Predictors of early recipient mortality after living donor liver transplantation in a tertiary care center in Egypt

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BACKGROUND: Living donor liver transplantation (LDLT) has evolved into a widely accepted therapeutic option. Many different risk factors may affect early mortality after LDLT.

OBJECTIVES: Analyze risk factors that can affect early (<6 months) mortality of patients after LDLT in a single center.

DESIGN: Retrospective chart review of patients who underwent LDLT.

SETTING: University hospital.

PATIENTS AND METHODS: Adult cirrhotic patients who underwent LDLT were classified by early (first 6 months) or late mortality. A full pre, intra- and post-operative evaluation had been done on all patients including a full history, examination and investigations to identify risk factors that might affect mortality post-LDLT.

MAIN OUTCOME MEASURES: Determination of pre-, intra- or postoperative factors that might affect recipient mortality post-LDLT.

SAMPLE SIZE: 123.

RESULTS: Pre-operative factors that increased early mortality in a univariate analysis were higher model for end-stage liver disease (MELD) scores, lower graft-recipient weigh ratio (GRWR), older donor age, and recurrent spontaneous bacterial peritonitis. Intraoperative factors included more transfusion units of blood, plasma, platelets and cryoprecipitate, a longer time for cold and warm ischemia, and a longer anhepatic phase among others. Postoperative factors included a longer ICU or hospital stay and abnormal postoperative laboratory data. In the final logistic regression model, the most significant factors were pre-operative GRWR, length of hospital stay, units of intraoperative blood transfusion, postoperative alanine aminotransferase, postoperative total leukocyte count, and MELD score.

CONCLUSION: LDLT outcomes might be improved by attempting to resolve clinical factors that have been identified as contributors to early post-LDLT mortality.

LIMITATIONS: More risk factors, such as those relevant to patient portal vein hemodynamics, should be included in an analysis of predictors of early mortality.

CONFLICT OF INTEREST: None.
Egypt is a densely populated country, with a high prevalence of hepatitis C virus (HCV) infection (about 26%).¹ Large numbers of Egyptian patients suffer from end-stage liver disease and need liver transplantation.¹ Living donor liver transplantation (LDLT) has evolved into a widely accepted therapeutic option to solve the problem of the deficiency of cadaveric livers for deceased donor liver transplantation (DDLT).² LDLT preparation is an important determinant of successful results for both donors and recipients. For that reason, LDLT preoperative work-ups are performed to provide accurate information about the anatomy, volume and function of the allograft and remnant donor liver. These are integrated with recipient clinical data to determine the best surgical strategy to obtain the best results and decrease deaths.³

Risk factors may affect early mortality after LDLT include preoperative factors (higher MELD scores, poor quality grafts and small grafts), operative factors (large amounts of intraoperative blood loss and technical failures) and postoperative factors (postoperative abnormal laboratory value).⁴ Identifying predictors of early mortality after LDLT is an important issue that can help to improve the outcome of LDLT.⁴ Our study aimed to analyze pre-, intra- and post-operative risk factors that can affect early (<6 months) mortality of patients after adult-to-adult LDLT.

PATIENTS AND METHODS
Our retrospective chart review was conducted on adult cirrhotic patients who underwent LDLT at the National Liver Institute, Ainshams University and Al-Azhar University Hospitals in Cairo over the ten-year period from 5 January 2005 to 1 January 2015. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the University Research Ethics Committee (REC). Pairing of donors and recipients was decided by the consensus of the liver transplantation committee, which comprised liver surgeons, hepatologists, radiologists, and anesthesiologists. Criteria for inclusion were end-stage liver disease (irrespective of indication for LDLT), age from 18 to 60 years, graft-recipient weigh ratio (GRWR) of >0.8 estimated by preoperative CT volumetry. Acute liver failure necessitating transplantation was an exclusion criterion. The procedure was explained to recipients and donors including the risks of morbidity and mortality. Consent forms (in addition to consent to participate in the study) were signed by the recipient and the donor. Patients were fully informed about the risks and the benefits of the operative procedures. All donors were >20 years old. A liver biopsy was done to evaluate liver quality. Steatosis of 15% or more was considered a contraindication for donation. In addition, ultrasound, psychological assessment and CT angiography and CT volumetry were performed.

