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Research Article

Factors Associated with Major Complications at 90-Days after Liver Transplantation

Antoni Sabate[1*], Marta Caballero[1], Rosa Gutierrez[2], Lourdes Pérez[1], Roger Pujol[3], Julia Vidal[3], Judith Penafiel[4], Annabel Blasi[3]

[1]Department of Anesthesiology, University Hospital of Bellvitge, University of Barcelona Health Campus, IDIBELL, Barcelona, Spain

[2]Department of Anesthesiology, University Hospital of Cruces, Bilbao, Spain

[3]Department of Anesthesiology, Clinic Hospital, University of Barcelona Health Campus, IDIBAPS. Barcelona, Spain

[4]Biostatistics Unit (UBiDi), University of Barcelona Health Campus, IDIBELL, Barcelona, Spain

[*]**Corresponding author:** Antoni Sabate, Department of Anesthesiology, University Hospital of Bellvitge, University of Barcelona Health Campus, IDIBELL, Barcelona, Spain

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Abstract

Purpose: Postoperative complications are associated with graft recipient loss or death in Liver Transplantation (LT). We aimed to explore perioperative factors associated with complications at 90 days after LT.

Methods: Secondary analysis of data for 176 patients from a multicenter randomized trial. Main exclusion criteria was patients at low risk for intraoperative transfusion (preoperative Hemoglobin [Hb] concentration >130 g/L). The primary outcome was the incidence of complications defined by a Clavien-Dindo classification of 3 to 5 (CDC 3-5) at 90 days after LT. The secondary outcome was acute kidney injury (AKI). We used a log-binomial regression model to evaluate associations.

Results: Forty-nine patients were classified as CDC 3-5 (27.8%, 95% CI 21.2%-34.5%) Baseline Hb concentration (adjusted relative risk [aRR] 0.79, 95% CI 0.62-1.00), high international normalized ratio of prothrombin time (PT/INR) (aRR 1.62, 95% CI 1.34-1.96), red blood cell (RBC) transfusion >2.5 units (aRR 2.02, 95% CI 1.09-3.73), and surgical time >390 minutes (aRR 2.55, 95% CI 1.25-6.03) were associated with CDC 3-5. AKI occurred in 27 patients (15.34%, 95% CI 10.02%-20.67%). Hb concentration (aRR 0.65, 95% CI 0.42-0.97), MELD score >23 (aRR 1.05 95% CI 1.00-1.09), PT/INR (aRR 2.2, 95% CI 1.77-2.75), and RBC transfusion of >5 units (aRR 2.64, 95% CI 1.16-6.15) were associated with AKI.

Conclusions: Anemia and major coagulation disorders expressed by PT/INR are associated with both AKI and CDC 3-5 grading. RBC transfusion of >2.5 units indicates risk for complications. Given these results, it seems worthwhile to consider the correction of preoperative anemia.

Abbreviations: $A10_{ExTem}$: MCF amplitude at 10 min by ExTem; $A10_{FibTem}$: MCF amplitude at 10 min by FibTem; CIT: Cold Ischemia Time; CRF: case record form; ExTem: Extrinsic Thromboelastometry For Fibrin Tissue Factor Activation; FibTem: Thromboelastometry For Fibrin Tissue Factor Activation And Platelet Inhibition; INR: International Normalized Ratio; IRB: Institutional Review Board; LT: Liver Transplantation; MCF: Maximum Clot Firmness; MELD: Model For End-Stage Liver Disease; NASH: Nonalcoholic Steatohepatitis; PT: Prothrombin Time

PT/INR: INR of PT; RBCs: Packed Red Blood Cells; RR/aRR: Unadjusted And Adjusted Relative Risk; UNOS: United Network for Organ Sharing

Keywords: Acute kidney injury; Blood component transfusion; Hemostasis; Liver transplantation; Mean hemoglobin concentration; Morbidity; Mortality

