

# PREDICTIVE FACTORS OF EARLY GRAFT LOSS IN LIVING DONOR LIVER TRANSPLANTATION

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**ABSTRACT** – *Context* - Living donor liver transplantation has become an alternative to reduce the lack of organ donation. *Objective* - To identify factors predictive of early graft loss in the first 3 months after living donor liver transplantation. *Methods* - Seventy-eight adults submitted to living donor liver transplantation were divided into group I with 62 (79.5%) patients with graft survival longer than 3 months, and group II with 16 (20.5%) patients who died and/or showed graft failure within 3 months after liver transplantation. The variables analyzed were gender, age, etiology of liver disease, Child-Pugh classification, model of end-stage liver disease (MELD score), pretransplantation serum sodium level, and graft weight-to-recipient body weight (GRBW) ratio. The GRBW ratio was categorized into < 0.8 and MELD score into ≥18. The chi-square test, Student *t*-test and uni- and multivariate analysis were used for the evaluation of risk factors for early graft loss. *Results* - MELD score ≤18 ( $P < 0.001$ ) and serum sodium level > 135 mEq/L ( $P = 0.03$ ) were higher in group II than in group I. In the multivariate analysis MELD scores > 18 ( $P < 0.001$ ) and GRBW ratios < 0.8 ( $P < 0.04$ ) were significant. *Conclusions* - MELD scores >18 and GRBW < 0.8 ratios are associated with higher probability of graft failure after living donor liver transplantation.

**HEADINGS** – Liver transplantation. Living donor. Prognosis. Primary graft dysfunction. Graft survival.

## INTRODUCTION

Liver transplantation is currently the treatment of choice to save the lives of patients with end-stage liver diseases or fulminant hepatic failure<sup>(2, 7, 8)</sup>. In 1963, Thomas Starzl performed the first three liver transplantations but without achieving 1-year survival<sup>(29)</sup>.

The 1-year survival after cadaveric donor liver transplantation is currently higher than 85% among adult or pediatric patients, with 5- and 10-year survival rates being higher than 70% and 60%, respectively<sup>(1, 11, 15)</sup>. The success of liver transplantation as a treatment for most types of acute and chronic liver failure has led to an increase in the number of transplant candidates without a proportional increase in the supply and availability of organs<sup>(2)</sup>. This situation resulted in the fact that, by the end of 2006, more than 17.000 patients were on the liver transplant waiting list in the United States<sup>(4)</sup>. However, although more than 6,000 liver transplants are performed per year, only one-third of the candidates were transplanted in the subsequent years<sup>(37)</sup>. Approximately 2,000 patients per year have died over the last 6 years without being transplanted<sup>(2)</sup>.

The constant shortage of organ donors is responsible for the failure to meet the growing demand for liver transplantation<sup>(9, 11, 12, 15, 37)</sup>. This imbalance between organ supply and patients awaiting liver transplantation is substantial and is a matter of concern, especially in East Asian countries such as South Korea, Japan, Hong Kong, and Taiwan<sup>(21, 24, 25, 26, 35, 37)</sup>. Within this context, living donor liver transplantation has become an appreciable and effective alternative to reduce the problem resulting from the lack of organ donation<sup>(11)</sup>.

The success of living donor liver transplantation in the pediatric population led to improvement of this technique for the adult population<sup>(10, 28)</sup>. However, factors influencing early graft survival in the 3 first months in living donor liver transplantation were not sufficiently investigated.

The objective of this study was to identify and to analyze factors predictive of early graft loss in the first 3 months after living donor liver transplantation.

## METHODS

An observational, retrospective and analytical study was conducted on 78 consecutive adult patients

Conflicts of interest: none.

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of both genders receiving a living donor liver transplant through the Transplant Program of A.C. Camargo Hospital and Sírio-Libanês Hospital (São Paulo, Brazil), between June 2004 and February 2010. Forty-nine (62.8%) transplant recipients were males and 29 (37.2%) were females. The mean age was  $50.7 \pm 6.8$  years (18 to 65 years).

