Donor Hepatectomy and Implantation Time Are Associated With Early Complications After Liver Transplantation: A Single-center Retrospective Study

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NG, SF, and NM participated in data acquisition and analysis.

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ABBREVIATIONS:

BMI, body mass index;

DBD, donation after brain death;

DCD, donation after circulatory death;

EAD, early allograft dysfunction;

HTK, histidine-tryptophan-ketoglutarate preservation solution;

NAS, nonanastomotic biliary strictures.

ABSTRACT:

Background. Donor hepatectomy and liver implantation time reduce long-term graft and patient survival after liver transplantation. It is not known whether these surgical times influence early outcomes after liver transplantation. **Methods.** This single-center study evaluated the effect of donor hepatectomy and implantation time on the risk of nonanastomotic biliary strictures occurring within 1 year and of early allograft dysfunction after deceased-donor solitary liver transplantation, adjusting for other donor, recipient, and surgical factors. **Results.** Of 917 transplants performed between 1/2000 and 12/2016, 106 (11.56%) developed nonanastomotic biliary strictures and 247 (27%) developed early allograft dysfunction. Donor hepatectomy time (median 35 min, IQR: 26-46) was an independent risk factor of nonanastomotic biliary strictures (adjusted hazard ratio (HR): 1.19, 95% CI: 1.04-1.35, $p=0.01$). Implantation time (median 80 min, IQR: 69-95) was independently associated with early allograft dysfunction (adjusted odds ratio (OR): 1.15, 95% CI: 1.07-1.23, $p<0.0001$). The risk of early allograft dysfunction was increased by anastomosis time of both portal vein (adjusted OR: 1.26, 95% CI: 1.12-14.42, $p=0.0001$) and hepatic artery (adjusted OR: 1.13, 95% CI: 1.04-1.22, $p=0.005$). The magnitude of these effects was similar in donation after circulatory death liver grafts. **Conclusions.** Donor hepatectomy and implantation time negatively affect short-term outcomes.

Introduction

Recent Eurotransplant Registry analyses revealed that both donor hepatectomy and implantation time reduce long-term patient, graft, and death-censored graft survival.^{1,2} These findings were in part confirmed in 2 retrospective analyses outside the Eurotransplant region for donor hepatectomy and implantation time, respectively.^{3,4} Despite the fact that early complications such as nonanastomotic biliary strictures (NAS)⁵ and early allograft dysfunction (EAD)⁶ are well-known to reduce long-term graft and patient survival, it is not known whether donor hepatectomy and implantation time also impact on these short-term outcomes.

Indeed, as far as we are aware, no previous study has investigated the impact of both donor hepatectomy and implantation time on the risk of NAS. In contrast, 2 single-center retrospective analyses investigated whether donor hepatectomy and implantation time increase the incidence of EAD, but their results are inconclusive. Adelman et al. observed that prolonged donor hepatectomy time increased EAD, but no adjustment was done for confounding factors.⁷ Buchholz et al. reported that prolonged portal vein anastomosis time (defined cutoff of >44 min), increased the probability of EAD.⁴ As portal vein anastomosis time was considered as a discrete variable (either above or below 44 min), it is unclear whether this – or any other – is a threshold value of implantation time below which the likelihood of EAD could be reduced. Additionally, the impact of hepatic artery anastomosis time on the probability to develop EAD was not investigated in the study by Buchholz et al. and remains unknown.

We therefore aimed to study whether donor hepatectomy and liver implantation time independently increase the risk of NAS and EAD after adjusting for the effect of possible confounders.

Materials and Methods

Study design

All adult recipients of a full-size, solitary, deceased-donor liver transplantation at University Hospitals Leuven, Belgium, between January 1st, 2000 and December 31st, 2016 were included (last follow-up December 31st, 2017). Clinical data were obtained from a prospective database and analyzed retrospectively. Our center operates within Eurotransplant, a nonprofit organization that manages cross-border sharing of organs and patient-oriented allocation of grafts.⁸ This study therefore includes liver grafts procured by our own team as well as grafts procured outside our region (34 procurement centers in total). Following the classification of the Eurotransplant Donor Risk Index,⁹ procurement centers were grouped as local (University Hospitals Leuven procurement team), regional (6 other procurement teams within Belgium), and extraregional (26 procurement teams within Eurotransplant but outside Belgium).

Donor hepatectomy time was defined as the time between the start of cold flush in the donor and the moment of graft immersion in ice-cold preservation solution in the donor hospital. Implantation time was defined as the time between the liver being taken out of the ice-cold preservation solution and restoration of total blood flow (both portal vein and hepatic artery) in the recipient's body. Portal vein anastomosis time was defined as the time between the liver being taken out of ice until release of the vascular clamp on the portal vein, and hepatic artery anastomosis time was defined as the time between the release of the clamp on the portal vein and the release of the clamp on the hepatic artery. Cold ischemia time was defined as the time between the start of cold flush in the donor and placement of the graft in the recipient's abdomen. For Donation after Circulatory Death (DCD), total donor warm ischemia time was defined as the time between the withdrawal of therapy and the start of cold flush in situ. Agonal warm ischemia time was defined as the time between decrease of mean arterial blood pressure to below 60 mmHg until the start of cold flush.

