalidity.

Variable	Valid Graft	Invalidated Graft	Univariate Study		Multivariate Study		
N	95	95	P-value	Odds Ratio (CI)	B EXP (B)	P-value	Odds Ratio (CI)
Age (years)	58 ± 16	63 ± 13	.060	0.565 (0.358 – 1.059)	-0.03 0.96	.070	0.724 (0.599 – 1.151)
Male	52 (54.7%)	47 (49.5%)	.200	0.792 (0.423 – 1.423)	1.05 2.98	.300	0.638 (0.472 – 1.382)
BMI (Kg/m^2)	26.87 ± 5.04	28.35 ± 4.57	.090	0.865 (0.483 – 1.573)	-0.34 0.7	.100	0.999 (0.626 – 1.083)
PAH	52 (54.7%)	53 (55.8%)	.500				
DM	17 (17.9%)	27 (28.4%)	.060	0.793 (0.392 – 1.382)	2.68 3.65	.090	
DLP	**18** (18.9%)	**40** (42.1%)	**.001**	**1.655 (1.269 – 2.159)**	**2.72 9.56**	**.010**	**1.989 (1.467 - 4.876)**
PMH – CVRF	**36** (37.9%)	**65** (68.4%)	**.001**	**1.909 (1.379 – 2.644)**	**3.36 7.32**	**.010**	**1.875 (1.639 - 3.826)**
PMH-QX-Ab	**16** (16.8%)	**34** (35.8%)	**.003**	**1.561 (1.194 – 2.040)**	**1.98 6.43**	**.020**	**1.743 (1.536 - 3.376)**
AST (IU/mL)	44 ± 50	49 ± 54	.400				
ALT (IU/mL)	57 ± 198	44 ± 57	.600				
GGT (IU/mL)	**48 ± 59**	**77 ± 69**	**.003**	**1.345 (1.234 – 2.043)**	**3.12 15.77**	**.030**	**1.628 (1.475 - 9.754)**
TBr (mg/mL)	**0. 55 ± 0.38**	**0.85 ± 0.53**	**.001**	**1.254 (1.136 – 1.908)**	**3.39 17.34**	**.040**	**1.589 (1.242 – 10.856)**
Na (mg/mL)	145 ± 8	146 ± 8	.200	0.678 (0.592 – 1.367)	0.82 1.08	.400	
Amines	**60 (63.2 %)**	**76** (80%)	**.040**	**1.558 (1.074 – 2.350)**	-1.01 0.67	.060	1.284 (0.832 – 1.457)
Amines dose (mcg/Kg/min)	**0.13 ± 0.18**	**0.21 ± 0.24**	**.040**	**1.689 (1. 145 – 2.679)**	-1.45 0.28	.080	1.302 (0.729 – 1.532)
Ultrasound	**81** (85.3%)	**55** (57.9%)	**.001**	**1.986 (1.178 – 2.457)**	**4.75 10.01**	**.030**	**1.675 (1.436- 8.546)**
Normal	**8** (8.4%)	**29**(30.5%)					
Pathological	**6** (6.3%)	**11** (11.6%)	**.001**	**1.986 (1.178 – 2.457)**	**4.75 10.01**	**.030**	**1.675 (1.436- 8.546)**
Not carried out							
HBVcAb	7 (7.4%)	11 (11.7%)	.300				
HCVAb	1 (1.1%)	2 (2.1%)	.600				

BMI: body mass index; PAH: pulmonary arterial hypertension; DM: diabetes mellitus; DLP: dyslipidemia; PMH–CVRF: past medical history other than cardiovascular risk factors; PMH-QX-Ab: personal history of abdominal surgery; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; TBr: total bilirubin; Na: sodium; HBVcAb: hepatitis C virus core antibody; HCVAb: hepatitis C virus antibody.

Table 2 – Comparison Between Subgroups of Invalidated Grafts With and Without a Pathological Biopsy Result (Univariate Study).