Introduction

Although clear improvements have been made in Liver Transplantation (LT) techniques over time, LT continues to be associated with high risk for postoperative complications, mainly when sicker patients are included in transplantation programs. [1] During the last decade, waiting lists began to incorporate older patients and more overweight and obese patients with nonalcoholic steatohepatitis.[2,3] Consequently, postoperative complications are present in more than half of patients and are associated with higher risk of graft recipient death or graft loss. [4] LT is also associated with a higher financial burden on survivors who do not achieve an optimal outcome. [5] Models combining age, MELD score (Model for End-Stage Liver Disease), and cold ischemia time (CIT) have been reported to predict complications. [6,7] However, the main factors determining risk in these models are high MELD scores and variability in organ allocation. Graft survival was significantly lower in recipients with MELD scores above 35 in one retrospective study, [8] and mortality after redo transplantations was significantly higher in patients with MELD scores over 30 in a prospective cohort. [9] Besides hepatic, coagulation and neurologic complications, lung and kidney failures are also present in patients with high MELD scores, influencing outcomes. [10,11] These patients are outliers in terms of their use of intraoperative resources during LT and Intensive Care Unit (ICU) requirements afterwards; therefore they should be studied separately. In addition, patients with equivalent MELD scores can have divergent post-transplantation outcomes, depending on severity of preoperative organ failure and graft characteristics [1].

Parallel to advances in surgical techniques, critical organ shortages have prompted greater utilization of higher risk grafts, from donors after brain or cardiac death, yet most outcome studies and meta-analyses have looked only at type of donor, without taking into consideration the method of preserving the graft. Normothermic and hypothermic oxygenation perfusion machines are increasingly used in most centers to improve graft viability after procurement, and today these validated methods represent the standard process for liver graft procurements [12-15]. Recently, a score for defining surgical difficulty in LT was published [16]; however, the score is based mostly on patients admitted to an ICU prior to surgery and on a donor risk index, although certain marginal cases with specific technical difficulties (e.g., split livers and non-standard arterial reconstruction) were also included. In another risk study, [17] surgical difficulty (defined by a higher percentile of blood loss and longer surgical time until graft reperfusion) was associated with liver disease decompensations prior to LT. In a recent large, multicenter retrospective series of LT, [18] one-year patient and graft survival rates were significantly lower in patients who required more than six units of packed Red Blood Cells (RBCs) during surgery, an amount considered to be a massive transfusion. Patients receiving such transfusions had a higher incidence of postreperfusion syndrome, possibly contributing to higher mortality in this group. Other than the risk factors identified by these studies on short- and long-term outcomes, certain factors such as perioperative hemodynamic instability, blood component requirements, fluid management, and unexpected technical vascular issues have not been extensively analyzed in prospective series set in the context of today's surgical and donor procurement processes. We aimed to explore all modifiable risk factors (preoperative, intraoperative, or postoperative within 24 hours of surgery) associated with major complications within 90 days after LT in a multicenter series of recipients registered prospectively for a randomized controlled trial of two strategies of fibrinogen correction during LT [19].

Methods

Data from a multicenter, hemoglobin-stratified, randomized controlled trial on fibrinogen administration and blood product requirements by our group [19] were used for a secondary analysis foreseen in the initial protocol. That protocol was approved by the Institutional Review Board (IRB) of the lead hospital (University Hospital of Bellvitge, approval number AC 033/18,) as well as the IRBs of the other participating centers (University Hospital of Cruces and Clinic Hospital of Barcelona). The trial was registered in the European Clinical Trials Database (EudraCT 2018-002510-13,) and at ClinicalTrials.gov (NCT01539057). Patients were enrolled if they gave their written informed consent.

Patients

All adults aged 18 to 80 years old who were scheduled for LT were assessed for eligibility from August 2, 2019, to November 2, 2021. Exclusion criteria were low risk of intraoperative transfusion

(preoperative hemoglobin concentration >130 g/L) or high risk of intraoperative transfusion (patients on aspirin, warfarin, or other anticoagulation therapy, and patients with complete portal vein thrombosis or a known history of thromboembolic events in the last 30 days or bleeding disorders). Also excluded were patients who were undergoing an acute retransplantation, whose indication for LT was familial polyneuropathy, or those who were receiving a graft from living donors given the variability in surgical techniques in those settings. Patients undergoing an emergency LT because of acute liver failure were likewise excluded.