EAD was defined according to the definition by Olthoff et al.⁶ NAS was defined as strictures of the intrahepatic biliary branches, provoking either clinical symptoms or biochemical abnormalities in the absence of hepatic artery thrombosis, occurring within 1-year posttransplant. Patients were screened either at the time of suspicion or at 1-year after transplantation, with magnetic or endoscopic cholangiography. Only clinically relevant and radiology-proven strictures were considered as event.

The study was approved by the local ethical committee (s61304) and all patients consented to the use of their data for study purposes.

Organ procurement and transplantation

Locally procured livers were extracted en bloc with the duodenum, pancreas, and spleen, after flushing and cooling through the abdominal aorta.^{10,11} Livers were then separated from the spleno-pancreatic block at the back-table, where they were immersed in ice-cold preservation solution.¹¹ Information on type of flush (aortic or dual aortic and portal flush) and on technique of liver extraction (hepatectomy alone or en bloc) used by other procurement centers was not available. Grafts were flushed and cold-stored either using University of Wisconsin solution, Histidine-Tryptophan-Ketoglutarate (HTK) solution or Institute George Lopez 1 solution.

All liver transplantations were performed by senior staff members. All recipients underwent replacement of the inferior vena cava with veno-venous bypass, except for caval-sparing piggy-back anastomosis in 1 recipient. The portal vein was reconstructed in a standard end-to-end fashion. The hepatic artery anastomosis was performed end-to-end and multiple anastomoses were performed in case of abnormalities of donor and/or recipient hepatic artery anatomy. All surgeons used sequential portal and arterial reperfusion, except for 1 surgeon who used simultaneous reperfusion. A standard triple immunosuppression regimen was used, including calcineurin inhibitor, steroids, and antimetabolite.

Statistical analyses

Continuous variables are expressed as median (interquartile range) and categorical variables as numbers (percentage). The effect of donor type, donation of thoracic organs, donor obesity, and procurement centers on the duration of donor hepatectomy time, and the effect of recipient obesity, pretransplant portal vein thrombosis, graft hepatic artery anatomy, multiple arterial anastomoses, and transplant surgeon on the duration of implantation time were investigated in univariate analysis with either the Mann-Whitney U test or the Kruskal-Wallis test.

In order to separately evaluate the relationships of each surgical time with outcomes of interest, a 2-step approach was used. In a first step a prediction model was constructed using a backwards stepwise procedure on a prespecified list of covariates explored in univariate analysis (donor and recipient demographics, and transplant characteristics). Multivariable Cox regression was used to identify predictors of NAS, and multivariable logistic regression to identify risk factors for EAD. In a second step, these models were extended adding either donor hepatectomy time, implantation time, or portal vein anastomosis and hepatic artery anastomosis time. Additionally, the prediction models were extended with interaction terms to assess if the effect of these surgical times on the risk of NAS and EAD was stronger in DCD than in Donation after Brain Death (DBD) grafts. The reported odds and hazard ratios refer to a 10-minute variation of the surgical times of interest.

Given the longevity of the study period, the effect of the transplant era on the risk of NAS and EAD was explored by an additional extension of the prediction models identified in the first step with the linear function of the year of transplantation.

To handle the presence of missing values, a multiple imputation approach was performed but missing values of surgical times of interest were not imputed. Additional details on statistical methodology can be found in SDC Materials and Methods, SDC, <http://links.lww.com/TP/B950>. A p-value of <0.05 on a 2-sided test was considered significant. Statistical analyses were performed using SAS (v9.4, SAS Institute, nv/sa, Tervuren, Belgium) or SPSS (v20, SPSS Inc. Chicago, IL, USA).

Results

Study population characteristics

Nine-hundred seventeen liver transplants meeting the inclusion criteria were identified. Donor, recipient, and postoperative characteristics of the study population are summarized in Table 1. DCD donors accounted for 124 (13.50%) transplants, of which 113 (12.32%) belonged to category-III, and 11 (1.20%) to category-V.^{12,13} Median warm ischemia time in DCD was 19 (15-24) minutes; median agonal warm ischemia was 14 (10-18) minutes. Total and agonal warm ischemia time in transplants developing early complications equaled that of uncomplicated transplants (Table S1, SDC, <http://links.lww.com/TP/B950>). Median cold ischemia in the overall population was 7.8 (6.1-9.5) hours [5.29 (4.52-6.46) hours in DCD, 8.18 (6.66-9.67) hours in DBD; $p<0.0001$]. Livers developing EAD/NAS were more frequently preserved with HTK ($p<0.05$; Table S2, SDC, <http://links.lww.com/TP/B950>). Mean arterial blood pressure measured at 5-minute after liver reperfusion was similar in transplants developing complications or not (Table S3, SDC, <http://links.lww.com/TP/B950>).

Median donor hepatectomy time was 35 (26-46) minutes (Figure 1A). The duration of hepatectomy time differed between procurement centers [local: 31 (24-40) minutes, regional: 36 (27-52) minutes, extraregional: 43 (33-57) minutes; $p<0.0001$] and was longer when thoracic organs were donated [nonthoracic organ donation: 30 (24-38) minutes, thoracic organ donation: 40 (30-50) minutes; $p<0.0001$]. Donor hepatectomy time was not influenced by donor type [DBD: 35 (26-47) minutes, DCD: 34 (28-41) minutes; $p=0.23$] or donor obesity [Body Mass Index (BMI) <30 : 34 (26-46) minutes, BMI ≥ 30 : 35 (26-50) minutes; $p=0.37$] (Figure S1, SDC, <http://links.lww.com/TP/B950>).