This study was conducted in accordance with the ethical standards accepted by the Declaration of Helsinki of the World Medical Association, adopted in 1964 and amended in 1996. The study was approved by the Research Ethics Committee (Protocol number 026/2010).

The inclusion criteria for living donor liver transplantation were adult age (>18 years) and a history of hepatic failure due to liver disease (upper digestive hemorrhage, ascites and hepatic encephalopathy) and/or hepatocellular carcinoma according to the Milan criteria (a single nodule measuring 5 cm or less in diameter or three nodules of less than 3 cm)<sup>(2)</sup>. Exclusion criteria of living donor liver transplant recipients were age less than 18 years and the presence of severe cardiopulmonary diseases, tumors at any site except the liver, and acquired immunodeficiency syndrome (AIDS).

Seventy-six (97.4%) of the 78 patients studied had liver cirrhosis and two (2.6%) had hereditary familial amyloidosis. Among cirrhotic patients, the most frequent etiology associated with liver disease was hepatitis C in 34 (43.4%), alcoholic hepatitis in 20 (25.6%), and hepatitis B in 10 (12.8%). All liver transplantations were performed using organs from ABO-compatible donors aged 18 to 50 years.

Donors considered suitable for donation presented normal parameters upon clinical-laboratory examination: blood count, biochemical tests, viral serology, tumor markers, chest X-ray, electrocardiogram, total abdominal ultrasound, and abdominal nuclear magnetic resonance imaging. All donors had a body mass index of 18 to 25 and no chronic diseases of any nature. Court authorization was obtained when the donor was not related to the recipient; the others donors were family related in first, second and third degree. The general characteristics of the transplant recipients are shown in Table 1.

The transplant recipients were divided into two groups: group I consisted of 62 (79.5%) patients with graft survival longer than 3 months and group II consisted of 16 (20.5%) patients who died and/or showed graft failure within 3 months after liver transplantation.

In the two groups were not differences between surgical techniques, warm and cold ischemia, blood loss and the kind of immunosuppressant used: tacrolimus or cyclosporine with or without mycophenolate and corticosteroids.

The following pretransplant variables of the liver transplant recipients were analyzed: gender, age, etiology of liver disease, Child-Pugh classification, MELD score (model of end-stage liver disease), and serum sodium level at the time of transplantation. Concerning the liver transplant procedure, the graft weight-to-recipient body weight (GRBW) ratio was analyzed. Liver graft survival of less than 3 months after transplantation was defined as “early loss”.

Risk factors for early liver graft loss, including gender, age, serum sodium level, MELD score, Child-Pugh classification, graft type, and GRBW, were submitted to univariate analysis. Categorical variables were analyzed by the chi-square test and numerical variables by the Student *t*-test. The probability of graft loss was calculated by uni- and multivariate logistic regression. A *P* value < 0.05 was considered to be significant. In addition to conventional descriptive analysis, nonparametric calculations were performed. The statistical programs used were the SPSS 16.0 for Windows 2007 (SPSS, Inc., USA).

## RESULTS

The average age of the 78 patients in both groups was  $50.7 \pm 6.8$  years (18 to 65 years). The mean age of 62 patients in group I was  $51.6 \pm 11.9$  years, meanwhile the mean age of 16 patients in group II was  $49.8 \pm 12.7$  years (*P* = 0.6). There were 37 (59.7%) men and 25 (40.3%) women in group I and 12 (75%) men and 4 (25%) women in group II (*P* = 0.4) (Table 1).

Sixteen (25.8%) patients in group I and 6 (37.5%) patients in group II were classified as Child-Pugh C (*P* = 0.3).