Graft and anesthesia management, surgery, and transfusion protocols

Liver allografts were preserved in University of Wisconsin solution. Organ recovery from controlled cardiac-death donors met the acceptance criteria established by the Spanish Liver Transplantation Society in all centers.[13] Those criteria stipulate normothermic regional perfusion in the recovery of organs from nonliving donors. The anesthesia protocol was monitored to ensure consistency and compliance across all the research centers. Vena cava preservation was attempted in all patients. If exceptionally such preservation was not feasible, a venovenous bypass or a complete caval clamp was used and the decision registered in the patient's electronic case record form. At the end of surgery, all patients remained mechanically ventilated on transfer to a postoperative ICU. The protocols for blood product transfusions were also monitored to ensure consistency and compliance across the three hospitals. Infusion criteria were as follows: RBCs to maintain hemoglobin above 80 g/L, platelet concentrates if a count fell below 30 000/mm^3, and intravenous tranexamic acid boluses of 500 mg if fibrinolysis (>15% lysis at 60 minutes) was detected by thromboelastometry for fibrin function (FibTem). Cell saver devices were not used. Hemostatic management was also guided by thromboelastometry. In case of massive bleeding (>150 mL/min), we monitored maximum clot firmness by extrinsic thromboelastometry amplitude at 10 minutes ($A10_{ExTem}$). If we detected a value of <15 mm or a clotting time >300 seconds by FibTem, we simultaneously transfused 4 units of RBCs, 1 g of tranexamic acid, 2 g of fibrinogen concentrate, 1 unit of apheresis platelets, and 15 mL/kg of fresh frozen plasma.

Primary Outcome, Other Outcomes of Interest, and Risk Factors

The primary outcome was the incidence of a composite of major postoperative complications defined by a Clavien-Dindo Classification [20] of 3 to 5 (CDC 3-5) at 90 days after LT. The main secondary outcome was the specific incidence of acute kidney injury (AKI) classified as grade 2 or 3 according to the guidelines of the Kidney Disease: Improving Global Outcomes) organization. [21] Other secondary outcomes were infectious complications (specifically respiratory infection when pneumonia was diagnosed), abdominal infection with signs of wall or organ/space involvement, and other (bladder or catheter-related infection); a need for mechanical ventilation for more than 24 hours; and prolonged length of hospital stay. Variables considered as possible risk factors included recipient and donor characteristics, intraoperative data related to LT, and anesthetic management. Recipient characteristics were age; sex; body mass index; diabetes mellitus; hypertension; cardiac disease; respiratory disease; indication for LT; MELD score; Child score; hospitalization when LT was scheduled; hemoglobin, creatinine, glomerular filtrate, plasma fibrinogen levels; and the international normalized ratio of prothrombin time (PT/INR); platelet count; and baseline thromboelastometry profile. Donor characteristics were type of donor (after brain or cardiac death), donor age, and CIT. Intraoperative data were surgical time; warm ischemia time; infusions of blood components, fibrinogen concentrate, tranexamic acid, crystalloids, and albumin; and the development of postreperfusion syndrome.

During LT and in the following 90 days, we recorded the incidence of intra- and postoperative thrombotic events in the graft or legs (assessed by Doppler ultrasound), and in the lung (assessed by computed tomography). Reoperations for any cause and retransplantations were also recorded. The following specific adverse events were registered: cardiac arrest, cardiac arrhythmia, pneumothorax, hepatic artery and portal vein anastomosis reconstruction, biliary reconstruction and reoperation for bleeding, and actuarial graft and patient survival rates.

All adverse events were recorded in the patient's electronic case record form, and the principal investigator (A.S.) was notified immediately. The data monitoring committee also reviewed all adverse events, and an annual safety report was sent to the Spanish Agency for Medicines and Medical Products and the IRBs that approved the protocol.

Statistical Analysis

Descriptive statistics for patients and surgeries were expressed as means (SD) for discrete variables and medians (interquartile range [IQR] or range) for continuous variables. Categorical variables were expressed as numbers of cases and percentages. Statistics related to actuarial graft and patient survival were also compiled. We used a log-binomial regression model to evaluate the associations between the risk factors and CDC 3-5 status. Associations between variables and AKI were also estimated. Risk was adjusted for age, sex, and MELD score based on their positive associations with the dependent outcome variables in most of the predictive models, indicating that these variables had substantial effects on associations between other modifiable variables and the outcome of interest. Relative risk

(RR) and adjusted RR (aRR) and 95% CIs were also calculated. Regression coefficients, standard errors and any constants were calculated for inclusion in supplementary data. All analyses were performed with the statistical software package R, version 4.1.0 for Windows (http://www.R-project.org, The R Foundation).

Data access statement: The protocol, informed consent sheets, statistical analysis plan, CRFs and datasets are stored by the IRB of the lead hospital and the IDIBELL Foundation.

The work has been reported in line with the STROBE Statement.