Preoperative evaluation
In the recipient, Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores were used for preoperative patient evaluation. In cases with hepatocellular carcinoma (HCC), Milan criteria were adopted in selection of patients. Evaluation of recipients included a detailed history including age, gender, and primary liver disease including HCV and hepatitis B virus (HBV). The history included symptoms that could reflect decompensated liver disease such as recurrent spontaneous bacterial peritonitis (SBP), recurrent encephalopathy, refractory ascites and recurrent variceal bleeding, in addition to comorbidities such as diabetes and hypertension. A full clinical examination for recipients included body mass index (BMI), signs that could reflect decompensated liver disease such as ascites, lower limb edema or jaundice. Other investigations included laboratory values, imaging (Doppler ultrasound), and upper gastro-intestinal endoscopy. Assessment also included relevant consultations.

Intraoperative evaluation
We recorded the amount of transfused blood, plasma, platelets and cryoprecipitate units, time of cold and warm ischemia, and the duration of the anhepatic phase. The recipient surgery consisted of a total hepatectomy of the native liver followed by implantation of the donor liver. The native hepatectomy was sometimes technically difficult, especially in patients with previous upper abdominal operations and severe portal hypertension. The ligamentous attachments of the liver were divided, followed by skeletonization of the hilar structures (bile duct, hepatic artery, and portal vein) to prepare for implantation of the new liver. Committing the patient to transplant, the bile duct and hepatic artery were divided. Vascular clamps were placed on the portal vein, and the liver was removed by transecting the portal vein. The donor liver was surgically prepared for implantation on the back table. Anastomoses were constructed between the donor liver and the recipient patient. Once the portal vein was anastomosed, clamps were removed and the liver was perfused with portal venous inflow.

Postoperative evaluation
Follow-up lasted 6 months. Patients alive at 6 months were classified as late postoperative death. In the early postoperative period, patients were closely monitored...
in the intensive care unit (ICU) for an average period of 5 to 7 days and then later in the surgical ward after their condition had stabilized. During their hospital stay, follow-up of patients was conducted by a team with a transplant surgeon and transplant hepatologist. After discharge, recipients were followed up at the outpatient transplant clinic weekly during the first month after transplantation, and monthly thereafter. Postoperative evaluation included comprehensive history taking with special attention to resuming normal feeding, bowel habits, the condition of the chest and signs of infection. Evaluation included a clinical examination with special care to vital signs, signs of hepatic decompensation, chest examination and urinary output. Laboratory evaluation included examination of cultures from biological fluids and surgical drains. Imaging included a daily chest radiograph, abdominal ultrasound and Doppler evaluation of the hepatic circulation.

**Statistical methods**

Data were coded and entered using the statistical package IBM SPSS (Armonk, NY: IBM Corp) version 21. Categorical data are expressed as frequency and percentage and analyzed with the chi-square or Fisher exact tests. Continuous data are expressed as the mean and standard deviation and compared with the t test or Mann Whitney test. For serial measurements, the non-parametric Friedman test and Wilcoxon test were used. Univariate analysis was used to detect the predictors of early mortality. P values less than .05 were considered statistically significant.

A backward stepwise logistic regression model was performed to identify predictors of early mortality among patients following LDLT. Variables entered on the first step included the significant explanatory variables on bivariate analysis: MELD score, donor age (years), preoperative graft size (g), intraoperative graft size (g), preoperative GRWR, number of intraoperative blood transfusion units, arm ischemia (minutes), length of the anhepatic phase, intraoperative GRWR, length of ICU stay, length of hospital stay, postoperative total leukocyte count (TLC), postoperative C-reactive protein, postoperative alanine transferase (ALT), postoperative total bilirubin, albumin, international normalized ratio (INR), and aspartate transaminase (AST). Other explanatory variables were excluded for either insignificant bivariate association with the early outcome or multicollinearity. A Kaplan-Meier survival analysis was performed to measure the cumulative probability of early mortality among study patients following LDLT. The maximum follow-up time was 6 months, without loss-to-follow-up among study participants.

