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***Retrospective Study***

**Association of donor hepatectomy time with liver transplantation outcomes: a multicenter retrospective study**

Hepatectomy time and liver transplantation outcomes

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**Abstract**

**BACKGROUND**

Prolonged donor hepatectomy time may be implicated in early and late complications of liver transplantation.

**AIM**

This study aimed to evaluate the impact of donor hepatectomy time on outcomes of liver transplant recipients, mainly early allograft dysfunction.

**METHODS**

This multicenter retrospective study included brain-dead donors and adult liver graft recipients. Donor-recipient matching was obtained through a crossover list. Clinical and laboratory data were recorded for both donors and recipients. Donor hepatectomy, cold ischemia, and warm ischemia times were recorded. Primary outcome was early

allograft dysfunction. Secondary outcomes included need for retransplantation, length of intensive care unit and hospital stay, and patient and graft survival at 12 months.

## RESULTS

From January 2019 to December 2021, a total of 243 patients underwent a liver transplant from a brain-dead donor. Of these, 57 (25%) developed early allograft dysfunction. The median donor hepatectomy time was 29 (23–40) min. Patients with early allograft dysfunction had a median hepatectomy time of 25 (22–38) min, whereas those without it had a median time of 30 (24–40) min ( $P = 0.126$ ).

## CONCLUSION

Donor hepatectomy time was not associated with early allograft dysfunction, graft survival, or patient survival following liver transplantation.

**Key Words:** Brain death; hepatectomy; liver transplantation; early allograft dysfunction; graft survival

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**Core Tip:** This study aims to evaluate the impact of donor hepatectomy time on outcomes of liver transplant recipients. This is a multicenter retrospective study that included brain-dead donors and adult liver graft recipients. A total of 243 patients underwent liver transplantation from brain-dead donors. The median duration of donor hepatectomy was 29 (23–40) minutes. Patients with early allograft dysfunction had a median hepatectomy time of 25 (22–38) min, while those without had a median time of 30 (24–40) min ( $P = 0.126$ ). Duration of donor hepatectomy was not associated with

early allograft dysfunction, graft survival, or patient survival following liver transplantation.

## **INTRODUCTION**

The main source of livers for transplantation is brain-dead donors <sup>1</sup>. During liver harvesting and storage processes, the organs are exposed to numerous cellular insults <sup>2</sup>. As a result, transplantation becomes a race against time. In order to mitigate the negative effects of ischemia, efforts have focused on organ preservation by reducing cold ischemia time and implementing different organ perfusion techniques <sup>3,4</sup>.

However, a novel concept has emerged regarding the development of early allograft dysfunction: donor hepatectomy time, also referred to as donor warm ischemia time <sup>5,6</sup>. Hepatectomy time is defined as the interval from aortic cross-clamping to placing the liver at low temperatures. Despite the brief duration of donor warm ischemia (minutes) in contrast to the long duration of cold ischemia (hours), in the warm phase the organs are maintained at relatively high temperatures and at high metabolic demands <sup>5,7</sup>.

Despite the significant role of donor hepatectomy time in graft outcomes, it has received insufficient attention <sup>6,8</sup>. Recently, Gilbo *et al* demonstrated an association between longer hepatectomy times and early surgical complications <sup>5</sup>. They showed that a 10-min increase in donor hepatectomy time produced a similar effect of 1-h increase in cold ischemia time. Similarly, Adelman *et al* demonstrated that hepatectomy time was independently associated with early allograft dysfunction <sup>8</sup>.

To address the shortage of organs and improve liver transplantation outcomes, it is crucial to continuously explore opportunities to enhance donor, graft, and recipient care. One such method involves reducing the duration of ischemic phases, which has been demonstrated to be of great importance. Therefore, our study <sup>2</sup> aimed to evaluate the impact of donor hepatectomy time on outcomes of liver transplant recipients.

## **MATERIALS AND METHODS**

This is a multicenter retrospective study. The study was approved by the reference Ethics Committee at the Universidade Federal Rio Grande do Sul (PROPESQ UFRGS, project number 5.526.176), Brazil. The study adheres to the guidelines set forth by the Helsinki Declaration, as well as to local standards and Brazilian legislation <sup>9</sup>. The Ethics Committee did not require informed consent due to the retrospective design and the anonymization of donors and recipients prior to analysis.