Median implantation time was 80 (69-95) minutes, portal vein anastomosis time was 45 (39-56) minutes, and hepatic artery anastomosis time was 33 (22-44) minutes (Figure 1B-D). Implantation time was longer in obese recipients [BMI <30 : 79 (68-92) minutes, BMI ≥ 30 : 85 (72-103) minutes; $p=0.0002$] and in transplants requiring multiple arterial anastomoses [single

anastomosis: 79 (68-92) minutes, multiple anastomoses with reconstruction at the back-table: 83 (78-100) minutes, multiple anastomoses during implantation: 96 (77-112) minutes; $p < 0.0001$]. Additionally, the duration of implantation time differed among transplant surgeons ($p < 0.0001$). Implantation time was not influenced by the type of reperfusion [sequential: 81 (69-95) minutes, simultaneous: 80 (71-92) minutes; $p = 0.48$], multiple donor hepatic arteries [single artery: 81 (70-93) minutes, multiple arteries: 79 (69-96) minutes; $p = 0.57$] or pretransplant portal vein thrombosis [patent portal vein: 80 (69-95) minutes, portal vein thrombosis: 81 (74-95) minutes; $p = 0.22$] (Figure S2, SDC, <http://links.lww.com/TP/B950>).

Donor hepatectomy time increases the risk of NAS

NAS occurred in 106 (11.56%) liver transplants. Risk factors for NAS identified in multivariable analysis (first step) were acute liver failure as indication for transplantation, retransplantation, donor age, donor type, nonlocally procured grafts, and cold ischemia time (Table 2). After extension of this prediction model, the era of the transplants had no effect on the risk of NAS (adjusted hazard ratio (HR): 0.99, 95% CI: 0.94-1.05, $p = 0.80$). Table 3 summarizes results from the second step. Donor hepatectomy time had a linear effect on the risk of NAS, increasing this risk by 19% for every 10-minute increase (adjusted HR: 1.19, 95% CI: 1.04-1.35, $p = 0.01$; Table 3; SDC Table S4, SDC, <http://links.lww.com/TP/B950>; Figure 1A). In contrast, the risk of NAS was not influenced by implantation time (adjusted HR: 1.03, 95% CI: 0.96-1.11, $p = 0.42$; Table 3; SDC Table S5, SDC, <http://links.lww.com/TP/B950>), portal vein anastomosis (adjusted HR: 0.98, 95% CI: 0.84-1.14, $p = 0.77$) or hepatic artery anastomosis time (adjusted HR: 1.06, 95% CI: 0.97-1.15, $p = 0.20$; Table 3; Table S6, SDC, <http://links.lww.com/TP/B950>).

The magnitude of the effect of a 10-minute increase in donor hepatectomy time was equal to the effect of a 1-hour increase in cold ischemia time (adjusted HR: 1.11, 95% CI: 1.001-1.24, $p = 0.048$) (Table S4, SDC, <http://links.lww.com/TP/B950>).

The risk of NAS increased more than 4-fold in DCD grafts (adjusted HR: 4.43, 95%CI: 2.33-8.43; $p<0.0001$; Table 3). After adjustment for donor type and warm ischemia time, donor hepatectomy time remained an independent predictor of NAS (Table S7, SDC, <http://links.lww.com/TP/B950>). However, no significant interaction between hepatectomy time and donor type was observed (adjusted HR of the interaction product: 0.78, 95%CI: 0.49-1.23, $p=0.29$; Table 3; Table S8, SDC, <http://links.lww.com/TP/B950>).

Amongst factors influencing the duration of hepatectomy time, only procurement center had a significant impact on the risk of NAS (Table 2) but donor hepatectomy time remained an independent predictor (Table S4, SDC, <http://links.lww.com/TP/B950>).

Implantation time increases the probability of EAD.

EAD occurred in 247 (27%) liver transplants. Risk factors for EAD identified in multivariable analysis (first step) were recipient lab model for end-stage liver disease score, cholestatic liver disease as indication to transplantation, nonlocally procured grafts, HTK preservation solution, and cold ischemia time. Recipient age and male gender were protective factors (Table 4). After extension of this prediction model, the era of the transplantation had no effect on the probability to develop EAD (adjusted odds ratio (OR): 1.001, 95% CI: 0.97-1.04, $p=0.94$).

The probability to develop EAD was not influenced by donor hepatectomy time (adjusted OR: 1.04, 95% CI: 0.93-1.16, $p=0.47$; Table 3; Table S9, SDC, <http://links.lww.com/TP/B950>). In contrast, implantation time had a linear effect on the probability of EAD, increasing the odds by 15% for every 10-minute increase (adjusted OR: 1.15, 95% CI: 1.07-1.23, $p<0.0001$; Table 3; Table S10, SDC, <http://links.lww.com/TP/B950>; Figure 1B). Both portal vein anastomosis (adjusted OR: 1.26, 95% CI: 1.12-1.42, $p=0.0001$) and hepatic artery anastomosis time (adjusted OR: 1.13, 95% CI: 1.04-1.22, $p=0.005$) significantly influenced the probability of EAD (Table 3; Table S11, SDC, <http://links.lww.com/TP/B950>; Figure 1C-D).

The magnitude of the effect of a 10-minute increase in implantation time equaled that of a 1-hour increase in cold ischemia time (adjusted OR: 1.10, 95%CI: 1.02-1.19, $p=0.02$) (Table S10, SDC, <http://links.lww.com/TP/B950>).