Variable	Pathological	Non-pathological	P-value
n	74 (78%)	21 (22%)	
Age (years)	62 ± 14	64 ± 12	.10
Males	35 (47%)	12 (57%)	.20
BMI (Kg/m^2)	28.46 ± 4.79	27.97 ± 3.78	.10
PAH	38 (51%)	15 (71%)	.09
DM	22 (30%)	5 (24%)	.08
DLP	33 (44%)	7 (33%)	.20
PMH – CVRF	26 (35%)	8 (40%)	.30
PMH–QX-Ab	26 (35.1%)	8 (38%)	.30
AST (IU/mL)	51 ± 47	44 ± 73	.20
ALT (IU/mL)	45 ± 48	42 ± 82	.08
GGT (IU/mL)	79 ± 71	71 ± 67	.20
TBr (mg/mL)	0.86 ± 0.53	0.82 ± 0.53	.50
Na (mg/mL)	146 ± 8	148 ± 10	.60
Amines	59 (80%)	17 (81%)	.50
Amines dose (mcg/Kg/min)	0.22 ± 0.25	0.17 ± 0.22	.09
Pathological ultra.	26 (35%)	3 (14%)	.07
HBVcAb	9 (12%)	4 (18%)	.20
HCVAb	2 (3%)	0 (0%)	.10

BMI: body mass index; PAH: pulmonary arterial hypertension; DM: diabetes mellitus; DLP: dyslipidemia; PMH-CVRF: past medical history other than cardiovascular risk factors; PMH-QX-Ab: personal history of abdominal surgery; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; TBr: total bilirubin; Na: sodium; HBVcAb: hepatitis C virus core antibody; HCVAb: hepatitis C virus antibody.

Discussion

One of the main difficulties faced by LT surgeons during the donation process is the in situ evaluation of liver grafts. This type of assessment is subjective and is based on accumulated personal experience.[11] Studies have shown that the risk of primary graft failure is systematically underestimated, especially for poorer quality organs. However, sometimes the decisions taken by surgeons about high-risk organs is based on more recent experiences than the scientific evidence available

Table 3 – List of Macroscopic Causes of Graft Invalidation Cited by the Liver Transplant Surgeon and by Anatomical Pathology Diagnosis.

Cause of Invalidity Cited by Surgeon	Non-pathological Biopsy	Pathological Biopsy	Total Cases (%)	Success Rate
n	**21**	**74**	**95 (100)**	**78**
Steatosis	4	25	29 (30)	86
Fibrosis	0	8	8 (8)	100
Macroscopic appearance	2	2	4 (4)	50
Others	1	2	3 (4)	67
Cirrhosis	0	3	3 (4)	100
Atheromatosis	2	0	2 (2)	0
Ischemia	0	1	1 (1)	100
Macroscopic appearance + atheromatosis	4	2	6 (6)	33
Steatosis + atheromatosis	1	5	6 (6)	83
Steatosis + ischemia	0	6	6 (6)	100
Steatosis + macroscopic appearance	1	4	5 (5)	80
Steatosis + cirrhosis	0	4	4 (4)	100
Steatosis + fibrosis	0	2	2 (2)	100
Macroscopic appearance + cirrhosis	0	2	2 (2)	100
Atheromatosis + ischemia	0	2	2 (2)	100
Macroscopic appearance + ischemia	0	1	1 (1)	100
Macroscopic appearance + fibrosis	0	1	1 (1)	100
Macroscopic appearance + atheromatosis + steatosis	1	2	3 (4)	67
Macroscopic appearance + fibrosis + others	2	1	3 (4)	33
Macroscopic appearance + atheromatosis + fibrosis	1	0	1 (1)	0
Macroscopic appearance + fibrosis + steatosis	1	0	1 (1)	0
Macroscopic appearance + atheromatosis + cirrhosis	0	1	1 (1)	100
Fibrosis + macroscopic appearance + atheromatosis + surgical problem	1	0	1 (1)	0

Success rate: (number of causes of invalidation with a pathological biopsy × 100) / total number of cases, expressed as a percentage (%).

in the academic literature.[12] In an attempt to assist the LT surgeon in on-site assessments, risk indexes for primary failure have been developed[13,14] that assess transplantee survival based on data from the donor and the recipient.[15–18]

However, in this current work our objective was to identify risk factors for invalidity when preparing the ONT offer using the variables included in the donation protocol. The main limitation of our study was that we were unable to compare the pathological anatomies between all the cases because we did not have biopsy data from the valid grafts at the beginning of the donation (these biopsies were carried out after the implantation reperfusion). From a methodological point of view, it would have been preferable to have calculated the sample size and prospectively compare the ONT donation protocol variables with biopsy data taken at the beginning of the extraction in both groups.

