



# Early Allograft Dysfunction Increases Hospital Associated Costs After Liver Transplantation—A Propensity Score–Matched Analysis

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Concepts to ameliorate the continued mismatch between demand for liver allografts and supply include the acceptance of allografts that meet extended donor criteria (ECD). ECD grafts are generally associated with an increased rate of complications such as early allograft dysfunction (EAD). The costs of liver transplantation for the health care system with respect to specific risk factors remain unclear and are subject to change. We analyzed 317 liver transplant recipients from 2013 to 2018 for outcome after liver transplantation and hospital costs in a German transplant center. In our study period, 1-year survival after transplantation was 80.1% (95% confidence interval: 75.8%–84.6%) and median hospital stay was 33 days (interquartile range: 24), with mean hospital costs of €115,924 (SD €113,347). There was a positive correlation between costs and laboratory Model for End-Stage Liver Disease score ( $r_s = 0.48$ ,  $P < 0.001$ ), and the development of EAD increased hospital costs by €26,229. ECD grafts were not associated with a higher risk of EAD in our cohort. When adjusting for recipient-associated risk factors such as laboratory Model for End-Stage Liver Disease score, recipient age, and split liver transplantation with propensity score matching, only EAD and cold ischemia increased total costs. **Conclusion:** Our data show that EAD leads to significantly higher hospital costs for liver transplantation, which are primarily attributed to recipient health status. Strategies to reduce the incidence of EAD are needed to control costs in liver transplantation. (*Hepatology Communications* 2021;5:526–537).

**L**iver transplantation remains the treatment of choice for end-stage liver disease and can additionally be a life-saving procedure in patients with hepatocellular malignancies. The continued mismatch of organ supply and demand may pose a problem for the continued application of this procedure.<sup>(1,2)</sup> Optimizing wait-list mortality remains a priority,<sup>(3,4)</sup>

as alternative concepts to ameliorate these discrepancies include, but are not limited to, the expansion of living-donor liver transplantation, donation after cardiac death, and the expansion of the donor pool to grafts from donors that meet extended criteria.<sup>(5,6)</sup>

Extended criteria donors (ECDs) fulfill certain parameters, such as higher age, elevated biochemical

*Abbreviations:* ALT, alanine aminotransferase; AST, aspartate Aminotransferase; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; EAD, early allograft dysfunction; ECD, extended criteria donor; ICU, intensive care unit; IQR, interquartile range; labMELD, laboratory MELD score; LOS, length of hospital stay; MELD, Model for End-Stage Liver Disease.

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laboratory parameters before transplantation, drug abuse, or steatosis hepatitis. The transplantation of such ECD grafts has been associated with an increase in primary nonfunction, early allograft dysfunction (EAD), and higher rates of retransplantation.<sup>(7-10)</sup> The expected temporal trends for higher age and steatosis hepatitis will most likely lead to an increasingly higher proportion of ECD grafts in the donor population in the near future.<sup>(11,12)</sup> Liver transplantation tends to be very resource-demanding, requiring highly specialized staff from different disciplines and on-call complication management if needed. Higher use of ECD grafts will therefore likely incur increased rates of complications. As costs play an essential role in resource management in health care plays, the effect of complications such as EAD on the individual health care departments are of special interest. EAD is not only associated with graft and patient survival after transplantation, but also later complications such as chronic kidney injury, potentially incurring higher costs through the necessity of dialysis.<sup>(7,13)</sup> Previously, studies identified the donor risk index (DRI), graft failure, length of hospital stay (LOS), as well as the recipient Model for End-Stage Liver Disease (MELD) status as cost factors for liver transplantation.<sup>(14-16)</sup>

The aim of this study was to investigate the association of EAD with the costs of the initial hospital stay of liver transplantation. To identify potential contributors to higher cost, we analyzed the effect of donor risk factors such as steatosis hepatitis, liver enzymes, and cold ischemia times, as well as recipient condition before transplant, and studied their interaction with EAD and costs of liver transplantation.<sup>(17)</sup>

## Materials and Methods

### STUDY DESIGN AND PARTICIPANTS

All patients receiving a liver transplantation over a 6-year period between 2013 and 2018 at the Department of Surgery, Charité Campus Mitte | Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Germany, were included in the study. Multi-organ recipients were not included. Patient data were extracted from the individual electronic health record and anonymized; data on organ donors were retrieved from Eurotransplant. All patients were monitored at an intensive care unit (ICU) after transplantation. Follow-up after transplantation was managed at our in-house outpatient clinic; data were equally retrieved. The study was approved by the institutional ethics board (EA1/369/16).