In group I, the pre transplant serum sodium levels was

**TABLE 1.** Clinical, functional and laboratory characteristics of patients undergoing living donor liver transplantation with graft survival higher than 3 months (group I) or lost graft before 3 months and/or died after liver transplantation (group II)

Pretransplant variables	Group I (n = 62)	Group II (n = 16)	<i>P</i>
Gender			
Male	37 (59.7%)	12 (75%)	0.4
Female	25 (40.3%)	4 (25%)	
Age (years)	$51.66 \pm 11.90$	$49.81 \pm 12.71$	0.6
Child classification	16 (25.8%)	6 (37.5%)	0.3
MELD $\geq$ 18	3 (4.8%)	6 (37.5%)	0.001*§
GRBW < 0.8	5 (8.1%)	4 (25%)	0.004*§
Serum sodium	$138.9 \pm 3.9\text{mEq/L}$	$134.5 \pm 6.4\text{mEq/L}$	0.01*§

n = number of patients

MELD = model of end-stage liver disease

GRBW = graft weight-to-recipient body weight ratio

§ = mEq/L

\* = significant

Chi-square test; Student *t*-test

§ uni- and multivariate logistic regression

138.9 ± 3.9 mEq/L, whereas in patients of group II this value was 134.5 ± 6.4 mEq/L. The serum sodium level of pre transplant in group I was significantly lower ( $P = 0.01$ ) than in patients of group II (Table 1).

The mean MELD ≤18 was found in three (4.8%) patients in group I and in six (37.5%) patients in group II. Only 4.8% of the patients in group I had MELD higher than 18 while in group II 37.5% patients had MELD higher than 18. The MELD score was significantly lower ( $P = 0.001$ ) in group I than in group II (Table 1).

GRBW ratio ≤0.8 was observed in five (8.1%) patients in group I and in four (25%) patients in group II and a significant difference ( $P = 0.004$ ) was observed (Table 1).

The variables presenting a  $P$  value < 0.1 (MELD score ≥18, pre-transplant serum sodium levels and GRBW ratio ≤0.8) were included in the multivariate analysis and only MELD score ≥ 18 (OR = 2.6;  $P = 0.001$ , CI = 2.8-68.2) and GRBW ratio ≤ 0.8 (OR = 1.6;  $P = 0.04$ ; CI = 1.0-24.1) were significant (Table 2). Multivariate logistic regression showed that MELD score ≥18 and GRBW ratio ≤ 0.8 were independently associated with early graft loss.

TABLE 2. Results of multivariate logistic regression including the variables MELD and GRBW of patients undergoing living donor liver transplantation with graft survival higher than 3 months (group I) or lost graft before 3 months and/or died after liver transplantation (group II)

	OR	P	CI
MELD	2.6	0.001*	2.8-68.18
GRBW	1.6	0.04*	1.0-24.14

MELD = model of end-stage liver disease

GRBW = graft weight-to-recipient body weight ratio

OR = odds ratio

CI = confidence interval

## DISCUSSION

Living donor liver transplantation is an important option for patients on the transplant waiting list and adequate selection of recipients is fundamental to prevent retransplantation and complications inherent to the procedure, including death of the transplant recipient due to graft failure<sup>(7, 12)</sup>.

Although the present study only included patients submitted to living donor transplantation, the results were similar to those reported for other Western series involving living or deceased donors<sup>(1, 9, 10, 22, 25, 33)</sup>. The most frequent etiology of liver disease that led to liver transplantation was hepatitis C and there was a predominance of males<sup>(11, 22)</sup>.

Few studies have investigated factors contributing to liver graft loss within the first 3 months after transplantation, especially factors associated with living donor liver transplantation<sup>(19)</sup>. There is studies investigating factors associated with liver retransplantation, such as hepatic artery thrombosis<sup>(23)</sup>, primary nonfunction<sup>(23)</sup>, small-for-size syndrome<sup>(22)</sup>, and hyperacute rejection<sup>(22)</sup>.

The present study evaluated 78 consecutive patients submitted to living donor liver transplantation divided into

two groups according to graft survival. Statistical analysis demonstrated the importance of MELD score and GRBW ratio for the prediction of post-transplant outcomes<sup>(5, 6, 27, 31, 36)</sup>.

An increase in survival and improved outcomes of living donor liver transplantation were obtained in different series conducted in Europe and the United States when rigorous selection criteria were applied to donors and recipients<sup>(9, 26, 28)</sup>. Thus, the establishment of criteria able to predict the success of the procedure is important for the continuous improvement of outcomes, since living donor liver transplantation is a highly complex surgery that involves another healthy subject (donor) who should only be submitted to donation if the chances of success are expressive<sup>(2, 9)</sup>.

