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Predictors of perioperative morbidity and mortality in adult living donor liver transplantations: report of results of a tertiary hospital

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Abstract

Background: The aim of this study was to investigate the risk factors effective in perioperative morbidity and mortality in 161 living donor liver transplantations (LDLT).

Results: The most common indication for living donor transplantation was cryptogenic cirrhosis. The most common complication was biliary problems in 62.16% cases. Sepsis was the most common cause of in 52%. Patients in whom sepsis was observed, significantly prolonged stay under mechanical ventilation and prolonged ICU stay were detected. In patient group in whom mortality was observed, higher amounts of erythrocytes, fresh frozen plasma (FFP), and platelets were transfused, and patients remained longer under mechanical ventilation treatment, and in the ICU.

Conclusion: Perioperative morbidity and mortality was found to be significantly related with higher amounts of erythrocytes and FFP transfusions and longer operative and warm ischemia times. Sepsis was found to be the most common cause of mortality.

Keywords: Liver, Living donor transplantation, Mortality

Background

Liver transplantation, starting from cadaveric donors in 1967, has become a successfully performed surgery for the treatment of end-stage liver disease (ESLD) patients in many countries. The developments in surgical techniques, postoperative care, and immunosuppressive pharmacy improved the outcomes of transplantation patients (Meirelles Júnior et al., 2015). Restricted number of cadaveric organs available for transplantation creates difficulties in the realization of transplantation in early-stage liver failure disease. The disease progresses in most of the waiting patients, and long-term survival rates of these patients with advanced stage disease are much worse

(Farkas et al., 2014). Thus, living donor liver transplantation (LDLT) is the most appropriate treatment alternative for the achievement of excellent long-term survival rates. When compared with major surgical interventions as liver resection and pancreatectomy, inevitably liver failure patients with preoperatively worse general health state had relatively higher peri- and postoperative mortality rates related to liver transplantation (Song et al., 2014). In this study, risk factors effective in perioperative morbidity and mortality in living donor liver transplantations in our center have been reported.

Methods
Study design
The retrospective cohort study has been conducted by the principles of the Helsinki Declaration and approved by the local Institutional Review Board (IRB No. 10840098-

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Hizarci *et al. Ain-Shams Journal of Anesthesiology*   (2020) 12:60

Page 2 of 6

604.01.01-e.5613). Between April 2014 and October 2017, liver transplantation was performed for 161 (18–71 years old) patients in our center. Data of all patients were retrospectively analyzed. The accepted definition of the "perioperative period" was "the duration of operation and postoperative first three months". The term morbidity included biliary complications, bleeding, small for size syndrome, incisional hernia, infectious diseases including sepsis, and other minor complications.

Outcome parameters

Regarding potential factors effective on perioperative morbidity, sepsis, and mortality, demographic data and body mass indices (BMIs) of the patients and donors, donor relationship, recipient's blood group, Child-Turcotte-Pugh scores, MELD (Model for End-Stage Liver Disease) scores, graft volume, the ratio between graft and body weight (GW/BW), cold and warm ischemia times, transfused erythrocyte, fresh frozen plasma (FFP), and platelet packs and durations of surgeries were accepted as outcome parameters. Immunosuppressive treatment after liver transplantation consists of calcineurin inhibitors, and methylprednisolone, and additionally mycophenolate mofetil or mycophenolic acid. Changes in doses or contents were individualized based on the clinical course of the disease. During post-transplantation period, the patients were followed up at least once a month for the first year, at 3-month intervals between the second, and fourth years, and yearly after the 5th postoperative year. During the follow-up period, all patients were examined using standard research program for liver transplantation including routine blood tests, virologic tests, hepatic Doppler ultrasound, computed tomographic angiography, portal reconstruction of the liver, pulmonary function tests, and cardiac examinations (Guler et al., 2013).

Statistical analyses

Data were analyzed using the IBM Statistical Package for Social Sciences v20 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using Kolmogorov-Smirnov test. Independent-samples t test was applied to data of normal distribution and Mann-Whitney U test was applied to data of questionably normal distribution. The distribution of categorical variables in both groups was compared using Pearson chi-square test. Data are expressed as the mean ± standard deviation (SD) or median (interquartile range), as appropriate. Continuous variables were analyzed using Spearman correlation coefficient. All differences associated with a chance probability of .05 or less were considered statistically significant.