There was no significant interaction between donor type and implantation time (adjusted OR of the interaction: 1.07, 95%CI: 0.90-1.27, $p=0.45$; Table 3; Table S12, SDC, <http://links.lww.com/TP/B950>).

Factors significantly influencing the duration of implantation time, such as recipient obesity and the need for multiple hepatic artery anastomoses, did not influence the probability of EAD (Table 4).

Discussion

In this single-center retrospective analysis of more than 900 liver transplants, donor hepatectomy time was an independent risk factor for NAS, and liver implantation time an independent risk factor for EAD. Both donor hepatectomy and implantation time had a linear effect on early complications, indicating that there is no threshold value below which the probability to develop them is negligible. DCD and DBD donors were equally susceptible to the detrimental effect of these surgical times.

Although NAS and EAD are well-known posttransplant complications, their incidence is not prospectively recorded in currently available transplant registries. Therefore, large single-center analyses as described here are needed to investigate the effect of donor hepatectomy and implantation time on NAS and EAD. Ideally, large multicenter studies should follow to confirm these findings. Furthermore, future registry analyses are likely needed to elucidate whether the detrimental effect of these surgical times on long-term outcomes is mediated by an increased incidence of early complications. Therefore, it would be essential that the necessary data are collected by available registries. That being said, the number of events in this single-center cohort allowed us to exclude that donor hepatectomy and implantation time are surrogate of other confounders that may impact on short term outcomes. In fact, by correcting for the effect

of donor and recipient obesity, procurement center, donor type, donor warm ischemia time, and type and number of anastomoses, we could identify a novel risk factor for NAS and deepen our understanding of the relationship between these surgical times and EAD. Indeed, we report for the first time that donor hepatectomy time is a risk factor for NAS, and that its effect is independent from that of donor type and of donor warm ischemia time in DCD liver transplantation. Every 10-minute increase in donor hepatectomy time had a detrimental effect on NAS similar to that of 1-hour increase in cold ischemia time. No significant interaction with hepatectomy time and donor type was observed, indicating that DCDs are equally susceptible to the effect of donor hepatectomy time. In the Eurotransplant registry analysis, examining the relationship of donor hepatectomy time with long-term outcomes,¹ donor hepatectomy time in DCD donors was longer and these grafts were more vulnerable to its detrimental effect. Our observations are likely explained by the fact that allocation for DCD livers in Belgium is centre-driven⁸ and circa 90% of DCD grafts transplanted in this series were procured by our own team, which reported shorter hepatectomy times (Figure S1, SDC, <http://links.lww.com/TP/B950>). The available data did not allow us to investigate the underlying reason for this difference in hepatectomy times.

Similarly to Adelman et al,⁷ we observed a significant univariate association of donor hepatectomy time and EAD. However, this association was not maintained when adjusting for possible confounders (Table 3), indicating that donor hepatectomy time is not an independent risk factor of EAD. In line with Buchholz et al,⁴ implantation time increased the probability to develop EAD but we observed a linear effect (Figure 1B). Therefore, even with shorter implantation times the probability of EAD is increased, precluding the possibility to identify a meaningful cutoff value that could serve for clinical guidance to reduce the likelihood of graft dysfunction. Additionally, we observed that the duration of hepatic artery anastomosis time also significantly increased the odds of EAD. Therefore, reducing the duration of portal vein

anastomosis time only, as suggested by Buchholz et al., may be insufficient to reduce the incidence of graft dysfunction.

The differential effects of donor hepatectomy and implantation time on the risk of NAS and EAD is intriguing, and may be partially explained by the different vulnerability of hepatocytes and cholangiocytes to warm ischemia^{5,14} and abrupt rewarming.¹⁵ Although we could not investigate the underlying pathogenic mechanisms in this clinical series, a recent study investigating changes in metabolites during heart procurement and transplantation reported that significant succinate accumulation occurs during heart cooling at the time of procurement and rewarming at the time of implantation.¹⁶ Succinate is a metabolite of the Krebs cycle and its accumulation facilitates radicals of oxygen formation, driving ischemia reperfusion injury.¹⁶ Since the Krebs cycle is impaired also during hepatic ischemia, it is possible that a similar mechanism takes place during donor hepatectomy and liver implantation, perhaps explaining the detrimental effect of these surgical times independently from characteristics that prolong their duration. Dedicated studies will need to test the validity of this hypothesis in the context of liver transplantation.

Although we could not determine independent factors influencing donor hepatectomy time, it is reasonable to assume that the surgical technique as well as the surgeon's experience play a role. Although details on the experience of the individual procuring surgeons were not available, we did observe a significant variation in hepatectomy time for livers procured locally, regionally, or extraregionally. Furthermore, procurement region was significantly associated with NAS and EAD in multivariable analysis, underpinning the importance of organ procurement. Specific training in organ procurement and standardization of donor procedures, as advocated by some authors,^{17,18} could be considered instrumental not only to reduce the duration of hepatectomy time but also to improve posttransplant outcomes. In our center, all procurement surgeons receive first a theoretical training to create awareness on the importance

of organ cooling, ischemic times, and diligent technique, followed by a practical training under supervision of an experienced donor surgeon.