**RESULTS**

Of the 123 adult cirrhotic patients who underwent LDLT, 110 (89.4%) were males and 13 (10.6%) were females. Ages ranged from 19 to 63 years with a mean (SD) of 48.7 (7.58) years. BMI ranged from 18.9 to 34 kg/m² with a mean (SD) 27.32 (3.18) kg/m². Indications for LDLT were post-viral hepatitis cirrhosis in 68.3% (62.6 % post-HCV and 5.7 % post-HBV), HCC in 22%, cryptogenic cirrhosis in 7.3%, and 0.8% for autoimmune cirrhosis, alcoholic cirrhosis and primary biliary cholangitis. The CTP score at the time of LDLT ranged from 5 to 13, while the MELD score ranged from 9 to 26 with a mean (SD) 18.2 (3.8).Liver grafts consisted of a right-lobe graft without the middle hepatic vein except one case that consisted of left lobe graft. Preoperative laboratory data for all patients is shown in Table 1.

Preoperative graft size ranged from 433 to 1300 grams. Other preoperative data presented by early or late mortality are also shown in Table 2. Forty (32.5%) patients had diabetes mellitus, 11.4% had hypertension, and 7.3% had dyslipidemia (Table 3). Table 4 shows indications for liver transplantation. Table 5 shows intraoperative clinical data and Table 6 shows early postoperative data. Table 7 shows postoperative laboratory results.

The mean (SD) follow-up period was 3.3 (1.5) months and the range was up to 6 months after transplantation.

| Table 1. Laboratory data from the early postoperative period (n=123). |
|-----------------|------|------|
| Hemoglobin (g/dL) | 8.9  | 0.8  |
| Total leucocyte count (10⁹/μL) | 9.8  | 3.9  |
| Platelets (10⁹/L) | 79.2 | 29.7 |
| CRP | 20.5 | 13.2 |
| AST (U/L) | 308.6 | 213.7 |
| ALT (U/L) | 245.8 | 240.6 |
| GGT (U/L) | 223.8 | 160.2 |
| ALP (U/L) | 204.5 | 154.9 |
| Total bilirubin (mg/dL) | 4.9  | 3.7  |
| Direct bilirubin (mg/dL) | 3.4  | 2.8  |
| International normalized ratio | 1.8  | 1.1  |
| Albumin (g/dL) | 2.7  | 0.3  |
| Creatinine (mg/dL) | 1.2  | 0.5  |

CRP: C-reactive protein, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GGT: gamma-glutamyltransferase
Apparent causes of death were sepsis in 10 patients, acute rejection in 3 patients, hepatic artery thrombosis in 2 patients, biliary leak in 3 patients, myocardial infarction in 3 patients, pulmonary embolism in 4 patients and cardiac arrhythmia in 3 patients. Small-for-size syndrome was diagnosed in 16 patients who died early and in 8 patients who died after 6 months.

The multiple logistic regression analysis showed that the MELD score, preoperative GRWR, length of hospital stay, number of intraoperative blood transfusion units, postoperative ALT level, and postoperative TLC were the significant predictors for early mortality (Table 8). The odds of early mortality increased by 41% for every unit blood received, by 32% for every unit increase in the MELD score, by 19% for every unit increase in the postoperative TLC, by 11% for every extra day stay in the hospital, and 1% for every unit increase in the preoperative GRWR. However, the odds of early mortality decreased by less than 1% for every unit increase in the preoperative GRWR. The final-step model adequately fitted the data and correctly predicted the outcome in 92.6%. The Kaplan-Meier survival analysis showed that the mean survival time was 5.2 months (SE: 0.15, 95% CI: 4.91–5.50). Moreover, 87%, 81% and 77% of patients were surviving at the 2-month, 4-month and 6-month times postoperatively.