Results

Of the 161 adult LDLT patients, 93 (57.8%) were males and 68 (42.2%) were females. Etiologic factors of ESLD

were diagnosed as cryptogenic cirrhosis ($n = 35$), hepatocellular carcinoma ($n = 23$), hepatitis B or delta hepatitis cirrhosis ($n = 20$), hepatitis C cirrhosis ($n = 12$), fulminant hepatitis ($n = 12$), autoimmune disease ($n = 9$), alcoholic cirrhosis ($n = 8$), primary biliary cirrhosis or primary sclerosing cholangitis ($n = 7$), and other liver diseases ($n = 35$), respectively.

Basic preoperative data of the recipients and donors were presented in Table 1. Clinical data during the intra and early postoperative phases were found to be significantly related to morbidity and mortality ratios (Table 2). Perioperative morbidity was seen in 74 patients (45.9%). The most common complications were biliary problems, which were observed in 46 (28.5%) of all the cases (Table 3). Of these 46 complications; 22 (47.83%) were biliary anastomotic strictures, 15 (32.61%) were biliary non-anastomotic strictures, and 9 (19.56%) were bile leakage. Biliary complications were followed by postoperative bleeding in 10 patients (6.2%), gastrointestinal bleeding in 5 patients (3.1%), and small for size syndrome in 4 (2.4%) patients. Sepsis was seen in 41 patients (25.4%). Mortality was seen 25 patients (15.5%). Table 4 indicates the mortality data for the study group. Sepsis was the most common cause of mortality and responsible for 13/25 (52%) deaths. There was no life-threatening complications and mortality in donors.

A significant difference was found between patient groups with, and without observed perioperative morbidity as for intergroup gender distribution ($p < .05$). Perioperative morbidity was significantly less frequently

Table 1 Characteristics of the recipients and donors

		Mean ± SD (range)
Recipient age (years)		42.3 ± 21.38 (18–71)
Recipient BMI (kg/m²)		26.16 ± 6.54 (19–45.6)
Recipient blood group: *n* (%)	0	50 (31.1)
	A	63 (39.1)
	B	37 (23)
	AB	11 (6.8)
MELD score		16.8 ± 6.97 (6–40)
Child-Turcotte-Pugh score		8.7 ± 2.02 (5–15)
Donor age (years)		35.4 ± 14.11 (18–65)
Donor gender: *n* (%)	Male	105 (65.2)
	Female	56 (34.8)
Donor BMI (kg/m²)		26.51 ± 3.95 (18.7–35.9)
Donor relationship: *n* (%)	Related	126 (78.3)
	Unrelated	35 (21.7)
Graft volume (grams)		774.90 ± 270.90 (680–1320)
GW/BW		1.49 ± 0.80 (0.53–5.00)

SD standard deviation, *BMI* body mass index, *GW/BW* the ratio between graft and body weight

Table 2 Clinical data during the intra and early postoperative phases

	Mean ± SD (range)	p
Cold ischemia time (minutes)	29.9 ± 14.41 (5–65)	> 0.05
Warm ischemia time (minutes)	39.3 ± 14.36 (13–121)	0.016*
Duration of surgery (hours)	7.5 ± 1.50 (6–14)	0.006*
Erythrocyte transfusions (units)	2.7 ± 3.04 (0–21)	0.01*
Fresh frozen plasma transfusions (units)	7.8 ± 5.78 (0–22)	0.037*
Platelet transfusions (units)	0.7 ± 1.27 (0–6)	0.009*
Duration of mechanical ventilation (days)	0.8 ± 1.61 (0–14)	0.001*
Duration of ICU stay (days)	2.2 ± 2.32 (0–21)	0.014*
Duration of hospitalization (days)	13.7 ± 9.44 (0–58)	0.011*

SD standard deviation, *ICU* intensive care unit; *$p < 0.05$

seen when female donors were preferred (32.1% vs. 67.9%). A significant difference was found between patients groups with and without sepsis with respect to the distribution of blood type, and Rh group of the recipients ($p < .05$). Sepsis was observed in less than 25% of recipients with blood groups 0 and A, while it was observed in around 40% of the recipients with blood group B. In recipients with blood group AB any evidence of sepsis was not encountered. Sepsis was observed in a higher percentage (54.5%) of Rh-negative transplant recipients when compared with Rh-positive recipients (23.3%). A significant difference was not found between patient blood group types with and without mortality ($p > .05$). Perioperative morbidity and mortality were found to be significantly correlated with higher amounts of FFP transfusions ($p = .037$), longer operative ($p = .006$) and warm ischemia times ($p = .016$), prolonged mechanical ventilation ($p = .001$) and ICU staying times ($p = .014$), and duration of hospitalization ($p = .011$) (Table 2). Patients in whom sepsis was observed, prolonged stay under mechanical ventilation ($p = .021$) and prolonged ICU stays were detected. In patient group in whom mortality was observed, higher amounts of erythrocytes ($p = .010$), FFP ($p = .005$), and platelets ($p = .009$) were transfused, and these patients remained longer under mechanical ventilation therapy ($p = .013$) and in the ICU ($p = .005$). Correlation

analyses between the patient characteristics and clinical parameters are shown in Table 5.