### RISK STRATIFICATION AND COST DATA

Donor data were classified into extended criteria risk factors as proposed by *Eurotransplant*.<sup>(17,18)</sup> These are donor age >65 years, donor body mass index (BMI) > 30 kg/m<sup>2</sup>, ICU stay > 7 days, sodium > 165 mmol/L, macrovesicular steatosis > 40%, aspartate aminotransferase (AST) > 90 U/L, alanine aminotransferase (ALT) > 105 U/L, and bilirubin > 51.3 μmol/l. The DRI was calculated as reported by Feng et al.; no donors in this study sample were of donations after cardiac death.<sup>(19)</sup> EAD was defined by peak ALT and AST values in the first

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7 days after transplantation  $>2,000$  U/L, in addition to bilirubin ( $\geq 170$   $\mu\text{mol/L}$ ) and international normalized ratio at day 7 ( $\geq 1.6$ ), as defined by Olthoff et al.<sup>(20)</sup> Cost data were requested from the medical controlling office and are structured according to the German Institute for the Hospital Remuneration System; they form the basis of payment according to the German diagnosis-related group (DRG) system. The current reimbursement for liver transplantation in Germany is based on preset DRG bundled costs. Quality control is performed through an independent party (Institute for Quality and Transparency in the Healthcare System) without direct financial consequences for each individual case. Costs were calculated from admission date to discharge date. Follow-up outpatient costs were not included. Data are categorized into the responsible department delivering therapy and respectively into personnel costs, medication, medical supply, and infrastructure costs for billing health insurances in Germany. These include the ICU, intermediate care unit, and normal ward of the following departments: nephrology/dialysis, anesthesiology, endoscopy, radiology, surgery, as well as the laboratory. In cases of retransplantation during the same hospital stay, the index transplantation was used for donor and recipient criteria, with costs summed for the entire hospital stay.

## STATISTICAL ANALYSIS

Statistical analysis was performed using the software solutions R (version 4.0.0) and R Studio (version 1.25) for macOS (R Foundation for Statistical Computing, Vienna, Austria)<sup>(21)</sup> Additional required packages for graph plotting and tabular analysis of statistics were ggplot2, ggpubr, ggstatsplot, scales, ggsci, gridExtra, BiocManager, DESeq2, mnormt, plyr, compareGroups, and arsenal. For descriptive statistics, variables were analyzed for normality and compared accordingly using one-way analysis of variance, Kruskal–Wallis test, Student *t* test, or Wilcoxon rank-sum test. Correlation was performed using Spearman's rank correlation coefficient. Categorical variables were compared using the Pearson's chi-squared test.

To account for differences in allocation of extended and nonextended criteria of donor livers to recipients of differing overall health, propensity score matching

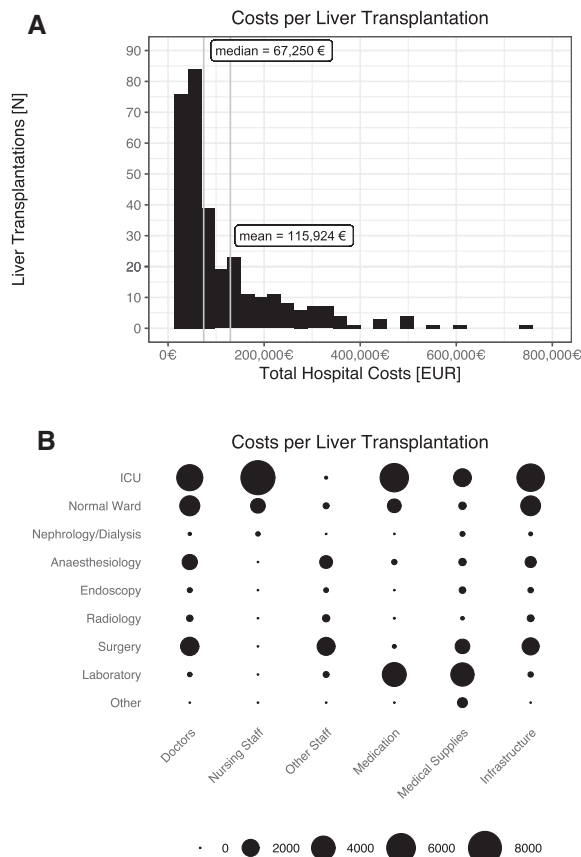
was done using the R software packages Matching and MatchIt. The binomial outcome variable was the transplantation of an extended or nonextended criteria organ. Included in generation of the propensity score were recipient age, BMI, and laboratory MELD score (labMELD). A caliper of 0.05 was tolerated for matching. Of the initial data set of 349 patients, 120 remained in the matched data subset (i.e., 60 per subgroup). Overall, a two-sided *P* value  $< 0.05$  was considered significant. Data are reported as median and interquartile range (IQR) and mean and SD. The currency format is Euro (€), which translates approximately to US \$1.15 in the third quarter of 2020. Yearly inflation in the study period was between 0.5% and 1.8% (2018); therefore, costs are not adjusted for inflation.<sup>(22)</sup>

## Results

### CLINICAL OUTCOME AND COSTS

In the 6-year study period, a total of 364 liver transplantations were performed. Of these, 15 transplantations were not included in the analysis due to overlapping costs in two different cost-calculation years; of the remaining 349 transplantations, 32 were retransplantations, and 4 patients received a third organ during the initial hospital stay. A total of 317 index cases were analyzed in this study. One-year survival after transplantation was 80.1% (95% confidence interval [CI]: 75.8%–84.6%). Median hospital stay was 33 days (IQR: 34), with a mean ICU stay of 10 days (IQR: 23). The mean total hospital costs associated with the transplantation procedure were €115,924 (SD €113,347); the median was €67,250 (IQR €106,070) (Fig. 1A). There were 10 (3.2%) outlier cases above €400,000 in the data set. Overall costs did not show any significant trend over the study period (*P* = 0.5), and most costs (52%) occurred during the ICU stay of the patients, while personnel costs dominated this subgroup (Fig. 1B). Average cost per hospital day was €2,120 (SD €2,382).