### *Study population*

This study included brain-dead donors from 19 regional centers in the state of Santa Catarina, Brazil, and adult liver transplant recipients from brain-dead donors at Hospital Santa Isabel, a general hospital in the city of Blumenau, state of Santa Catarina, Brazil, from January 2019 to December 2021. In order to be eligible, patients had to be over 18 years of age and have received a liver transplant in the Liver Transplantation Center at Hospital Santa Isabel. Exclusion criteria were retransplantation, grafts from living-related donors, split liver grafts, and intraoperative death.

Donor-recipient matching was obtained through a crossover list provided by the regional organ distribution center of the state of Santa Catarina. Clinical and laboratory data were recorded for both donors and recipients, and the donor risk index (DRI) was calculated to assess organ quality <sup>10</sup>. The DRI considers 8 donor characteristics, namely age, height, ethnicity, cause of death, donation after circulatory death, donor hospital location, split liver graft, and cold ischemia time. The DRI assesses the risk of graft loss in comparison to an ideal donor <sup>10,11</sup>. A DRI score  $\geq 1.4$  predicts graft failure <sup>11</sup>. Model for end-stage liver disease (MELD) scores were calculated for recipients. The MELD score is a prospectively developed and validated scoring system for assessing the severity of chronic liver disease that uses patients' laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict 3-month survival <sup>12</sup>.

Donor hepatectomy time as well as cold and warm ischemia times were analyzed. Donor hepatectomy time, also known as donor warm ischemia time, is the interval from

the start of aortic cold flush in the donor to the completion of donor hepatectomy, during which the liver is transferred to ice-cold preservation solution on the back table<sup>7</sup>. Cold ischemia time refers to the interval from the start of cold flush (both aortic and portal) in the donor to the moment the liver is removed from ice storage and placed in the recipient abdomen for implantation<sup>7</sup>. Warm ischemia time in the recipient is the interval between the removal of the liver from the cold solution and organ reperfusion in the recipient<sup>5,7</sup>.

The criteria for early allograft dysfunction were defined as the presence of any of the following postoperative laboratory findings: 1) serum bilirubin >10 mg/dL on day 7 after transplant; 2) INR >1.6 on day 7 after transplant; and 3) alanine or aspartate aminotransferase levels >2000 IU/L within the first 7 days after transplant<sup>13</sup>. Graft survival was defined as the time from liver transplantation to either retransplantation or death from any cause<sup>14</sup>. Patient survival was defined as the time from transplantation to death from any cause. Graft and patient survival were evaluated at 12 months. Patients were followed up until their last visit to the Liver Transplantation Center at Hospital Santa Isabel.

Primary outcome was early allograft dysfunction. Secondary outcomes included need for retransplantation, length of intensive care unit (ICU) and hospital stay, and patient and graft survival at 12 months.

#### *Organ procurement and transplantation*

Livers were procured regionally at 19 centers in the state of Santa Catarina, Brazil. The procedure involved isolating the liver and extracting it after dissection of the biliary duct, portal vein, and hepatic artery, along with en bloc resection of the celiac trunk and aortic patch. The liver was then flushed and cooled through both the abdominal aorta and portal vein and immersed in ice-cold preservation solution (Institute George Lopez 1 solution). Skilled senior staff members performed all liver transplants, with most recipients receiving an inferior vena cava-sparing piggyback anastomosis, although some required replacement of the inferior vena cava. The portal

vein was reconstructed in a standard end-to-end fashion. An end-to-end hepatic artery anastomosis was performed, with multiple anastomoses performed in cases of abnormal donor or recipient hepatic artery anatomy. Sequential portal and arterial reperfusion were employed. A standard triple immunosuppression regimen consisting of a calcineurin inhibitor, steroids, and an antimetabolite was administered to all patients<sup>15</sup>.