Another limiting factor was that we considered grafts with more than 30% steatosis as invalidated. During the data collection phase of this study, our independent prioritisation system did not allow donor–recipient matching, and so grafts were offered to recipients with high Model for End-stage Liver Disease (MELD) scores. Based on the scientific evidence, the use of grafts with moderate steatosis (31%–60%) is recommended in recipients with low MELD scores.[19] In June 2019 our prioritisation system changed and we started accepting grafts with moderate steatosis and allowed recipients to be selected according to the donor characteristics. Another limitation was the use of the 'macroscopic appearance' option included in the ONT donation protocol as a reason for graft invalidation.[9] In our opinion, this is a confounding factor because variables such as steatosis, cirrhosis, etc. are included as part of this invalidity assessment call, thus making it an ambiguous argument. In a national series study,[22] the cause of invalidity was not related to the anatomopathological diagnosis. However, in our work, the lowest correct diagnosis rate was related to this finding alone, regardless of all the other factors (Table 3).

Literature related to supporting decision-making among LT surgeons is scarce, and even fewer studies have tried to determine the risk factors for non-validity.[20,21] In 2017, the ONT started using pathological ultrasound results and a history of alcohol consumption as independent risk factors for invalidity in its reports.[22] However, the data we obtained in this current study only supports the use of the former (pathological ultrasound) and not the latter (a history of alcohol consumption). Here we provide evidence for DPL, PMH-CVRF, PMH-QXAB, GGT (normal values: 10–50 IU/L), and TBr (normal values: 0.1–1.20 mg/dL) as independent variables for liver graft invalidity. Unlike the ONT report[22] or the series published by Czerwiński et al.,[20] donor age was not a statistically significant factor in this current work ($p = 0.06$). Donor age has always been a controversial issue. While it is considered a risk factor for primary graft failure and graft survival that has been validated by its inclusion in different prognostic scales,[13,15–18] paradoxically, the mean age of liver donors has increased in recent years without a concurrent worsening in patient survival rates.[23,24] Indeed, according to the ONT, the average age of liver donors increased from 50 years in 2001 to 61 years in 2017.[25]

Considering each factor separately, the macroscopic cause of graft non-validity most often given by LT surgeons was steatosis (30%), which coincides with the ONT report (27%)[22]

and the series by Shamsaeefar et al. (62.5%).[21] If we sum all the cases in which 'steatosis' appeared (Table 2), either as an isolated cause or in association with other causes, we registered 55 (58%) cases. This data is worrying, because this is an increasingly common pathology in developed countries that affects 20%–30% of the general population.[26] The use of grafts with moderate or severe steatosis is associated with a higher incidence of primary failure and an upward trend in mortality at one month.[27,28] In fact, some studies have shown that this is an independent risk factor for graft survival, together with the Donor Risk Index factors.[29] In our series, steatosis, together with fibrosis, cirrhosis, or poor perfusion, were the invalidation causes most often identified by LT surgeons (Table 3). Perhaps in the short term, steatosis will no longer be a determining factor for invalidation, thanks to ex situ perfusion machines.[30,31]

The second objective of this present study was to assess rate at which the LT surgeon's judgment coincided with that of the anatomopathologist for invalidated donors. This occurred in 74 of the 95 cases studied (78% success rate). Czerwiński et al.[20] reported a 65% success rate, which is lower than the rate we obtained here. Ideally, to optimise this success rate, a pathological study should be carried out in situ. Interestingly, in our case, the impact of systematically adding the anatomical pathology study results to the decision about whether to accept grafts could have increased the number of transplanted grafts by 22%. Even though the use of liver biopsy at the beginning of the donation process saves costs and improves the organ allocation efficiency,[32] this service is not available at every hospital accredited by the ONT as a donor centre. Unfortunately, atheromatosis is a finding that does not correspond to histopathological findings that contraindicate graft viability. In fact, together with the 'macroscopic appearance' atheromatosis was the most frequent cause of confusion for our LT surgeons. Nonetheless, it remains unclear if atheromatosis is related to the independent variables of non-validity from our multivariate study.

Based on the independent variables we identified for liver graft invalidity, we are developing an algorithm using artificial intelligence techniques that will allow us to predict the risk of invalidity similar to existing practices in the case of kidney transplants.[33] In our opinion, this tool could help improve decision-making about liver graft acceptance.

Conclusions

We identified six independent factors for liver graft invalidation that are currently collected as part of the ONT donation protocol (TBr, DLP, pathological liver ultrasound, PMH-CVRF, PMH-QxAb, and GGT). The success rate of the LT Surgeon, based on their subjective assessment, was 78%. We must base our decision to invalidate a graft based on objective findings (steatosis, cirrhosis, fibrosis, or poor perfusion) and try to avoid judgements based on the 'macroscopic appearance' of the liver. The systematic availability of intraoperative biopsy samples during donation is essential to optimise the success rate of these decisions.

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Conflict of Interests

The authors of this article declare that they have no conflicts of interest.

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