Discussion

The only effective treatment for end-stage liver insufficiency is liver transplantation (Shukla et al. 2013). Living donor liver transplantation has allowed widespread implementation of liver transplantation in many countries having difficulties in procurement of cadaveric organs as is the case in Turkey (Akbulut & Yilmaz, 2015).

Complications most frequently occur during the first 3 months after liver transplantation which is termed as early postoperative period (Moreno & Berenguer, 2006). Unfortunately, deaths occurring during the first postoperative year are also encountered mostly in this period (Gilbert et al., 1999; Razonable et al., 2011). Complications after liver transplantation basically develop both as a result of surgical and non-surgical factors. Major surgical complications are as follows: bleeding, portal vein thrombosis, hepatic artery thrombosis, hepatic vein stenosis, and biliary problems. Surgical complications develop most frequently within the first 2–4 weeks (Chen et al., 2007). Predominant non-surgical causes include pulmonary problems, infections, sepsis, renal failure, and graft rejections. As predisposing factors for infection and sepsis, preoperative malnutrition, blood

Table 3 The perioperative morbidity data for the study group

	Number (percent)
Biliary complications	46 (28.5)
Infectious complications	41 (25.5)
Gastrointestinal bleeding	5 (3.1)
Small for size syndrome	4 (2.4)
Incisional hernia	3 (1.8)
Postoperative bleeding	10 (6.2)
Others	6 (3.7)

Table 4 The mortality reasons data for the study group

	Number (percent)
Sepsis	13 (52)
Disseminated intravascular coagulopathy	4 (16)
Cardiovascular events	3 (12)
Cerebrovascular events	2 (8)
Pulmonary embolism	2 (8)
Primary nonfunction	1 (4)
Total	25 (100)

Table 5 Correlation analyses between the patient characteristics and clinical parameters

		Recipient age	Recipient BMI	Donor age	Donor BMI	Child-Turcotte-Pugh score	MELD score	Graft volume
Cold ischemia time	r	0.033	0.120	− 0.039	− 0.091	0.053	0.109	0.077
	p	0.689	0.142	0.632	0.265	0.537	0.239	0.346
Warm ischemia time	r	**0.197**	**0.203**	0.086	0.130	− 0.091	**− 0.203**	**0.282**
	p	**0.015**	**0.013**	0.289	0.109	0.291	**0.027**	**0.000**
Erythrocyte transfusions	r	**0.176**	0.098	− 0.145	− 0.017	**0.305**	**0.312**	**0.210**
	p	**0.025**	0.220	0.066	0.832	**0.000**	**0.000**	**0.007**
Fresh frozen plasma transfusions	r	**0.400**	**0.341**	0.061	− 0.001	0.154	0.101	**0.522**
	p	**0.000**	**0.000**	0.440	0.992	0.063	0.259	**0.000**
Platelet transfusions	r	0.117	**0.213**	0.009	− 0.018	**0.179**	0.216	**0.209**
	p	0.138	**0.007**	0.905	0.822	**0.030**	0.015	**0.008**
Duration of mechanical ventilation	r	0.054	0.056	− 0.056	0.049	0.058	0.025	0.045
	p	0.493	0.487	0.483	0.539	0.487	0.781	0.575
Duration of hospitalization	r	− 0.075	− 0.057	− 0.063	− 0.049	0.140	**0.218**	− 0.068
	p	0.349	0.478	0.435	0.543	0.095	**0.016**	0.397
Duration of ICU stay	r	0.008	− 0.015	− 0.088	0.077	0.052	0.053	0.031
	p	0.922	0.855	0.266	0.332	0.535	0.557	0.697

transfusions, prolonged surgery, and immunosuppression have been held responsible (Sanchez et al., 2006; Chen et al., 2007; Yaprak et al., 2011).