### *Statistical analysis*

Categorical variables were expressed as percentages. Continuous data were presented as mean (SD) if normally distributed, or median (IQR) if not. Patients with and without early allograft dysfunction were compared using Student's *t* test, Mann-Whitney *U* test, or chi-square test, as appropriate. Correlations between variables were calculated using Spearman's test. For patient and graft survival analyses, Kaplan-Meier survival curves with the log-rank test were constructed while censoring graft survival for death with a functioning graft to account for competing events. The discriminative power of donor hepatectomy time to predict the outcome was determined by analyzing receiver operating characteristic (ROC) curves, and patients were divided into two groups: below and above the cutoff. Values were statistically significant if  $p < 0.05$ . Statistical analyses were conducted using SPSS 21.0 (Chicago, IL, USA).

## **RESULTS**

### *Patient characteristics*

Between January 2019 and December 2021, a total of 243 patients underwent a liver transplant from a brain-dead donor. Table 1 presents the main baseline characteristics of donors, recipients, and surgical procedures. The donors were predominantly male ( $n = 150$ , 62%), with a mean age of 41 (SD, 14) years. Stroke was the leading cause of brain death ( $n = 118$ , 48.6%), followed by traumatic brain injury ( $n = 96$ , 39.5%) and anoxic encephalopathy ( $n = 19$ , 7.8%). The median DRI was 1.3 (1.1–1.6). The recipients were mostly male ( $n = 175$ , 72%), with a mean age of 56 (SD, 11) years and a body mass index

(BMI) of 27.8 (SD, 4.8) kg/m<sup>2</sup>. The primary indications for liver transplantation were viral hepatitis ( $n = 78$ , 32%), alcoholic liver disease ( $n = 63$ , 26%), and non-alcoholic fatty liver disease ( $n = 29$ , 12%).

Donor hepatectomy time ranged from 15 to 93 min, with a median of 29 (23–40) min. There was a difference in hepatectomy time between local and regional organ procurement centers (22 [25–46] *vs* 30 [24–41] min, respectively,  $p \leq 0.001$ ). Donor BMI was associated with hepatectomy time. For donors with BMI <30 kg/m<sup>2</sup>, the median hepatectomy time was 28 (23–38) min, whereas for donors with BMI  $\geq 30$  kg/m<sup>2</sup> it was 35 (25–46) min ( $P = 0.031$ ). Regarding ischemia times, the median cold ischemia time was 405 (329–492) min, while the median warm ischemia time was 34 (30–37) min.

#### *Primary outcome*

Early allograft dysfunction was observed in 57 patients (25%). The median donor hepatectomy time had no impact on the development of early allograft dysfunction. Patients with early allograft dysfunction had a median donor hepatectomy time of 25 (22–38) min, whereas those without it had a median time of 30 (24–40) min ( $P = 0.126$ ) (Table 2). Similarly, other surgical times were not associated with early allograft dysfunction (Table 2).

When each of the 3 criteria for early allograft dysfunction was analyzed separately, no significant correlation was found between donor hepatectomy time and postoperative markers of liver graft function on ICU admission, day 1, or day 7 (Table 3).

#### *Secondary outcomes*

Donor hepatectomy time did not differ significantly between survivors and non-survivors (29 [24–38] *vs* 26 [21–42] min,  $P = 0.787$ ), patients with and without graft survival at 12 months (29 [24–38] *vs* 27 [21–45] min,  $P = 0.893$ ), or patients requiring and not requiring retransplantation (30 [24–42] *vs* 29 [24–40] min,  $P = 0.951$ ).



To better understand the impact of donor hepatectomy time, we categorized patients based on the discriminative power of hepatectomy time to predict the outcome determined by the ROC curve, which was set at 23 min. The effects of hepatectomy time below and above this cutoff are detailed in Table 4. Figure 1 illustrates the survival analysis for grafts (Panel A) and for patients (Panel B) according to hepatectomy times below and above the cutoff value (23 min).

#### *Exploratory outcomes*

Arterial anatomy type was not associated with donor hepatectomy time. The median procedure duration was 29 (23–38) min for donors with standard arterial anatomy and 28 (24–41) min for donors with unusual arterial anatomy ( $P = 0.688$ ).