The implantation technique as well as the expertise of the transplanting surgeon is also likely to influence the duration of implantation time. Indeed, the outcome after liver transplantation is influenced by an important center effect.¹⁹ We also observed a significant difference in the duration of implantation time between transplant surgeons in univariate analysis. However, we did not adjust the analyses for the effect of ‘transplant surgeon’, since by doing so the effect of implantation time would represent a variation in risk between patients transplanted by the same surgeon and having different durations of implantation time, thereby reducing the generalizability of our results given the monocentric nature of our study. A reason for adjusting for the effect of the ‘transplant surgeon’ would be to assess whether differences in risk appetite or patient case-mix have a significant impact on the probability of EAD. However, donor and recipient demographics that capture such differences were all considered in the analyses, whilst patient-oriented allocation of grafts via Eurotransplant⁸ ensures homogeneity of case-mix. When we repeated the analyses with the inclusion of transplant surgeon as a covariate results did not change. Implantation time remained an independent predictor of EAD, and donor hepatectomy time an independent predictor of NAS (Table S13 and S14, SDC, <http://links.lww.com/TP/B950>).

Our findings are clinically relevant because donor hepatectomy and implantation time are amenable of modifications. Minimizing their duration may reduce the incidence of EAD and NAS. During multiorgan procurement, the heart is procured first, followed by lungs, liver and/or pancreas, and kidneys. Expectedly, the concomitant donation of thoracic organs lengthened donor hepatectomy time in this cohort. Since lungs are more tolerant to warm ischemia than livers,^{20,21} modifying the order of organ procurement with hepatectomy preceding pneumonectomy may shorten the duration of donor hepatectomy time. However, the feasibility and safety of such technique remains to be shown. Similarly, provided technically feasible, graft

implantation should be quick, and if multiple arterial anastomoses are required, arterial reconstructions should be done during back-table preparation while the organ is kept cold. Considering our findings showing an independent effect of both donor hepatectomy and implantation time on the risk of early complications, whether optimizing graft cooling and preventing graft rewarming effectively reduces the incidence of NAS and EAD warrants further investigation.

The strength of this analysis is the use of a large database (>900 transplants) capturing enough information to exclude that the detrimental effect of donor hepatectomy and implantation time is a surrogate of characteristics known to be associated with surgical complexity. For instance, we report that recipient BMI, pretransplant portal vein thrombosis, and the type and number of arterial anastomoses do not influence the probability of EAD, underpinning the independent effect of implantation time. However, insufficient details were available to tease out whether the technique of graft procurement (ie, hepatectomy alone vs. en bloc) and flush-cooling (ie, single aortic or dual aortic and portal flush) influence the duration of donor hepatectomy time and/or the risk of NAS. Additionally, as surgical complexity per se is difficult to quantify, we cannot exclude that these surgical times may also pick on the effect of other characteristics capturing surgical complexity of the donor or recipient procedure that are currently unknown, and that could not be accounted for in these analyses. A limitation inherent to this study is its monocentric and retrospective nature. Nevertheless, to reduce the bias derived from incomplete data we used multiple imputation, which is an accepted method to handle concerns related to missing data. It is possible that hepatic steatosis influences graft vulnerability to donor hepatectomy and implantation time. However, since grafts biopsies are taken only sporadically in our center, we were not able to investigate this aspect. Future studies should therefore include baseline biopsies to adequately evaluate this possible confounding effect. Additionally, we could not investigate the effect of donor hepatectomy and implantation time on the probability of graft primary nonfunction, due to the a very small number of events in our cohort. Finally,

analyses evaluating the impact of both surgical times on the risk of acute kidney injury after liver transplantation would also be of value.

In conclusion, prolonged donor hepatectomy during organ procurement significantly increases the risk of NAS. Prolonged implantation time during transplantation significantly increases the odds of EAD; both portal vein and hepatic artery anastomosis time contribute to this risk. Efforts should be made to reduce the duration of both surgical times. How to optimize organ cooling during procurement, and to prevent abrupt rewarming of the graft during transplantation and their efficacy on reducing the incidence of nonanastomotic stricture and graft dysfunction warrants further investigation.

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Figures Legend

Figure 1. Donor hepatectomy time and liver implantation time linearly increase the risk of nonanastomotic biliary strictures and early allograft dysfunction, respectively. Hazard ratio of NAS (A) and odds ratios of EAD (B-D) with 95% pointwise CI and histograms representing the distribution of the duration of donor hepatectomy time (A), implantation time (B), portal vein anastomosis time (C) and hepatic artery anastomosis time (D). Hazard and odds ratios compare each value of the surgical times of interest with the mean value in the dataset (therefore, HR and OR equal by definition 1 at the mean value). IQR: inter quartile range.

Table 1 Overview of baseline donor, recipient, and postoperative characteristics of the study population.

Characteristics	Value	Missing data (%)
Donor		
Age, years	52 (40-62)	0 (0.00)
Gender, No. (%)		0 (0.00)
Female	400 (43.62)	
Male	517 (56.38)	
Donor Type, No. (%)		0 (0.00)
DBD	793 (86.48)	
DCD	124 (13.52)	
Donor warm ischemia time, minutes	19 (15-24)	4 (3.23)
BMI, Kg/m ²	24.40 (22.50-26.20)	0 (0.00)
ICU stay, days	3 (2-6)	9 (0.98)
Cause of death, No. (%)		16 (1.75)
Trauma	419 (46.50)	
Cerebrovascular accident	381 (42.29)	
Hypoxia	82 (9.10)	
Others	19 (2.11)	
Highest AST, IU/L	50 (30-80)	4 (0.44)
Highest ALT, IU/L	30 (20-60)	5 (0.55)
Highest Bilirubin, mg/dL	0.60 (0.40-0.90)	21 (2.29)
Arterial hypotension, No. (%)		66 (7.20)
No	510 (59.93)	
Yes	341 (40.07)	
Cardiac arrest, No. (%)		30 (3.27)