Though complications such as pneumonia and wound infection may be observed after every kind of major surgery, liver transplantation patients are more prone to such infectious complications. However, biliary and vascular problems are major and difficult-to-treat complex complications of transplantation surgery. Development of biliary complications after living donor liver transplantations has been reported in 24–60% of the cases (Kasahara et al., 2006). Biliary complications in our series (28.5%) constitute an important problem similar to the cases in the whole world. Each center has different applications for the surgical technique and the suture material used. The superiority of non-absorbable suture material over absorbable material was reported regarding prevention of inflammation, and fibrosis that might happen during absorption of the absorbable material. In a series of 339 cases with right lobe transplantation, bile leakage, and bile duct stenosis were reported in 13, and 35.7% of the cases, respectively (Chang et al., 2010). When compared with cadaveric donor transplantations, development of biliary complications after living donor liver transplantation was reported as 41.9% vs. 24.5% (Hwang et al., 2006). In the present series, of the 46 biliary complications, 22 were anastomotic stricture, 15 were non-anastomotic stricture, and 9 were bile leak. As for the postoperative morbidity in our series, transfused units of fresh frozen plasma, durations of surgery,

and warm ischemia times were all found as morbidity increasing factors.

Kyoto group reported an early postoperative mortality rate of 18.9% (total *n* = 576) after adult living donor liver transplantations, and they emphasized infections as the most frequent cause of mortality (Egawa et al., 2006). In the same study MELD score above 25, treatment in an ICU before transplantation, ABO incompatible transplantation, and retransplantation were detected as risk factors related to mortality (Kaido et al., 2009). A significant correlation between increased MELD score and postoperative mortality was also confirmed by the research performed by Patkowski. He also emphasized that the presence of preoperative ascites and encephalopathy have also been reported as factors effective on mortality (Patkowski et al., 2009). Lee et al. reported early postoperative mortality in 10.6% of 311 living donor transplantations, and directly correlated preoperative poor health state with mortality (Lee et al., 2002). MELD scoring system which was started to be implemented in the United States of America has been developed to predict 3-month survival rates of the patients in the liver donation waiting list. In a study encompassing 21,673 liver transplantations recorded in the UNOS system, increased MELD score, treatment in ICU before transplantation, and retransplantation were detected as postplantation poor prognostic criteria (Rana et al., 2008). Sepsis was the leading cause of mortality in our patient group. When the results of our investigation were taken into consideration, prolonged stay under mechanical ventilation and increased duration

of ICU stay were both found as sepsis and mortality increasing factors.

When living donor liver transplantation was performed for a patient with liver insufficiency, donor safety is the most important issue. Since a healthy person is operated, donor hepatectomy should be performed in extremely experienced centers. For the year 2006, a total of 19 living donors exited in the whole world, and mortality risk of operation was reported as 0.15% (Trotter et al., 2006). Since remnant volume is smaller than the volume of donated left lobe, right lobe donors are more frequently exposed to morbidities. In a multicenter article on outcomes of 3565 living donors, rates of reoperation and bile leakage were reported as 1.1% and 6.1% of the right lobe donors, respectively (Hashikura et al., 2009). In our series, similar rates were found in our donors, and any life-threatening complication or mortality was not observed in any of our donors.

Conclusion

In conclusion, higher amounts of FFP transfused, longer operative and warm ischemia times were risk factors for developing perioperative morbidity. Prolonged stay under mechanical ventilation, prolonged ICU stay, and duration of hospitalization were risk factors for developing sepsis and mortality. Recognition of these factors is useful in identifying individuals who are at risks of morbidity and mortality after liver transplantation and taking extra care for such points may improve the postoperative results. Early detection and prevention of these factors may lead to less postoperative complications and improved postoperative outcomes in individuals at risk for morbidity and mortality after liver transplantation.

Abbreviations
LDLT: Living donor liver transplantations; MELD: Model for end-stage liver disease; FFP: Fresh frozen plasma; ICU: Intensive care unit; ESLD: End-stage liver disease; BMIs: Body mass indices; GW/BW: The ratio between graft and body weight

Authors' contributions
Individual contributions of all authors to the article are stated below. For this, the initials of the authors were used. All authors read and approved the final manuscript. B.H.: The author collected, analyzed, and interpreted the patient data and wrote the manuscript. P.K.: The author collected, analyzed, and interpreted the patient data and wrote the manuscript. G.E: The author collected and analyzed the patient data. M.Y.: The author collected and analyzed the patient data. Y.D.: The author collected and analyzed the patient data. H.O: The author interpreted the patient data and wrote the manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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Hizarci *et al. Ain-Shams Journal of Anesthesiology*　　(2020) 12:60

Page 6 of 6

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