Results

A total of 306 LTs were performed during the period of analysis, and 93 of the operated patients were excluded because their hemoglobin indicated they would be at low risk for transfusion (>130 g/L). Thirty-one patients were excluded for other reasons listed above. A total of 182 patients were enrolled in the trial. [19] After 6 procedures were cancelled, 176 patients were finally included in the analysis. The primary composite outcome of major postoperative complications indicated by CDC 3-5 status was present in 49 patients (27.8%, 95% CI, 21.2%-34.5%). Twenty-two patients required reintervention, 11 of them for postoperative bleeding, three for biliary complications, 6 for organ/space infection, and one for vascular thrombosis; one required a redo LT within 90 days of the first. Thrombotic complications (hepatic artery, portal vein, and other systemic thromboses) developed in 8 patients. Infective complications that required specific treatment occurred in 21 patients; 8 of these patients had pneumonia, 6 had abdominal organ/space infections, and 7 had catheter infections. Two pneumothoraxes occurred related to central venous line placement. Four patients required cardioversion for arrhythmias. The median (IQR) length of hospital stay in the full cohort was 15 days (11-27 days), and 27 patients (15.3%) required mechanical ventilation for more than 24 hours. Four patients died within 90 days of the LT; another patient died after 90 days but during hospitalization for the surgery and was therefore classified as CDC 5. Later, four patients were readmitted and died within one year of the LT, all of them from multiorgan failure and previously graded CDC 3-5. Two additional patients died after the one-year follow-up period; neither of them experienced CDC 3-5 complications during the trial period.

Patient, donor, and surgical characteristics and blood product requirements were similar for patients in the two CDC grade ranges shown in Table 1. Donor age and transplantation of a graft from a cardiac death donor were also similar in the two CDC grade ranges. Only PT/INR and RBC requirements during LT and up to 24 hours afterwards were significantly associated in the bivariate analysis. RRs and aRRs for CDC 3-5 status are shown in Figure 1. A low baseline hemoglobin concentration was associated with this outcome in the bivariate analysis, whereas a concentration over 94.86 g/L conferred protection. That threshold had a sensitivity of 0.65 (95% CI, 0.5-0.78) a specificity of 0.54 (95% CI, 0.44-0.62), a negative predictive value of 0.8 (95% CI, 0.7-0.88), and a positive predictive value of 0.35 (95% CI, 0.25-0.46). High PT/INR values were associated with CDC 3-5 status. Intraoperative RBC transfusion volume during LT and up to 24 hours afterwards was likewise associated with these major complications, and the association was strongest in the higher quartiles (> 2.5 units): aRR 2.02 (95% CI, 1.09-3.73). A surgical time >390 minutes was also associated with CDC 3-5 grading. However, we found no associations between CDC 3-5 and CIT, intra- and postoperative fluid administration, reperfusion syndrome, tranexamic acid infusion, donor type or age, warm ischemia time, or initial patient diagnoses. AKI occurred in 27 patients (15.34%, 95% CI, 10.02%-20.67%), and renal replacement therapy was required by 4 patients (2.27%). Body mass index was higher in AKI patients (mean [SD] 29.8 [4.01] kg/m^2 vs. 26.8 [4.66] kg/m^2, p=0.001), and the MELD score was also higher (median [IQR] 21 [15-25-5] vs. 18 [13-22], p= 0.039). RRs and aRRs for AKI are shown in Figure 2. Higher median baseline hemoglobin concentrations, baseline platelet counts, and higher baseline A10 ExTem values protected against AKI. In contrast, a MELD score higher than 23, a higher baseline PT/INR, and plasma sodium levels at the high end of the normal range were associated with risk for AKI. RBC transfusion of ≥5 units was likewise associated with AKI. On the other hand, baseline plasma creatinine concentration, age and type of donor, and tranexamic acid infusion were not associated with risk. Reperfusion syndrome occurred in 17 patients with AKI (63% of the 27 patients with that complication) and 65 patients without AKI (43.6% of 149 patients). This difference, however, did not reach statistical significance (p= 0.1 and aRR 1.95, (95% CI 0.96-4.19).