No	685 (77.23)	
Yes	202 (22.77)	
Need for vasopressors, No. (%)		21 (2.29)
No	195 (21.76)	
Yes	701 (78.24)	
Procurement team, No. (%)		0 (0.00)
Local (own center)	447 (48.75)	
Regional (6 other Belgian procurement teams)	271 (29.55)	
Extraregional (26 Eurotransplant procurement team outside Belgium)	199 (21.70)	
Type of preservation solution, No. (%)		0 (0.00)
HTK	218 (23.77)	
UW	615 (67.07)	
IGL-1	84 (9.16)	
Type of preservation solution for DCD grafts, No. (%) ^a		
HTK	33 (26.61%)	
UW	51 (41.13%)	
IGL-1	40 (32.26%)	
Common bile duct flush, No. (%)		17 (1.85)
No	32 (3.56)	
Yes	868 (96.44)	
Multiple hepatic artery anatomy, ^b No. (%)		69 (7.52)
Single	452 (53.30)	
Multiple	396 (46.70)	
Concomitant donation of thoracic organs, No. (%)		8 (0.87)

No	363 (39.93)	
Yes	546 (60.07)	
Recipient		
Age, years	58 (49-65)	0 (0.00)
Gender, No. (%)		0 (0.00)
Female	347 (37.84)	
Male	570 (62.16)	
Lab MELD, points	15 (11-22)	0 (0.00)
UNOS score, No. (%)		0 (0.00)
Hospitalized in ICU	109 (11.89)	
Hospitalized in a ward	186 (20.38)	
At home	622 (67.83)	
BMI, Kg/m ²	26 (23-29)	2 (0.22)
Indication to transplantation, ^c No. (%)		0 (0.00)
Retransplantation	73 (7.96)	
Acute liver failure	71 (7.74)	
Metabolic disease	71 (7.74)	
Hepatocellular carcinoma	289 (31.52)	
Post-ethyl cirrhosis	300 (32.72)	
Post-hepatitis C cirrhosis	110 (12.00)	
Post-hepatitis B cirrhosis	46 (5.02)	
Cholestatic liver disease	116 (12.65)	
Pretransplant portal vein thrombosis, No. (%)		0 (0.00)
No	844 (92.04)	
Yes	73 (7.96)	

<i>Surgical times</i>		
Donor hepatectomy time, minutes	35 (26-46)	76 (8.29)
Cold ischemia time, hours	7.80 (6.10-9.50)	4 (0.44)
Implantation time, minutes	80 (69-95)	28 (3.05)
Portal vein anastomosis time, minutes	45 (39-56)	20 (2.18)
Hepatic artery anastomosis time, minutes	33 (22-44)	32 (3.49)
Hepatic artery anastomosis type, No. (%)		16 (1.75)
Single	788 (87.46)	
Multiple, during implantation	74 (8.21)	
Multiple, during back-table	39 (4.33)	
<i>Postoperative</i>		
Mean arterial blood pressure 5min after reperfusion, No. (%)		67 (7.31)
> 100 mmHg	357 (42%)	
80-100 mmHg	249 (29.29%)	
60-80 mmHg	139 (16.35)	
<60 mmHg	105 (12.35)	
Peak AST, IU/L	690 (370-1320)	3 (0.33)
Peak ALT, IU/L	680 (350-1230)	4 (0.44)
Bilirubin on day 7 th , mg/dL	2.20 (1.10-5.60)	20 (2.18)
INR on day 7 th	1.10 (1.00-1.20)	55 (6.00)
ICU stay, days	4.00 (2.00-7.00)	24 (2.62)
Hospitalization, days	19 (14-30)	27 (2.95)
EAD, No. (%)	247 (26.94)	0 (0.0)
NAS, No. (%)	106 (11.56)	0 (0.00)

Data are expressed as median (IQR) when not differently indicated.

ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; DBD, donation after brain-death; DCD, donation after circulatory death; EAD, early allograft dysfunction; HTK, histidine tryptophan ketoglutarate preservation solution; ICU, intensive care unit; IGL-1, institute George Lopez 1 preservation solution; INR, international normalized ratio; MELD, model for end stage liver disease; NAS, nonanastomotic biliary strictures; UNOS, united network for organ sharing; UW, university of Wisconsin preservation solution.

^aPercentages are calculated based on the total number of DCD liver transplantations (n=124)

^bAs reported by the procuring surgeon.

^cIndications to transplantation are not mutually exclusive.

Table 2 Univariable and multivariable Cox regression identifying risk factors for nonanastomotic biliary strictures.