Liver transplant recipients were predominantly male (63%) with a median age of 55 years (IQR: 17). The median labMELD, as a surrogate parameter of overall health before transplantation, was 19 (IQR: 17) (Table 1).



**FIG. 1.** Costs per liver transplantation. (A) Histogram of total hospital-associated costs (median and mean costs indicated). (B) Balloon plot of cost per liver transplantation distribution (larger dots equal higher costs). Currency format is EURO (€), which translates approximately to US \$1.15 in the third quarter of 2020.

## COST-ATTRIBUTING FACTORS

Analysis of total hospital costs after liver transplantation revealed ECD donors, donor age, donor BMI, EAD, retransplantation, split transplantation, recipient labMELD, and recipient ICU stay to be major attributing factors (Figs. 2 and 3). Recipients of ECD grafts indeed had a mean reduction in cost of €39,028 ( $P = 0.02$ ). The same was true for livers from elderly donors (€24,521 less;  $P = 0.03$ ) and donors with obesity (€16,094 less in overall hospital costs;  $P = 0.05$ ). The remaining ECD factors had no direct effect. On the recipient side, split liver transplantation ( $P = 0.001$ ) or early retransplantation ( $P < 0.001$ ) was associated with an increase in cost of €33,158 and €143,034, respectively. There was a positive correlation between costs and recipient labMELD ( $r_s = 0.45$ ;

$P < 0.001$ ) as well as costs and the length of ICU stay ( $r_s = 0.8$ ;  $P < 0.001$ ).

## EARLY ALLOGRAFT DYSFUNCTION

During the study period, EAD occurred in 120 cases (38%) and was associated with a reduced 1-year survival rate of 70% (95% CI: 62.3%-78.7%) compared with 86.3% (95% CI: 81.6%-91.2%) in patients without graft EAD ( $P < 0.001$ ) (Table 1). Retransplantation after EAD was three times more frequent and occurred in 21 cases (18%). Development of EAD was associated with higher donor or recipient BMI ( $P = 0.001$  and  $P = 0.03$ , respectively) and higher donor gamma-glutamyl-transferase levels ( $P = 0.03$ ). Additionally, reported donor steatosis was an influence on the development of EAD ( $P = 0.02$ ). Donor cause of death did not differ in between grafts that developed EAD and those that did not. There was no direct association between extended donor criteria and EAD, even when accounting for the number of ECD factors met. The DRI did not differ ( $P = 0.66$ ) and was above 2.3 in either group. Recipient labMELD was not associated with development of EAD ( $P = 0.57$ ); however, CIT was approximately 45 minutes longer in the patient group, which developed EAD ( $P = 0.01$ ).

Development of EAD increased total hospital costs by a mean of €26,229 and a median of €21,845 ( $P = 0.008$ ), which resulted in a cost per day increase by €656. In further subgroup analysis of respective department costs, the largest increase in costs was doctor and nursing staff in the ICU, while ward cost through different categories was significantly lower (Supporting Table S1). Additionally, imaging and subsequent accumulated costs in the Radiology department, as well as costs in the Surgical department (i.e., the operating room) added to the overall cost increase of EAD. Further major factors were medications and medical supplies costs: both with €5,851 ( $P = 0.02$ ) and €4,934 ( $P = 0.03$ ) increase per case of EAD, respectively.

## PROPENSITY SCORE MATCHING FOR EXTENDED DONOR CRITERIA

In univariate analysis, relevant recipient-associated factors such as recipient labMELD, recipient