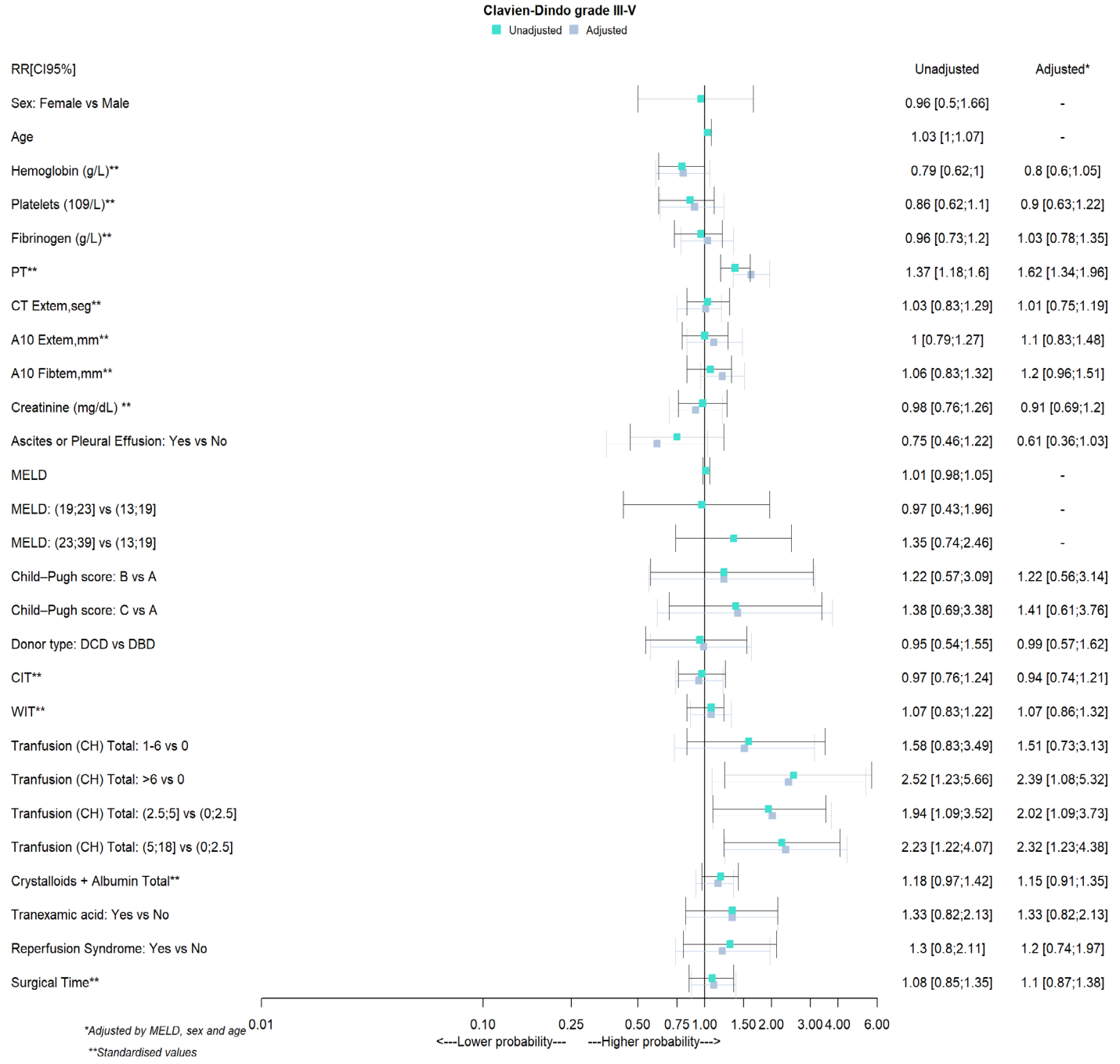

Figure 1: RRs and aRRs for CDC 3-5 status.