**DISCUSSION**

Liver transplantation is a challenging surgical and medical field. Pre- and postoperative logistics, infrastructural conditions of specialized centers, surgeon experience, and anesthesiologic and medical management approaches present complex factors that impact procedure success. In Egypt, the presence of deceased donors remains exceedingly limited, because traditional religious and emotional causes present obstacles in regard to performing DDLT. For this reason, LDLT is the main type of liver transplantation in Egypt. In our study, conducted on a series of 123 adult cirrhotic patients who underwent LDLT, highlights the different factors that may be intimately related to increased recipient mortality after LDLT, including preoperative factors such as higher MELD scores, lower GRWR, older donor age, and recurrent SBP. Intraoperative factors that can affect postoperative mortality included greater amounts of transfused blood, plasma, platelets and cryoprecipitate

**Table 2.** Preoperative data on early and late mortality patients.

| Variables                  | Early postoperative death (n=28, 22.8%) | Late postoperative death (n=95, 77.2%) | P value |
|----------------------------|----------------------------------------|--------------------------------------|---------|
| Sex                        |                                        |                                      |         |
| Male                       | 23                                     | 87                                   | .17     |
| Female                     | 5                                      | 8                                    |         |
| Recipient age (years)      | 48.0 (9.0)                             | 48.7 (7.2)                           | .624    |
| Body mass index (kg/m²)    | 26.7 (2.9)                             | 27.5 (3.2)                           | .15     |
| MELD score                 | 22.3 (1.5)                             | 17.0 (3.4)                           | <.001   |
| Preoperative graft size (g)| 872.9 (123.4)                          | 931.3 (114.8)                        | .04     |
| Preoperative GRWR          | 0.9 (0.12)                             | 1.1 (0.2)                            | <.001   |
| Donor age (years)          | 34.6 (3.4)                             | 27.3 (4.4)                           | <.001   |

Data are mean (standard deviation). GRWR: graft recipient weight ratio, MELD: Model for end-stage liver disease.

**Table 3.** Prevalence of comorbid diseases.

| Variables            | Early postoperative death (n=28, 22.8%) | Late postoperative death (n=95, 77.2%) | P value |
|----------------------|----------------------------------------|--------------------------------------|---------|
| Diabetes mellitus    | 11 (39.3)                              | 29 (30.5)                           | .385    |
| Hypertension         | 6 (21.4)                               | 8 (8.4)                             | .085    |
| Hyperlipidemia       | 4 (14.3)                               | 5 (5.2)                             | .42     |

Data are numbers (percentages).

**Table 4.** Indications for liver transplantation.

| Variables                        | Early postoperative death (n=28, 22.8%) | Late postoperative death (n=95, 77.2%) | P value |
|----------------------------------|----------------------------------------|--------------------------------------|---------|
| CTP score                        |                                        |                                      |         |
| A                                | 1 (3.6)                                | 0                                    |         |
| B                                | 7 (25.0)                               | 14 (14.7)                           | .092    |
| C                                | 20 (71.4)                              | 81 (85.3)                           |         |
| Recurrent hepatic encephalopathy| 10 (35.7)                              | 31 (32.6)                           | .761    |
| Recurrent SBP                    | 15 (53.6)                              | 30 (31.6)                           | .034    |
| Refractory ascites               | 11 (39.3)                              | 36 (37.9)                           | .894    |
| Recurrent GI bleeding            | 11 (39.3)                              | 31 (32.6)                           | .514    |

Data are numbers (percentages). CTP: Child-Turcotte-Pugh, SBP: spontaneous bacterial peritonitis, GI: gastrointestinal.
units, and longer times for cold and warm ischemia, as well as a longer anhepatic phase time. In addition, postoperative factors included more transfused blood units, longer length of ICU and/or hospital stay and abnormal postoperative laboratory data.

Different scoring systems have been proposed to predict the outcome of deceased-donor liver transplantation, but their impact on the outcome in living LDLT has not yet been elucidated. Our results show that the MELD score has a great impact on mortality post-LDLT, being significantly higher in the early mortality patients. The same result was reported by Rogério et al., who found that higher MELD scores were associated with higher early mortality after LDLT. Nevertheless, Chok et al found that the higher MELD score group had comparable early postoperative mortality in comparison to lower MELD score group.