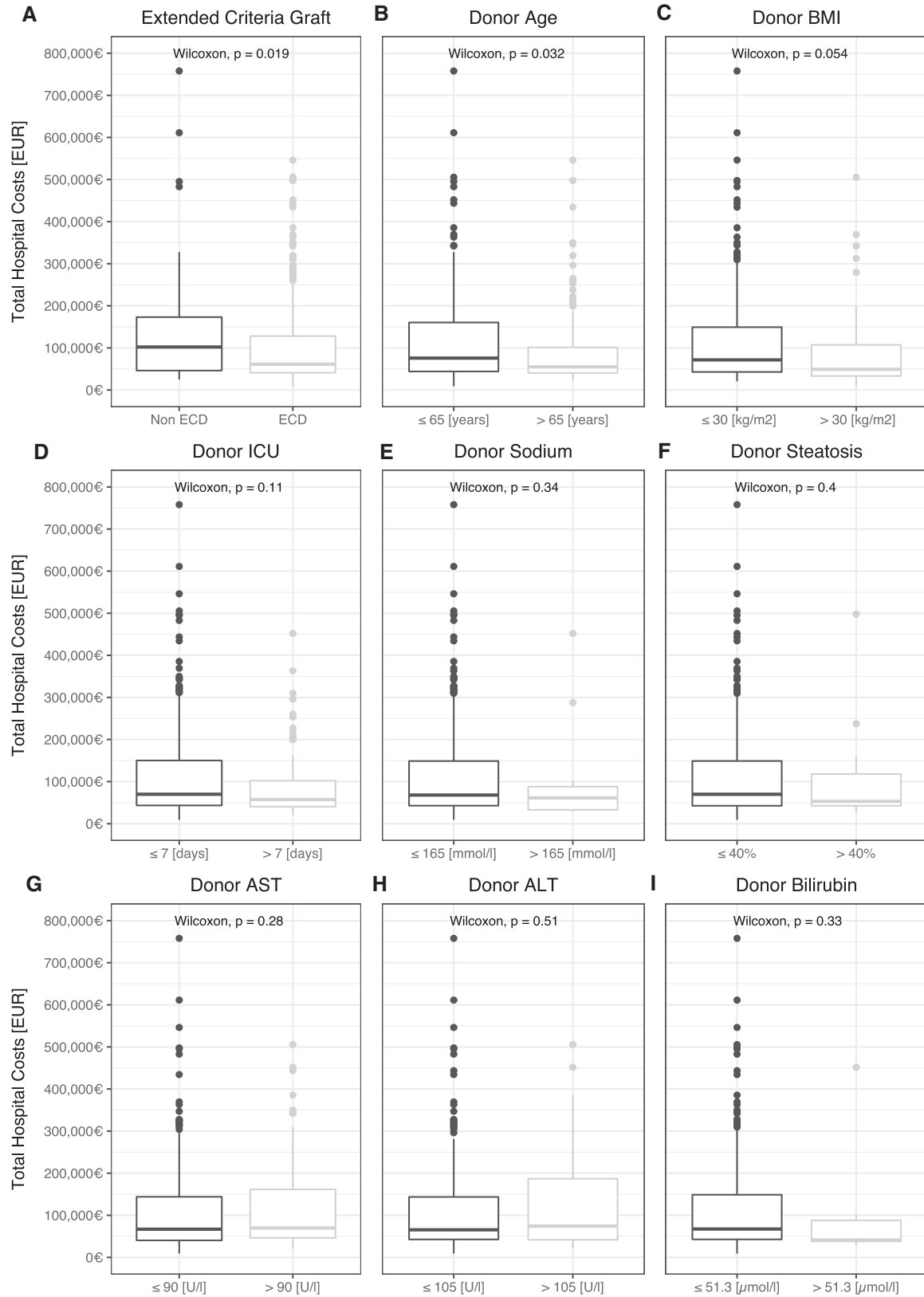
TABLE 1. EARLY ALLOGRAFT DYSFUNCTION

	Early Allograft Dysfunction (n = 120)	No Early Allograft Dysfunction (n = 197)	Total (n = 317)	P Value
Donor age (years)	58 (23)	55 (29)	56 (26)	0.79
Donor BMI (kg/m <sup>2</sup> )	26 (5)	25 (5)	26 (5)	0.001
Donor gender (female)	63 (52.5%)	101 (51.3%)	164 (51.7%)	0.92
Donor ICU (days)	3.5 (6)	4 (5)	4 (5)	0.55
Donor CPR	13 (10.8%)	14 (7.1%)	27 (8.5%)	0.34
Donor sodium (mmol/L)	147 (11)	148 (10)	148 (10)	0.59
Donor AST (U/L)	57 (94)	46 (85)	50.4 (88.2)	0.40
Donor ALT (U/L)	39.3 (59.2)	31.5 (61.8)	36 (62.4)	0.09
Donor GGT (U/L)	58.5 (94)	41.1 (82)	51 (88)	0.03
Donor bilirubin (μmol/L)	9.3 (11)	8.4 (8.6)	8.6 (9.7)	0.17
Donor quick (%)	75 (24)	79 (28)	78 (27.2)	0.13
Donor INR	1.2 (0.26)	1.17 (0.27)	1.17 (0.27)	0.20
Donor steatosis	57 (47.5%)	66 (33.5%)	123 (38.8%)	0.02
Donor cause of death				0.88
Anoxia	20 (16.7%)	32 (16.2%)	52 (16.4%)	
CVA	65 (54.2%)	112 (56.9%)	177 (55.8%)	
Trauma	19 (15.8%)	25 (12.7%)	44 (13.9%)	
Other	16 (13.3%)	28 (14.2%)	44 (13.9%)	
Split transplantation	4 (3.3%)	12 (6.1%)	16 (5.1%)	0.41
Recipient age (years)	56 (13.2)	54 (20)	55 (17)	0.06
Recipient gender (female)	43 (35.8%)	74 (37.6%)	117 (36.9%)	0.85
Recipient BMI (kg/m <sup>2</sup> )*	26.7 (5.59)	25.4 (5.14)	25.9 (5.35)	0.03
Recipient labMELD	17.5 (16.4)	19 (17)	19 (17)	0.57
Recipient CIT (minutes)	603 (235)	558 (147)	571 (173)	0.01
Recipient ICU (days)	13 (31)	9 (20)	10 (23)	0.004
Recipient hospital stay (days)	35 (36)	31 (32)	33 (24)	0.11
ECD factors				0.74
None	28 (23.3%)	48 (24.4%)	76 (24.0%)	
One	41 (34.2%)	79 (40.1%)	120 (37.9%)	
Two	13 (10.8%)	16 (8.12%)	29 (9.15%)	
Three	34 (28.3%)	49 (24.9%)	83 (26.2%)	
Four	4 (3.33%)	5 (2.54%)	9 (2.84%)	
ECD organ	92 (76.7%)	149 (75.6%)	241 (76%)	0.94
Donor age > 65 years	37 (30.8%)	65 (33%)	102 (32.2%)	0.78
BMI > 30 kg/m <sup>2</sup>	19 (15.8%)	18 (9.1%)	37 (11.7%)	0.11
Steatosis hepatitis > 40 (%)	9 (7.5%)	8 (4.1%)	17 (5.4%)	0.29
Donor AST > 90 U/L	37 (30.8%)	62 (31.5%)	99 (31.2)	1
Donor ALT > 105 U/L	24 (20%)	38 (19.3%)	62 (19.6%)	0.99
Donor sodium > 165 mmol/L	5 (4.2%)	6 (3%)	11 (3.5%)	0.83
Donor bilirubin > 51.3 μmol/L	2 (1.7%)	4 (2%)	6 (1.9%)	1
Donor ICU > 7 days	31 (25.8%)	45 (22.8%)	76 (24%)	0.64
DRI	2.45 (0.92)	2.34 (0.83)	2.36 (0.85)	0.66
Retransplantation	21 (17.5%)	7 (3.5%)	28 (9.8%)	<0.001