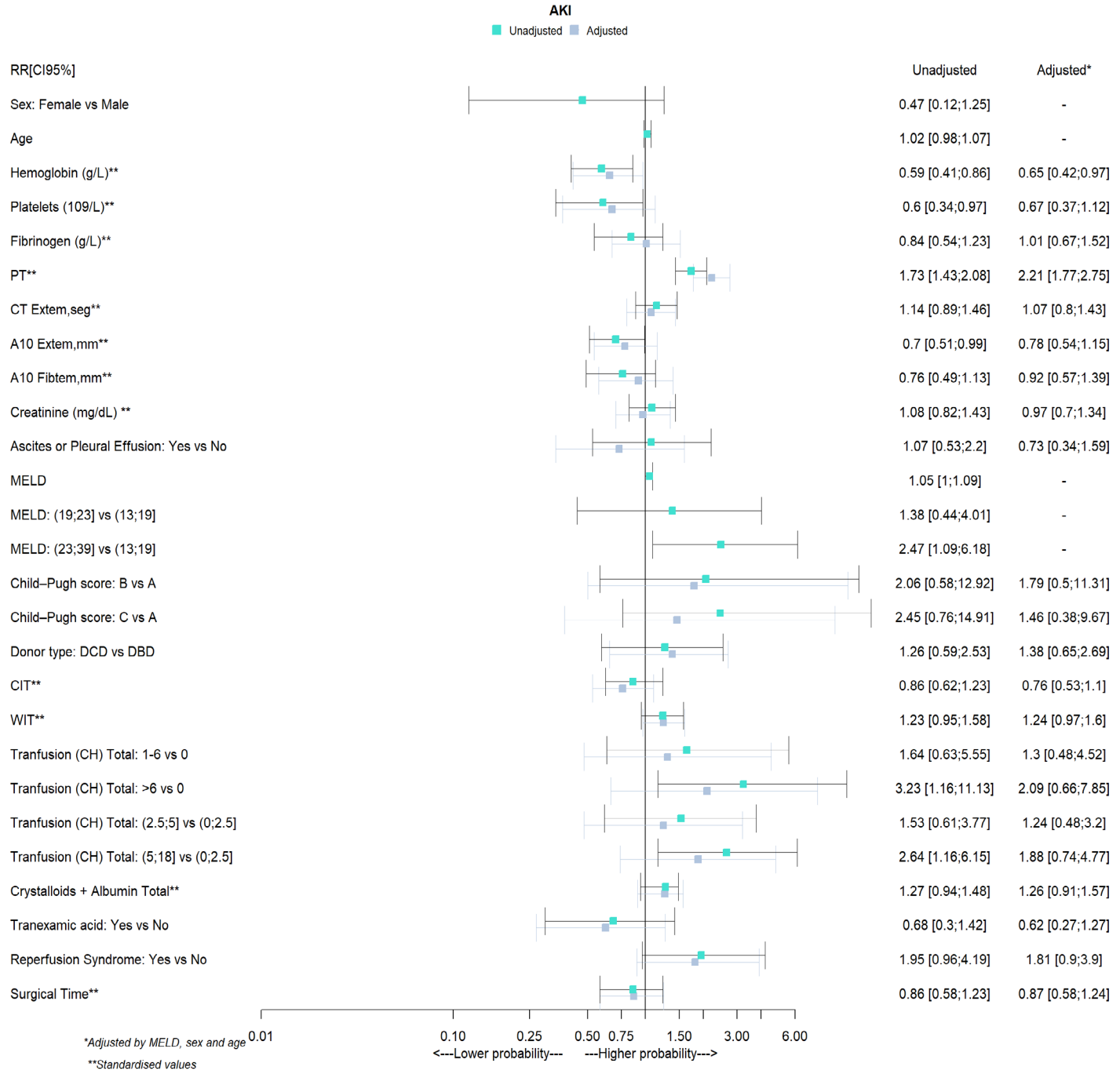

Figure 2: RRs and aRRs for AKI.

Variables	**Patients**		
	All (n=176, 100.%)	**CDC grade, 3-5 (n= 49, 27.8.%)**	**CDC grade, 0-2 (n=127, 72.2%)**
Patient characteristics			
Age (years)†	59.0 (55.0-64.2)	61.0 (56.0-65.0)	59.0 (53.0-64.0)
Male	79%	79.6%	78.7%
Female	21%	20.4%	21.3%
Weight (kg)*	78.2 (15.0)	79.64 (14.67)	77.61 (15.20)
Height (cm)*	169 (8.92)	168.88 (8.71)	169.39 (9.04)
BMI ($kg \cdot m^2$)*	27.3 (4.68)	27.88 (4.36)	27.02 (4.80)
Diagnoses, preoperative data			
Indications for LT			
Alcoholic cirrhosis	58%	55%	59%
NASH	9.06%	10.2%	8.66%
Hepatocarcinoma	9·66%	8.16%	10.3%
Biliary cirrhosis	7.39%	8.16%	7.0%
Other	15.89%	18.84%	15.04%
Prior abdominal surgery	32.4%	42.86%	28.35%
Diabetes	33%	38.78%	30.71%
Partial portal thrombosis	6.82%	4.08%	7.87%
Abnormal echocardiogram	16.5%	12.24%	18.11%
Pulmonary disease	17.6%	16.32%	18.11%
Ascites/pleural effusion	54%	46.93%	56.69%
Preoperative kidney dysfunction	26.1%	22.45%	27.56%
Sodium (mEq/L)†	136 (131-139)	136 (131-140)	136 (131-139)
Creatinine (mg/dL)†	0.94 (0.76-1.22)	0.98 (0.76-1.26)	0.94 (0.75-1.22)
MELD score†	19.0 (13.0-23.0)	19.0 (14-24)	19.0 (13-22.5)
Child–Pugh score			
A	15.5%	12.25%	16.53%
B	33.9%	32.65%	35.4%
C	50.6%	55.1%	48.03%