	Nonanastomotic biliary Strictures			
	Univariable		Multivariable ^a	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Donor age (years)	1.01 (0.995-1.02)	0.28	1.02 (1.004-1.03)	0.01
Donor gender (ref.: female)	0.91 (0.62-1.34)	0.64	-	-
Donor type (ref.: DBD)	1.62 (1.002-2.60)	0.05	4.43 (2.33-8.43)	<0.0001
Donor warm ischemia time (10 minutes)	1.51 (0.93-2.47)	0.09	-	-
Donor BMI (Kg/m ²)	1.01 (0.96-1.07)	0.61	-	-
Donor ICU stay (log2(y+1)) (days)	1.04 (0.85-1.26)	0.73	-	-
Donor death for trauma (ref.: other)	1.09 (0.74-1.59)	0.67	1.40 (0.92-2.12)	0.11
Donor highest AST (log2) (IU/L)	0.95 (0.81-1.11)	0.49	-	-
Donor highest ALT (log2) (IU/L)	0.91 (0.79-1.06)	0.24	-	-
Donor highest bilirubin (log2) (mg/dL)	0.92 (0.75-1.14)	0.46	-	-
Donor arterial hypotension (ref.: no)	0.87 (0.58-1.32)	0.52	-	-
Donor cardiac arrest (ref.: no)	0.96 (0.60-1.52)	0.85	-	-
Donor need for vasopressors (ref.: no)	1.11 (0.69-1.79)	0.66	-	-
Procurement team (ref.: local)	1.00	<0.0001	1.00	<0.0001
Regional	3.03 (1.93-4.77)	<0.0001	3.48 (2.02-5.99)	<0.0001
Extraregional	2.17 (1.23-3.67)	0.004	1.63 (0.81-3.28)	0.17
HTK preservation solution (ref.: no)	1.82 (1.22-2.72)	0.004	-	-
Donor common bile duct flush (ref.: no)	0.32 (0.17-0.61)	0.0005	0.52 (0.25-1.09)	0.08
Multiple hepatic arteries ^b (ref.: single artery)	0.98 (0.66-1.45)	0.90	-	-
Concomitant donation of thoracic organs (ref.: no)	0.92 (0.62-1.35)	0.66	-	-
Recipient age (years)	1.001 (0.99-1.02)	0.86	-	-

Recipient gender (ref.: female)	1.09 (0.73-1.62)	0.66	1.40 (0.89-2.20)	0.15
Lab MELD score (log2) (points)	1.22 (0.94-1.59)	0.14	-	-
Recipient UNOS score (ref.: at home)	1.00	0.18	-	-
Hospitalized in ICU	1.19 (0.64-2.20)	0.58	-	-
Hospitalized in a ward	1.53 (0.99-2.38)	0.06	-	-
Recipient BMI (Kg/m ²)	0.97 (0.93-1.01)	0.15	0.96 (0.92-1.01)	0.12
Indication to transplantation				
Retransplantation (ref.: no)	1.45 (0.78-2.71)	0.24	1.95 (1.01-3.78)	0.05
Acute liver failure	2.12 (1.23-3.66)	0.01	2.81 (1.47-5.37)	0.002
Metabolic disease	0.70 (0.31-1.60)	0.40	-	-
Hepatocellular carcinoma	0.90 (0.59-1.36)	0.61	-	-
Post-ethyl cirrhosis	0.82 (0.54-1.24)	0.35	-	-
Post-hepatitis C cirrhosis	0.93 (0.51-1.69)	0.81	-	-
Post-hepatitis B cirrhosis	1.54 (0.75-3.17)	0.24	-	-
Cholestatic liver disease	0.99 (0.56-1.77)	0.98	-	-
Pretransplant portal vein thrombosis (ref.: no)	0.95 (0.46-1.94)	0.88	-	-
Hepatic artery anastomosis type (ref.: single)	1.00	0.66	-	-
Multiple, during implantation	1.24 (0.65-2.39)	0.51	-	-
Multiple, during back-table	1.36 (0.59-3.11)	0.47	-	-
Cold ischemia time (hours)	1.09 (0.997-1.18)	0.06	1.11 (1.001-1.24)	0.05

^aResults from a multivariable proportional hazard regression model predicting the risk to develop NAS obtained after backwards stepwise selection based on multiple imputation (10 datasets). The analysis is based on 97 events from 841 subjects.

^bas reported by the procuring surgeon.

ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; DBD, donation after brain-death; HTK,

histidine tryptophan ketoglutarate preservation solution; ICU, intensive care unit; MELD, model for end stage liver disease; UNOS, united network for organ sharing.

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Table 3 Summary of the adjusted effect of donor hepatectomy time, implantation time, portal vein anastomosis time, and hepatic artery anastomosis time on the risk EAD and NAS. The effect of the interaction of donor hepatectomy time or implantation time with donor type is also reported.

	Early allograft dysfunction		Nonanastomotic biliary strictures	
	Adjusted analysis ^a		Adjusted analysis ^a	
	OR (95% CI)	p-value	HR (95% CI)	p-value
Donor hepatectomy time (10 minutes)	1.04 (0.93-1.16)	0.47	1.19 (1.04-1.35)	0.01
Implantation time (10 minutes)	1.15 (1.07-1.23)	<0.0001	1.03 (0.96-1.11)	0.42
Portal vein anastomosis time (10 minutes)	1.26 (1.12-1.42)	0.0001	0.98 (0.84-1.14)	0.77
Hepatic artery anastomosis time (10 minutes)	1.13 (1.04-1.22)	0.005	1.06 (0.97-1.15)	0.20
<i>Interaction analysis</i>				
Donor hepatectomy time				
Effect when DBD	1.05 (0.94-1.18)	0.37	1.22 (1.06-1.40)	0.005
Effect when DCD	0.82 (0.51-1.34)	0.43	0.95 (0.61-1.47)	0.82
Interaction	0.78 (0.48-1.28)	0.33	0.78 (0.49-1.23)	0.29
Implantation time				
Effect when DBD	1.14 (1.05-1.23)	0.001	1.04 (0.95-1.14)	0.45
Effect when DCD	1.21 (1.04-1.41)	0.02	0.98 (0.85-1.14)	0.83
Interaction	1.07 (0.90-1.27)	0.45	0.95 (0.80-1.13)	0.55

^aThe final multivariable regression models for EAD and NAS obtained after selection of covariates with a stepwise backwards approach (see Table 2 and 3) were extended introducing separately in the model each of the considered surgical times. Lastly, the effect of the interaction of donor hepatectomy time or implantation time with donor type was explored. Detailed results of the single model extensions are provided in SDC, <http://links.lww.com/TP/B950>.