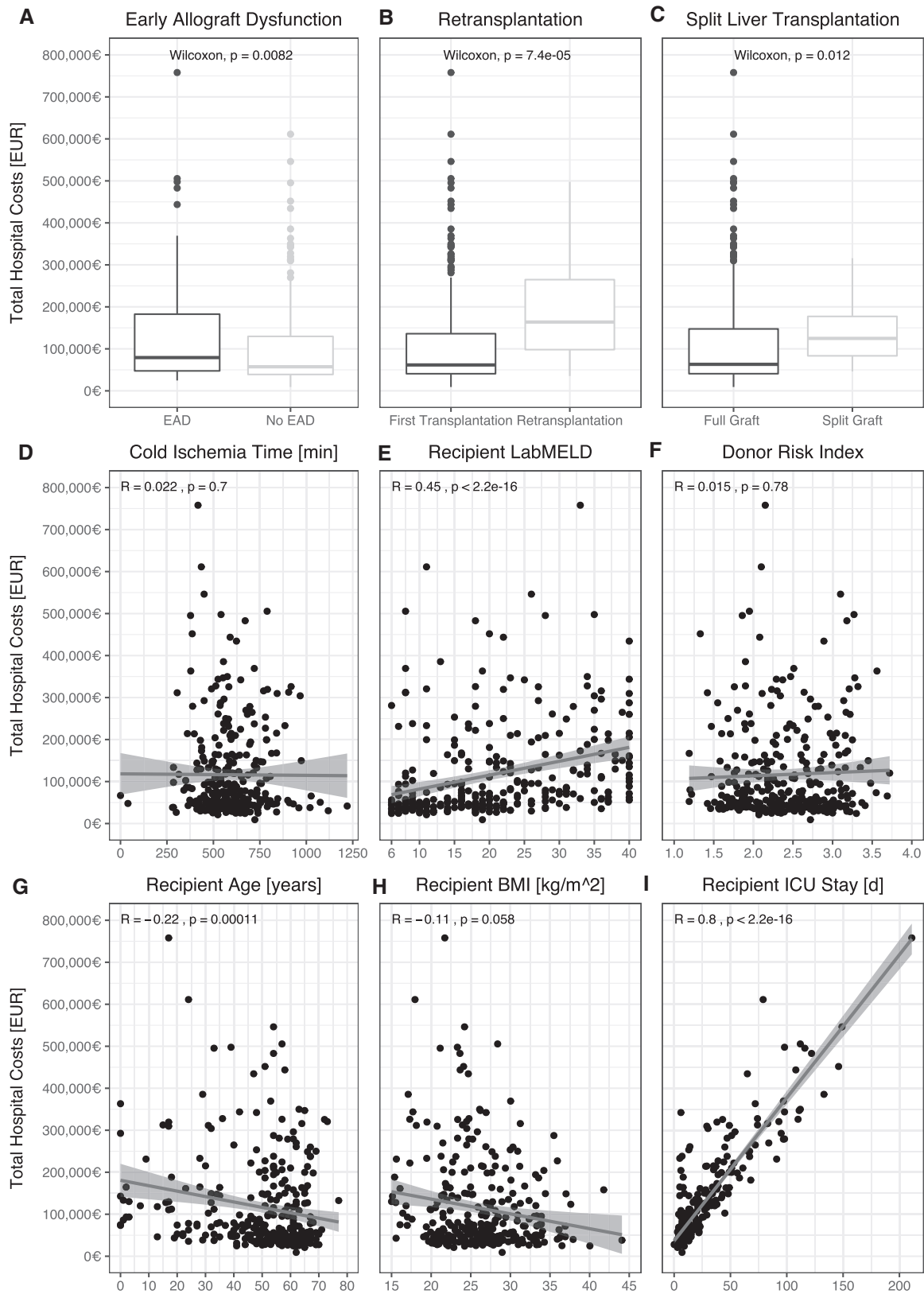
Note: Data are reported as median (IQR). Currency format is EURO (€), which translates approximately to US \$1.15 in the third quarter of 2020.