Location on UNOS classification At home On ward ICU	56.25% 34.09% 9.66%	59.18% 34.69% 6.12%	55.12% 33.86% 11.02%
Hemoglobin (g/L)†	93 (84-108)	89.0 (84-104)	96.0 (84-110)
Platelet count (10^3/mm^3)†	74·0 (52·5 -101)	66.5 (47.2-101)	75.0 (53.5-101)
PT (sec)†	1·20 (1·06-1·36)	1.21 (1.01-1.41)	1.20 (1.06-1.35)
PT/INR†	1·55 (1·33-1·81)	1.62 (1.41-2.08)	1.54 (1.30-1.77)
Fibrinogen (g/L)†	2·00 (1·31-3·0)	2.00 (1.44-2.799	2.00 (1.30-3.07)
ExTem†			
Coagulation time (s)	65 (59-75)	64 (59-74.8)	65 (60-75)
MCF (mm)	51 (43-60)	52 (43.8-60.2)	50 (42.5-59.5)
Lysis (%)	0 (0-0)	0 (0-0)	0 (0-0)
A10 FibTem MCF (mm)	11 (6-16)	12 (7-16)	10 (6-15.8)
Donor type			
Brain death	68.2%	69.4%	67.72%
Cardiac death	31.8%	30.6%	32.28%
Donor age (years)*	59 (18-84)	58 (25-84)	60 (18-78)
Length of surgery (min)†	380 (302-1422)	435 (330-1420)	380 (295-1448)
Cold ischemia time (min)†	374 (284-445)	357 (272-445)	380 (287-444)
Warm ischemia time (min)†	37.0 (26.8-52.0)	35 (26-52)	40 (27-52)
Reperfusion syndrome	46.6%	53%	44%
Transfusion during LT			
RBC (units) †	2 (0-4)	3 (1-5)	1 (0-3)
Patient RBC needs, by volume			
0 units	33.5%	24.48%	37%
1-6 units	57.4%	65.3%	54.33%
>6 units	9.09%	10.2%	8.66%
Fresh frozen plasma	12.50%	16.33%	11.02%
Apheresis platelets	13.64%)	20.41%	11.02%
Tranexamic acid administration	39.2%	44.9%	35.5%
Crystalloids (ml)†	2280 (1228-3424)	2300 (1600-3583)	2100 (1200-3242.75)
Albumin	67.43%	61.22%	69.84%

Total transfusion during LT and 24 h after			
RBC (units)†	2.5 (0-5)	4 (2-7)	2 (0-4)
Patient RBC needs, by volume			
0 units	26.1%	16.3%	29.9%
1-6 units	55.7%	55.1%	55.9%
>6 units	18.2%	28.57%	14.17%
Fluid therapy including albumin (mL)†	5234 (4153-7184)	5511 (4125-8400)	5184 (4153-6766)

Data are percentages of patients, unless otherwise indicated as mean (SD)*, or median (interquartile range)†, or median (range)‡. Donor age expressed as median and range. ExTem , extrinsic thromboelastometry for fibrin tissue factor activation; FibTem=thromboelastometry for fibrin tissue factor activation and platelet inhibition; ICU, intensive care unit; MCF, maxim clot firmness; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PT, prothrombin time; PT/INR, international normalized ratio of PT; UNOS, United Network for Organ Sharing.

Table 1: Patient characteristics and surgical data.