DBD, donation after brain-death; DCD: donation after circulatory death.

Table 4 Univariable and multivariable logistic regression identifying risk factors for early allograft dysfunction.

	Early allograft dysfunction			
	Univariable		Multivariable ^a	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Donor age (years)	0.997 (0.99-1.01)	0.50	-	-
Donor gender (ref.: female)	0.85 (0.63-1.14)	0.28	-	-
Donor type (ref.: DBD)	0.54 (0.34-0.89)	0.01	-	-
Donor warm ischemia time (10 minutes)	0.53 (0.26-1.09)	0.09	-	-
Donor BMI (Kg/m ²)	1.02 (0.98-1.06)	0.34	1.04 (0.99-1.08)	0.14
Donor ICU stay (log2(y+1)) (days)	1.11 (0.96-1.30)	0.16	-	-
Donor death for trauma (ref.: other)	1.05 (0.78-1.41)	0.75	-	-
Donor highest AST (log2) (IU/L)	0.96 (0.86-1.08)	0.53	-	-
Donor highest ALT (log2) (IU/L)	1.05 (0.95-1.17)	0.35	-	-
Donor highest bilirubin (log2) (mg/dL)	0.97 (0.82-1.14)	0.68	-	-
Donor arterial hypotension (ref.: no)	0.86 (0.63-1.18)	0.34	-	-
Donor cardiac arrest (ref.: no)	0.74 (0.51-1.07)	0.11	-	-
Donor need for vasopressors (ref.: no)	1.15 (0.80-1.65)	0.46	-	-
Procurement team (ref.: local)	1.00	<0.0001	1	0.003
Regional	1.86 (1.31-2.66)	0.0006	1.57 (1.06-2.33)	0.02
Extraregional	3.32 (2.29-4.80)	<0.0001	2.31 (1.42-3.75)	0.0008
HTK preservation solution (ref.: no)	2.36 (1.71-3.26)	<0.0001	1.74 (1.16-2.59)	0.007
Donor common bile duct flush (ref.: no)	0.60 (0.29-1.26)	0.18	-	-
Multiple hepatic arteries ^b (ref.: single artery)	1.04 (0.76-1.41)	0.83	-	-
Concomitant donation of thoracic organs (ref.: no)	1.03 (0.77-1.40)	0.83	-	-
Recipient age (years)	0.98 (0.67-0.99)	0.0008	0.98 (0.97-0.99)	0.003

Recipient gender (ref.: female)	0.71 (0.53-0.96)	0.03	0.65 (0.46-0.91)	0.01
Lab MELD score (log2) (points)	1.48 (1.21-1.82)	0.0002	1.48 (1.14-1.93)	0.004
Recipient UNOS score (ref.: at home)	1.00	0.02	-	-
Hospitalized in ICU	1.81 (1.83-2.77)	0.006	-	-
Hospitalized in a ward	0.92 (0.63-1.35)	0.67	-	-
Recipient BMI (Kg/m ²)	1.003 (0.97-1.03)	0.87	-	-
Indication to transplantation				
Retransplantation (ref.: no)	1.56 (0.94-2.58)	0.08	-	-
Acute liver failure	1.63 (0.99-2.71)	0.06	0.58 (0.30-1.11)	0.10
Metabolic disease	1.33 (0.79-2.24)	0.28	-	-
Hepatocellular carcinoma	0.88 (0.64-1.21)	0.44	1.43 (0.96-2.13)	0.08
Post-ethyl cirrhosis	0.84 (0.61-1.15)	0.28	-	-
Post-hepatitis C cirrhosis	0.97 (0.62-1.52)	0.89	-	-
Post-hepatitis B cirrhosis	1.07 (0.56-2.07)	0.84	-	-
Cholestatic liver disease	1.26 (0.82-1.92)	0.29	1.66 (1.02-2.71)	0.04
Pre-transplant portal vein thrombosis (ref.: no)	0.81 (0.46-1.42)	0.47	-	-
Hepatic artery anastomosis type (ref.: single)	1.00	0.58	-	-
Multiple, during implantation	1.27 (0.76-2.12)	0.37	-	-
Multiple, during back-table	1.25 (0.62-2.51)	0.54	-	-
Cold ischemia time (hours)	1.18 (1.11-1.27)	<0.0001	1.10 (1.02-1.19)	0.02

^aResults from a multivariable logistic regression model predicting the probability to develop EAD obtained after backwards stepwise selection based on multiple imputation (10 datasets). The analysis is based on 239 events from 889 subjects.

^bas reported by the procuring surgeon.

ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; DBD, donation after brain-death; HTK,

histidine tryptophan ketoglutarate preservation solution; ICU, intensive care unit; MELD, model for end stage liver disease; UNOS, united network for organ sharing.

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Figure 1