\*Data are reported as mean (SD).

Abbreviations: CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; GGT, gamma-glutamyltransferase; INR, international normalized ratio.



**FIG. 2.** Donor criteria and total hospital costs. (A-I) Donor risk factors and association with total hospital cost. Currency format is EURO (€), which translates approximately to US \$1.15 in the third quarter of 2020.



**FIG. 3.** Recipient criteria and total hospital costs. (A-I) Recipient risk factors and association with total hospital cost. Currency format is EURO (€), which translates approximately to US \$1.15 in the third quarter of 2020.

age, and BMI affected the development of EAD and therefore the overall cost after liver transplantation. These factors differed in patients receiving ECD or non-ECD liver grafts (Table 2). When adjusting for recipient-associated risk factors such as labMELD, recipient age, split liver transplantation, or recipient BMI with propensity score matching, the effects were no longer significant (Table 3). In the propensity score-matched subgroup, EAD was equally distributed ( $P = 0.83$ ) for ECD and non-ECD graft, and the development of EAD was only associated

with prolonged CIT (665 SD [166 minutes] vs. 562 SD [119 minutes];  $P = 0.002$ ). The DRI was slightly higher at 2.45 (IQR: 0.9) and did not differ between ECD groups.

When analyzing the effect of ECD criteria on costs associated with liver transplantation in the matched subgroup, only donor age over 65 years reduced overall costs ( $P = 0.047$ ) (Fig. 4). The presence of one factor or more than one ECD factor ( $P = 0.8$ ) was neither associated with an increase nor decrease of total hospital costs.

**TABLE 2. EXTENDED CRITERIA GRAFTS**

	Extended Criteria Organ (n = 241)	Nonextended Criteria Organ (n = 76)	Total (n = 317)	PValue
Split transplantation	7 (2.9%)	9 (11.8%)	16 (5.1%)	0.004
Recipient age (years)	55 (14)	52 (30.2)	55 (17)	0.08
Recipient gender (female)	89 (36.9%)	28 (36.8%)	117 (36.9)	1.00
Recipient BMI (kg/m <sup>2</sup> )*	26.5 (5.32)	24 (5.04)	25.9 (5.35)	<0.001
Recipient labMELD	18 (16)	20 (17.5)	19 (17)	0.14
Recipient CIT (minutes)	575 (166)	558 (182)	571 (173)	0.80
Recipient ICU (days)	9 (17)	15 (25.75)	10 (23)	0.04
Recipient hospital stay (days)	33 (28)	35.5 (45.7)	33 (34)	0.30
DRI	2.49 (0.89)	2.17 (0.62)	2.36 (0.85)	0.006
Retransplantation	21 (8.7%)	7 (9.2%)	28 (8.8%)	1.0
Early allograft dysfunction	92 (38.2%)	28 (36.8%)	120 (37.9%)	0.94

Note: Data are reported as median (IQR).

\*Data are reported as mean (SD).