Low GRWR is another factor that can cause early graft dysfunction and increased mortality. Previous studies have suggested that inadequate graft size was associated with early graft dysfunction development. Our study highlights the importance of GRWR in liver transplantation, showing that preoperative GRWR was significantly lower in the early mortality patients. The same results were reached by Rogério et al, who found that lower preoperative GRWR was associated with a higher early postoperative mortality.

Recipient weight, as a predictor of post-transplant outcomes, has been addressed by many studies. In our results, recipient BMI was lower in the early mortality patients, but the difference did not reach statistical significance. In 2013 Kaido and colleagues showed that low BMI was closely related to early post-transplant mortality in patients undergoing LDLT. Donor age seems to be another important factor which affects postoperative LDLT mortality. Appropriate donor-recipient match has not been explored well in LDLT unlike DDLT. In our series, donor age was higher in the early mortality patients, and the difference was statistically significant. This result is consistent with the results of Moon et al who found that donor age was the only significant risk factor for patient early postoperative mortality according to a multivariate analysis. In contrast to these results, Pratschke et al found that donor age did not affect early postoperative mortality after liver transplantation. To solve these non-consistent results, we think that further studies are needed for determination of a cut-off value for donor age that may increase postoperative mortality.

Many efforts have been devoted to explore effects of recipient sex and age on post-LDLT mortality. Our analysis showed that no statistically significant differences between the early and late mortalities were observed for recipient sex. Nonetheless, evidence for recipient age showed that higher MELD scores were associated with older recipient age. In contrast to our results, Burroughs et al, found that recipient sex and age did not affect early postoperative mortality. In contrast to our results, Burroughs et al, found that increased early mortality after liver transplantation was associated with older recipient age. In our view, further research is needed to derive a cut off value for recipient age that may significantly affect postoperative mortality.

LDLT as an efficient treatment for end-stage liver disease. Clinical indications for transplantation are diverse and may include recurrent variceal bleeding, recurrent encephalopathy, refractory ascites and recurrent SBP. In the present study, we found that there were no statistically differences differences between the early and late mortalities were observed for recipient sex. Nonetheless, evidence for recipient age showed that higher MELD scores were associated with older recipient age. In contrast to our results, Burroughs et al, found that recipient sex and age did not affect early postoperative mortality. In contrast to our results, Burroughs et al, found that increased early mortality after liver transplantation was associated with older recipient age. In our view, further research is needed to derive a cut off value for recipient age that may significantly affect postoperative mortality.

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Table 7. Postoperative laboratory results.

|                    | Early postoperative death (n=28, 22.8%) | Late postoperative death (95, 77.2%) | P value |
|--------------------|----------------------------------------|-------------------------------------|---------|
| Hemoglobin (g/dL)  | 8.3 (0.6)                              | 9.1 (0.8)                           | <.001   |
| Total leucocyte count (10³/µL) | 12.6 (6.3)                           | 9.0 (2.3)                           | <.001   |
| Platelets (10⁹/L)  | 50.4 (17.8)                            | 87.7 (27.0)                         | <.001   |
| CRP                | 34.7 (15.9)                            | 16.3 (8.7)                          | <.001   |
| AST (U/L)          | 497.8 (455.7)                          | 252.9 (199.2)                       | <.001   |
| ALT (U/L)          | 520.8 (378.9)                          | 164.7 (68.8)                        | <.001   |
| GGT (U/L)          | 356.2 (204.7)                          | 184.8 (120.5)                       | <.001   |
| ALP (U/L)          | 348.8 (184.3)                          | 162.0 (115.6)                       | <.001   |
| Total bilirubin (mg/dL) | 8.3 (4.6)                           | 3.9 (2.6)                           | <.001   |
| Direct bilirubin (mg/dL) | 6.0 (3.5)                           | 2.7 (2.1)                           | <.001   |
| Albumin (g/dL)     | 2.6 (0.3)                              | 2.8 (0.2)                           | <.001   |
| International normalized ratio | 2.4 (2.1)                           | 1.6 (0.3)                           | <.001   |
| Creatinine (mg/dL) | 1.7 (0.5)                              | 1.0 (0.4)                           | <.001   |

Data are mean (standard deviation). CRP: C-reactive protein, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GGT: gamma-glutamyltransferase.