Donors with hepatectomy time <23 min were receiving vasopressors in a similar number to those with hepatectomy time >23 min ( $n = 55$  [90.2%] *vs*  $n = 146$  [80.2%], respectively,  $P = 0.075$ ). Likewise, donors who had hepatectomy times either above or below the cutoff (23 min) required similar doses of preoperative vasopressors. The dose administered was 0.12 (0.04–0.22) mcg/kg/min for donors above the cutoff and 0.13 (0.05–0.26) mcg/kg/min for donors below the cutoff ( $P = 0.507$ ).

## **DISCUSSION**

In this multicenter retrospective study involving liver recipients from brain-dead donors, we did not find any evidence of an association between donor hepatectomy time and the development of early allograft dysfunction. Furthermore, our findings indicate that longer hepatectomy times did not affect either graft or patient survival.

Previous literature reports donor hepatectomy time ranging from 32 to 51 min, with a median of 40 min <sup>5,16</sup>. Two <sup>1</sup> single-center retrospective studies investigated whether donor hepatectomy and implantation time increased the incidence of early allograft dysfunction, but their results were inconclusive <sup>5,8</sup>. Adelman *et al* suggested that prolonged donor hepatectomy time increased the risk of early allograft dysfunction, but no adjustment was made for confounders, such as cold ischemia time <sup>8</sup>.

Conversely, Gilbo *et al* showed that the risk of developing early allograft dysfunction was not influenced by donor hepatectomy time but rather by <sup>1</sup>implantation time, which had a linear effect on the development of early allograft dysfunction, increasing the risk by 15% for every 10-min increase in time <sup>5</sup>. Our findings align with these results, as we showed that donor hepatectomy time was not associated with an increased risk of early allograft dysfunction. It is reasonable to conceive that hepatectomy times in our province are sufficiently short (11 min below the median time reported in the literature) to allow for reduced risk of early allograft dysfunction or other clinical outcomes.

Although consensus on the optimal donor hepatectomy time remains inconclusive, studies have suggested that minimizing ischemia times <sup>7,17</sup>, especially cold ischemia time <sup>18,19</sup>, is associated with better outcomes and fewer early surgical complications, including non-anastomotic biliary strictures <sup>5,20</sup>. However, the impact of donor hepatectomy time, which is relatively brief compared to other ischemia times, on clinical outcomes has received limited attention. In this study, we showed that donor hepatectomy time was not associated with graft or patient survival, need for retransplantation, or length of ICU or hospital stay. Probably, other donor, recipient, and surgical procedure characteristics, such as previous comorbidities <sup>21</sup>, age <sup>22</sup>, underlying disease <sup>19</sup>, and bleeding volume <sup>23,24</sup>, are better determinants of these outcomes than hepatectomy time itself. For instance, liver grafts recovered from donors after cardiac death undergo distinct ischemic insults during procurement, exhibiting differences in nature and severity of injury. Using the Eurotransplant Registry data, Jochmans *et al* reported that the impact of donor hepatectomy time is more pronounced in livers from donors after cardiac death than in those after brain death <sup>6</sup>. In donors after cardiac death, cold preservation follows a prolonged period of warm ischemia during treatment withdrawal, progression to asystole, and hepatectomy itself, making these grafts more vulnerable to insults. Recently, a retrospective study using the United States national data including 3,810 Liver transplants from donors after cardiac death demonstrated that prolonged donor hepatectomy time significantly increased the risk of 1-year graft loss and patient mortality. This study showed that prolonged donor

hepatectomy time, defined as  $\geq 42$  min, is a significant risk factor impacting short-term outcomes, along with the receptor age and MELD score <sup>25</sup>. We believe that the exceptionally short median donor hepatectomy time of <29 minutes in our study, along with the absence of prolonged warm ischemia typical of donors after cardiac death, explains the lack of association between donor hepatectomy time and outcomes in our cohort of brain-dead donors.