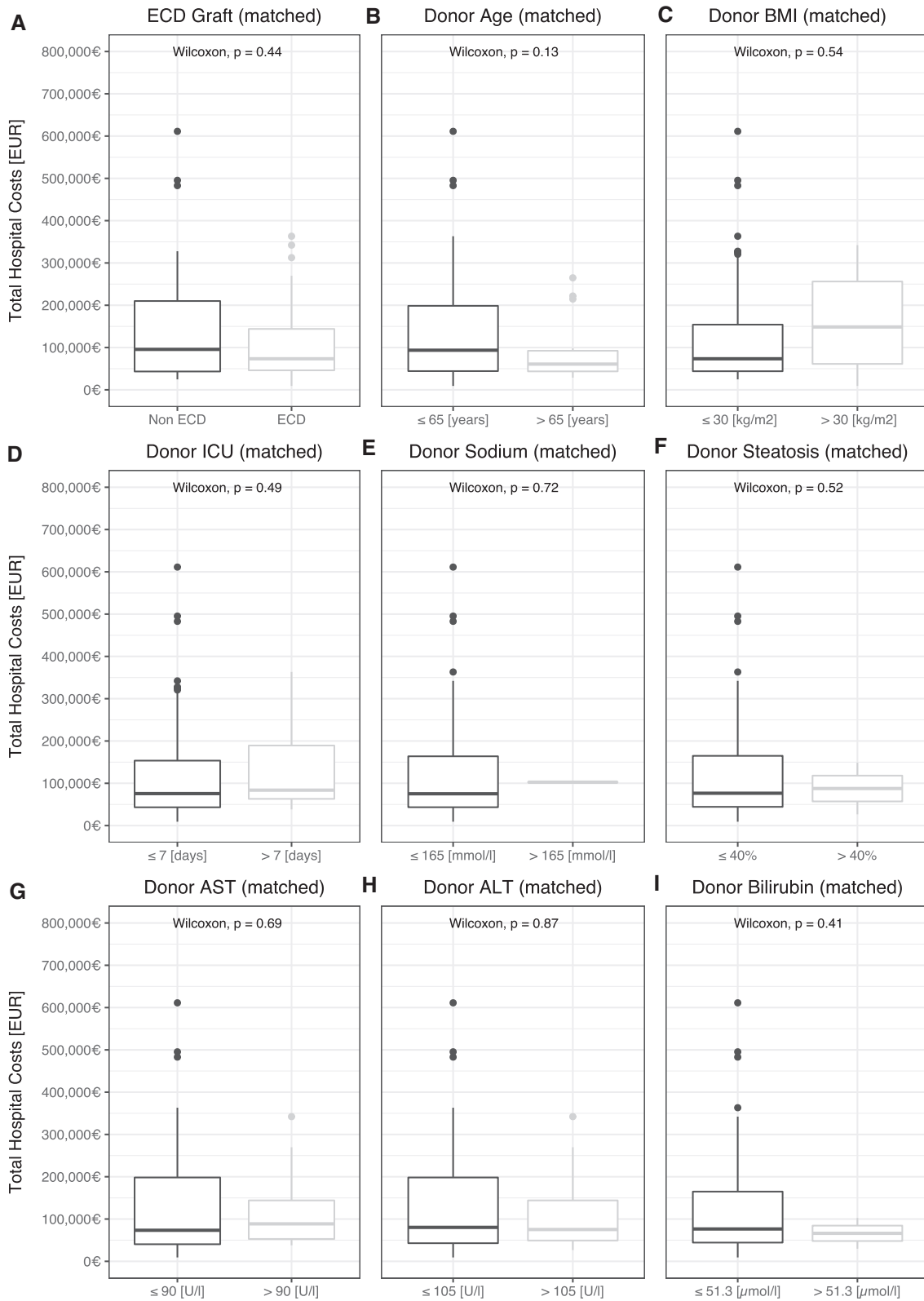
**TABLE 3. EXTENDED CRITERIA GRAFTS AFTER PROPENSITY SCORE MATCHING**

	Extended Criteria Organ (n = 49)	Nonextended Criteria Organ (n = 49)	Total (n = 98)	PValue
Split transplantation	2 (4.1%)	5 (10.2%)	7 (7.1%)	0.44
Recipient age (years)	51 (19)	59 (27)	54 (23)	0.17
Recipient gender (female)	16 (32.7%)	15 (30.6%)	31 (31.6%)	1.00
Recipient BMI (kg/m <sup>2</sup> )	25 (5.2)	25 (5.5)	25 (5.1)	0.68
Recipient labMELD	21 (11)	20 (15)	20.5 (13)	0.35
Recipient CIT (minutes)*	592 (135)	609 (157)	600 (146)	0.56
Recipient ICU (days)	9 (21)	15 (36)	12 (27.5)	0.09
Recipient hospital stay (days)	37 (27)	37 (49)	37 (40.3)	0.96
DRI	2.45 (0.9)	2.22 (0.68)	2.34 (0.82)	0.17
Retransplantation	6 (12.2%)	3 (6.1%)	9 (9.2%)	0.48
Early allograft dysfunction	17 (34.7%)	19 (38.8%)	36 (36.7%)	0.83
Propensity score*	0.26 (0.09)	0.26 (0.09)	0.26 (0.01)	0.88

Note: Data are reported as median (IQR).

\*Data are reported as mean (SD). Included in the generation of the propensity score were recipient age, BMI, and labMELD.





**FIG. 4.** Donor criteria and total hospital costs after propensity score matching. (A-I) Donor risk factors and association with total hospital cost after propensity score matching for recipient risk factors. Currency format is EURO (€), which translates approximately to US \$1.15 in the third quarter of 2020.

## Discussion

The continued mismatch between liver allograft demand and supply has, among other strategies, led to broader acceptance of organs that meet extended donor criteria. As transplantation medicine is especially resource-demanding, we studied how these acceptance policies have affected costs after liver transplantation.

We show in this single-center retrospective study of 317 cases that most costs can be attributed to the recipient health status before liver transplantation. By careful selection of ECD organs, costs of liver transplantation do not increase, even when matching for recipient-associated risk factors. However, the occurrence of EAD had disastrous effects on patient survival, retransplantation rate, and therefore overall costs. Developing EAD is generally associated with ECD or high-risk factors such as prolonged CIT, despite there being no direct effect in our study sample.<sup>(7,13,23)</sup> We assumed a selection bias and possibly limited applicability of ECD criteria, such as higher donor age, for this case. Previous cost-modeling approaches have, however, found similar results.<sup>(24)</sup> Nonetheless, it is clear that the examined donors were overall of high risk, with a median DRI of 2.36 and 228 cases (72%) with a DRI  $\geq 2$ .<sup>(10,14,19)</sup> Additionally, in our patient group, there was a larger number of patients with a high labMELD  $\geq 35$  ( $n = 45$ , 14%), which is an accepted, albeit not perfect, predictor of mortality after liver transplantation, LOS, and disease burden.<sup>(25-27)</sup>

Our propensity score matching tried to address this problem. It is common practice for organs through rescue allocation (i.e., mostly ECD organs) to be transplanted in patients with considerably good remnant liver function (i.e., patients with a hepatocellular carcinoma and low labMELD score). When negating these effects through matching, the total cost of transplantation was still almost double in recipients of non-ECD organs. However, accepting organs for transplantation is always an individual decision, reflected by the surgeon/hepatologist in charge and equally depends on the current health of the recipient, logistical factors in procurement and donor quality. At least from a financial standpoint, our results would suggest that with careful selection, ECD organs are not only feasible for transplantation in times of organ scarcity, but do not affect the total cost of a hospital

stay. Zhang et al. proposed a more aggressive use of ECD grafts after analyzing over 75,000 donors from the United Network for Organ Sharing database.<sup>(28)</sup> However, we would like to highlight that the development of EAD was associated with donor quality and prolonged CIT. In our own center, we could show that macrovesicular steatosis hepatitis, especially in cases with long CIT, leads to EAD in up to 70% of cases.<sup>(29)</sup> The trend of increasing percentage of ECD donors required to be accepted for transplantation therefore comes with a literal price. If the graft does develop an early dysfunction, the associated cost and complications are immense.