Discussion

Because 90-day mortality was low (2.8.%) in our patients at intermediate risk for complications enrolled in the trial, [19] we chose CDC 3-5 status as the primary outcome, as that grading system includes mortality. The incidences of this outcome (27.8%) and AKI (15.34%), the main secondary outcome, were similar to findings in other series [4,14,21,22] and gave us sufficient data to explore relative risk. Both CDC 3-5 grades and AKI were associated with a low baseline hemoglobin concentration (<95 g/L). Thus, our findings confirm the relevance of preoperative anemia, consistent with two retrospective series in which anemia was linked to major complications and 90-day and one-year mortality. [23,24] Both series applied the World Health Organization's criteria for anemia (e.g., <130 g/L for men). [25] However, we excluded all patients with hemoglobin levels above that mark because we sought to identify the critical level associated with complications. Our entire cohort was at least at intermediate risk for transfusion, with a median hemoglobin concentration of 93 g/L, allowing us to identify 95 g/L as the cut-point at which patients might benefit from a preoperative optimization strategy. Hemoglobin optimization in patients with liver disease is clinically challenging, [26] but we concur with others who suggest that it merits further consideration. [27] Our findings suggest a starting point for testing the feasibility of strategies before possibly moving on to a randomized trial.

Likewise, both CDC 3-5 status and AKI were associated with high PT/INR values, but with none of the variables derived from ExTem or FibTem. Those findings indicate that a major deficit of liver-produced coagulation factors is influencing the development of complications, and that PT/INR is more sensitive than the thromboelastometry data. So far, however, efforts to improve baseline hemostasis and coagulation before LT by preventive administration of coagulation factors has been considered contraindicated based on consensus, [28] and our group recently showed it offered no benefit in a randomized trial. [19] Longer duration of surgery and RBC requirements were associated only with CDC 3-5 status, confirming previous studies on surgical difficulty. [16,17] Diagnoses leading to LT, comorbidities, CIT, and thromboelastometry readings during LT, however, did not emerge as risk factors for either the primary or secondary outcomes. Nor were donor type or age risk factors for the primary outcome; this is unsurprising given that normothermic and hypothermic oxygenation perfusion machines currently improve graft viability after procurement. [12-15] AKI was associated with both MELD score and body mass index in our prospective cohort, consistent with findings from a retrospective study. [29] Preoperative plasma sodium level in the upper range of normal was associated with AKI, an observation that is consistent with the findings of another retrospective series. [30] Sodium concentration may reflect systemic vascular filling status, influenced by the use of diuretic drugs, which lead to higher sodium values. [31] In contrast, creatinine level and preoperative ascites were not associated with AKI. The prevalence of hepatorenal syndrome in LT candidates is currently low, related to early albumin replacement in patients with ascites; this treatment is also recommended during LT [32].

Intraoperative variables associated with AKI in the unadjusted analysis were mainly recorded during graft reperfusion (e.g., the occurrence of reperfusion syndrome and massive bleeding requiring tranexamic acid); however, after adjustment for the MELD score, the association was not significant. The

importance of such intraoperative events has been reported in a large systematic review of modifiable risk factors for AKI. [31] A small patient sample size, the main limitation of this study, was related to the necessary exclusions during the trial. [19] From all the LT procedures in the three hospitals during the trial period, we excluded 31 (around 10% of the 306 LTs performed during the period of the trial) because the patients presented acute-on-chronic liver failure or were on coagulation therapies. Five of these excluded patients died (16.1%), due to acute decompensation related to neurologic, respiratory, and kidney failure already present before LT. The relevance of such complications are the main causes of mortality, depending on the grade of liver failure. [33] We also excluded 93 patients with hemoglobin levels >130 g/L, who were at low risk for transfusion and complications. In these excluded patients, 90-day mortality was 2.15%, and the two deaths were related to donor graft viability and major surgical events. With these exclusions of both high- and low-risk patients, our cohort represented patients at intermediate risk. Such patients account for the majority of those waiting for liver grafts in European registries, where the mean MELD score is 18.7 and only 10% are classified as urgent. [34,35] Strengths of the study are the participation of three high-volume LT hospitals, on-time compliance with the short patient recruitment period in spite of the SARS-CoV-2 pandemic, prospective data collection, high adherence to protocols, and the monitoring of data quality by an independent committee. We conclude that major coagulation disorders expressed by a high PT/INR plus preoperative anemia and the volume of RBCs transfused are the factors that influence major complications as reflected in CDC 3-5 status and the development of AKI after LT. We hypothesize that in spite of the challenges of correcting preoperative anemia, intravenous iron infusion in patients on waiting lists may be feasible. If so, blood component consumption could possibly be reduced and improved outcomes could possibly be demonstrated in a randomized controlled trial.

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This trial was registered in the European Clinical Trials Database (EudraCT 2018-002510-13,) and ClinicalTrials.gov (NCT01539057).

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