Unstable patients and those with unusual arterial anatomy may have prolonged hepatectomy times. In our study, the presence of unusual arterial anatomy or vasopressor dose had no significant impact on donor hepatectomy time, although this result should be considered exploratory.

Our study is one of the few studies that have been specifically designed to investigate the association between donor hepatectomy time and the development of early allograft dysfunction. Nevertheless, given the multicenter nature of the study, it is essential to acknowledge some limitations. First, although this study represents the largest dataset to test this hypothesis, it is still underpowered. Based on the 5-min difference that we found in median hepatectomy time between patients with and without early allograft dysfunction, our results have a power of 71%. However, it is highly unlikely that an increment in sample size would change results, as a very short hepatectomy time was observed overall. Second, since donor hepatectomy time is not considered crucial, surgeons may have provided less accurate information in this regard, but data were collected from patients' medical records. Third, the retrospective nature of the study resulted in some missing information, including 15 patients without the primary outcome. Fourth, unfortunately we do not have data on the impact of donor hepatectomy time after cardiac death, as well described <sup>26</sup>, because this type of donation is not currently available in Brazil.

## **CONCLUSION**

In conclusion, donor hepatectomy time was not associated with early allograft dysfunction, graft survival, or patient survival following liver transplantation. While

there is a need for policies and interventions to enhance post-transplant outcomes, it appears that the current donor hepatectomy time is already sufficiently short to further mitigate risks. We suggest that future research efforts should focus on exploring alternative strategies other than further reducing donor hepatectomy time

## **ARTICLE HIGHLIGHTS**

### ***Research background***

To address the shortage of organs and improve liver transplantation outcomes, it is crucial to explore opportunities to enhance donor, graft, and recipient care. One such method involves reducing the duration of ischemic phases, which has been demonstrated to be of great importance.

### ***Research motivation***

There is a need for policies and interventions to improve post-transplant results, it appears that the donor's hepatectomy time may be a factor contributing to this improvement

### ***Research objectives***

This study aimed to evaluate the impact of donor hepatectomy timing on outcomes in liver transplant recipients, particularly early allograft dysfunction. We know that transplantation is a race against time, and better understanding the importance of these times is essential for a more accurate strategy.

### ***Research methods***

This is a multicenter retrospective study. The study included brain-dead donors from 19 regional centers in the state of Santa Catarina, Brazil, and adult liver transplant recipients from brain-dead donors at Hospital Santa Isabel, a general hospital in the city of Blumenau, state of Santa Catarina, Brazil, from January 2019 to December 2021. The discriminative power of donor hepatectomy time to predict the outcome was

determined by analyzing <sup>2</sup> receiver operating characteristic (ROC) curves, and patients were divided into two groups: below and above the cutoff.

### ***Research results***

In this multicenter retrospective study involving liver recipients from brain-dead donors, we did not find any evidence of an association between donor hepatectomy time and the development of early allograft dysfunction. Furthermore, our findings indicate that longer hepatectomy times did not affect either graft or patient survival. We believe that the exceptionally short median donor hepatectomy time of <29 minutes in our study, along with the absence of prolonged warm ischemia typical of donors after cardiac death, explains the lack of association between donor hepatectomy time and outcomes in our cohort of brain-dead donors.

### ***Research conclusions***

Donor hepatectomy times did not affect either graft or patient survival

The new methods that this study proposed was to evaluate hepatectomy time in centers where this time is already reduced in relation to other centers already studied

### ***Research perspectives***

While there is a need for policies and interventions to enhance post-transplant outcomes, it appears that the current donor hepatectomy time is already sufficiently short to further mitigate risks. We suggest that future research efforts should focus on exploring alternative strategies other than further reducing donor hepatectomy times.

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SIMILARITY INDEX

PRIMARY SOURCES

1	Nicholas Gilbo, Steffen Fieuws, Nicolas Meurisse, Frederik Nevens et al. "Donor Hepatectomy and Implantation Time Are Associated With Early Complications After Liver Transplantation: A Single-center Retrospective Study", Transplantation, 2020 <small>Crossref</small>	43 words — 1%
2	<a href="http://www.science.gov">www.science.gov</a> <small>Internet</small>	22 words — 1%