Previous publications have highlighted that the DRI is an attributing factor to LOS and that donors with a DRI  $> 2.5$  can lead to increased costs of up to US \$50,000.<sup>(14)</sup> Previous studies from Germany have shown rising costs of liver transplantation since the introduction of labMELD-based allocation as well as increasing costs with increasing MELD score.<sup>(30,31)</sup> The effect of labMELD on costs after liver transplantation has additionally been shown in a cohort of 403 patients in Switzerland, with double the overall costs in a high MELD group.<sup>(16)</sup> Interestingly, health care costs during the waiting time for an allograft appear to be about €9,500 in Germany; patients with a lower MELD score had especially higher costs, due to a longer waiting time.<sup>(31)</sup> Despite there being no time trend in the costs during our limited study period of 6 years, the mean difference in comparison with data from our own center over a decade ago, accounting for inflation, was €54,186.<sup>(15)</sup> This coincides with the introduction of the MELD-based allocation by Eurotransplant in December 2006, and confirms that MELD base allocation has significantly affected costs of liver transplantation.

Allocation policies using labMELD will likely not change in the foreseeable future, and patients with high MELD scores will continue to incur high costs on the health care system if these patients cannot be transplanted earlier. Manageable or preventable effects on graft function and associated costs, however, can be addressed. Our data show that prolonged CIT was most relevant for EAD in our recipient risk factor-matched subgroup. CIT has been linked directly to LOS and prolonged LOS after liver transplantation.<sup>(32)</sup> When considering costs in liver transplantation, priority should be in preventing EAD and consequent retransplantation of patients. With careful matching of donors and

recipients, this can, in part, be avoided. Nevertheless, we show in our propensity score–matched subgroup that CIT remains of utmost relevance to the developments of EAD. Consequently, we propose focusing on methods to reduce CIT and therefore potentially limit the disastrous effect that EAD has on patient and graft survival and, to an extent, the resource-limited liver transplantation field in general.

Future strategies such as bioengineering of autologous liver grafts have previously been proposed as potential methods to broaden the donor pool.<sup>(33)</sup> Other technologies such as *ex vivo* machine perfusion appear, at this time, to be more feasible and readily applicable as a potential evaluation and reconditioning tool.<sup>(34,35)</sup> Studies for renal transplantation have shown hypothermic perfusion to be superior to static cold storage in outcome and costs.<sup>(36,37)</sup> We are not aware of any such comparisons for liver transplantation at time of writing. However, EAD, which is also defined by a peak AST/ALT in the first 7 days, could be reduced by as much as 50% in first clinical trials of normothermic *ex vivo* machine perfusion (NEVLP).<sup>(38)</sup> Controlled oxygenated rewarming before transplantation yielded equal results,<sup>(39)</sup> and a combination of hypothermic and normothermic machine perfusion showed a reduction in ischemia reperfusion injury.<sup>(40)</sup> Furthermore, there is current research on potential manipulation of the lipid metabolism (i.e. defatting of grafts) through NEVLP.<sup>(41)</sup> *Ex vivo* machine perfusion could therefore be a valuable tool for careful organ selection and optimization before transplantation. However, at this time, no specific approach has been unilaterally agreed upon concerning perfusion temperature, stage in allocation procedure, or perfusate substance.<sup>(42)</sup> Considering the potential benefit of reducing EAD and therefore improving cost effectiveness does seem promising. Moreover, the additional costs of liver machine perfusion might be worth the potential for cost reduction by lowering the incidence of EAD.

Our data are limited by the single-center, retrospective study design as well as the relatively high proportion of high DRI grafts transplanted, long median LOS, and lower 1-year survival rate compared with most transplant centers in North America.<sup>(43)</sup> Additionally, absolute costs described here may not reflect costs in other countries outside the European Union, where labor costs could be lower or higher. Nonetheless, the relative effects we show are, in

our opinion, of utmost relevance for the transplant community, especially in low donation countries. Furthermore, our detailed cost structure for each liver transplantation enables a detailed comparison of individual cost-driving factors and adds valuable insight for liver transplantation.

In conclusion, we show that EAD leads to significantly higher hospital costs for liver transplantation. While ECD criteria do not directly affect the total hospital costs of liver transplantation, costs can be attributed primarily to recipient health status as measured in the labMELD, and CIT as the most important donor risk factor. Because the MELD-based allocation system will not change in the foreseeable future, we propose, not only from a financial standpoint, to focus on reduction of EAD and CIT, potentially by using liver-preservation technologies such as *ex vivo* machine perfusion.

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