Table 8. Backward stepwise logistic regression model for predictors of early mortality in patients after living donor liver transplantation (N=123).

|                | β     | S.E.  | Wald  | df  | Sig.  | Odds ratio (95% confidence interval) |
|----------------|-------|-------|-------|-----|-------|-------------------------------------|
| MELD score     | 0.277 | 0.136 | 4.121 | 1   | 0.042 | 1.319 (1.010-1.723)                 |
| Preoperative GRWR | -8.668 | 4.318 | 4.029 | 1   | 0.045 | 0.0002 (0.000-0.815)                |
| Length of hospital stay (days) | 0.103 | 0.043 | 5.649 | 1   | 0.017 | 1.108 (1.018-1.206)                 |
| Intraoperative blood transfusion (units) | 0.343 | 0.139 | 6.106 | 1   | 0.013 | 1.409 (1.074-1.850)                 |
| Postoperative ALT (U/L) | 0.005 | 0.002 | 6.441 | 1   | 0.011 | 1.005 (1.001-1.009)                 |
| Postoperative TLC (10³/µL) | 0.177 | 0.088 | 4.051 | 1   | 0.044 | 1.193 (1.005-1.418)                 |
| Intercept      | -7.864 | 5.206 | 2.282 | 1   | 0.131 | -                                   |

TLC: Total leucocyte count, ALT: Alanine aminotransferase, GRWR: Graft recipient weight ratio, MELD: Model for end-stage liver disease

Model fit and predictive measures: Deviance (-2LL): 48.874, Nagelkerke χ²: 0.75, Omnibus Tests of Model Coefficients: 82.56, df=6, <.001. Classification accuracy: 92.6%.
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Differences were statistically highly significant. Agopian and colleagues also found that cold and warm ischemia times were independent predictors of early postoperative mortality after liver transplantation.23 Four years before the Agopian study, Patkowski and colleagues also found that cold and warm ischemia times were major prognostic factors of early patient mortality.24

Duration of hospital course after LDLT may predict early postoperative mortality. In fact, two studies showed that increased early postoperative mortality was associated with a longer ICU stay.25 Post-operative laboratory results can also predicts outcomes of LDLT. Theoretically, patients with abnormal laboratory results such as impaired liver function tests or renal dysfunction are prone to worse outcomes. The present study showed that leukocyte count, total and direct bilirubin, AST, ALT, GGT, ALP, INR and creatinine were statistically significantly higher in patients with early postoperative mortality. Gebhard et al reported similar results, showing that bilirubin levels, INR, AST, and serum creatinine levels were significantly higher in an early mortality group than in a non-early mortality group after transplantation.27

In addition, we found that mean hemoglobin, platelet count, and albumin were lower in patients with early postoperative mortality, and the differences were statistically highly significant. These results are consistent with those of Pratschke et al, who found that a significant fall in platelet count predicted early mortality, although no difference in hemoglobin levels was found between early mortality and non-early mortality groups in the same study.16

Our logistic regression analysis showed that the MELD score, preoperative GRWR, length of hospital stay, intraoperative blood transfusion units, postoperative ALT level, and postoperative TLC were the significant predictors for early mortality following LDLT. The most significant predictors (highest odds ratios) were the number of intraoperative blood transfusion units and MELD score. These results highlight the importance of considering these parameters during LDLT.

LDLT outcomes might be improved by addressing the factors that have been identified as contributors to early post-LDLT mortality. Nevertheless, no single study could include all these factors. In this study, we tried to include as many factors as we could that might add to the armamentarium of predictive. Factors that do not seem to affect recipient mortality after LDLT include recipient BMI, sex, and age. Our results need to be reproduced in other series on larger number of LDLT patients for objective validation of factors that affect recipient mortality after LDLT. Moreover, further studies on a large number of patients are needed to incorporate other reliable parameters that could predict postoperative mortality (such as those relevant to patient portal vein hemodynamics, postoperative complications, patient’s nutritional status pre-and postoperatively, and need for retransplantation) in an effort to improve the outcome of LDLT.
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