In the present study, the GRBW ratio was significantly lower in patients with early graft loss as also reported by other investigators<sup>(4)</sup>. Fisher et al.<sup>(11)</sup> observed that, when patients with an MELD score > 25 were transplanted, 1-year functional survival of the graft occurred in only 25% of the recipients, whereas liver graft survival was achieved in 77.8% of cases when grafts with a GRBW ratio > 0.8 were used. Gruttadauria et al.<sup>(19)</sup> showed that MELD score and serum sodium level are significantly associated with early graft dysfunction. This means that the higher the MELD score and the lower serum sodium, the higher is the probability of early graft loss. Kiuchi et al.<sup>(24)</sup> reported a graft survival rate of 92% after 1 year of living donor liver transplantation when the GRBW ratio was > 1, but graft survival was only 42% when GRBW ratio was < 0.8.

Theoretically, a partial graft with a GRBW ratio less than 0.8 is unable to provide the metabolic requirements for critically ill patients with high MELD scores, thus increasing the chance of liver graft failure. There are few studies correlating pretransplant MELD score with survival after living donor liver transplantation<sup>(6, 20, 33, 35)</sup>. Hayashi et al.<sup>(20)</sup> found no association between MELD score and patient survival in living donor liver transplantation recipients. However, the MELD scores were low in that study even among patients who died. The mean MELD score was 13 in the 59 patients who survived and 15 in those who died. Terrault et al.<sup>(33)</sup> and Uchida et al.<sup>(35)</sup> showed that a high pretransplant MELD score was significantly associated with reduced long-term survival in living donor liver transplantation.

Weismüller et al.<sup>(36)</sup> compared the outcomes of cadaveric liver transplantation after organ allocation based on MELD score, in which patients with a higher score were transplanted resulting in a decrease of survival from 88.6% to 76.9% in the first 3 months after the procedure. A retrospective study conducted by Brandão et al.<sup>(6)</sup> associated MELD score and Child classification with survival in 436 cadaveric transplant recipients. The 3-, 6- and 12-month survival rates were lower in patients with a MELD score ≥ 21 and classified as Child C.

The results of the present study indicate that an MELD score >18 is significant for the prediction of early liver graft loss, i.e., the probability of graft loss within the first 3 months is high in transplant recipients with an MELD score > 18 and small graft size (GRBW < 0.8), and this probability increases with increasing MELD score. These results are

important since they show that patients with a high MELD score ( $> 18$ ) should not receive small grafts due to the risk of graft loss. The present study therefore suggests caution when indicating living donor liver transplantation for critically ill patients with a MELD score  $> 18$  since this score was found to be a significant predictor of the success of transplantation.

Londoño et al.<sup>(27)</sup> demonstrated that MELD score and natremia are important prognostic factors for 3- and 12-month survival of living donor transplants in patients on the liver transplant waiting list. Consequently, the higher the MELD score and the lower natremia, the higher will be the mortality of patients awaiting organ transplantation. Hyponatremia is an important marker of poor prognosis in patients awaiting liver transplantation and is also associated with increased mortality of patients with advanced cirrhosis and portal hypertension<sup>(3, 5, 13, 31)</sup>. It is possible that the value of natremia adds information of severity to the MELD score. Dawwas et al.<sup>(13)</sup> investigated the correlation between the presence of

hyponatremia and mortality after cadaveric transplantation. In that series, serum sodium level was correlated with a lower survival rate of transplant recipients. In the present study, the higher pretransplant serum sodium level was associated with early graft loss. However, although being related to the severity of liver disease, this finding was not independently associated with early graft loss. Only MELD score  $> 18$  and a GRBW ratio  $< 0.8$  were independently associated with early liver graft loss after logistic regression analysis.

## CONCLUSIONS

The present results show that an MELD score  $> 18$  and a GRBW ratio  $< 0.8$  are associated with a higher probability of failure of living donor liver transplantation. However, further studies analyzing factors predictive of early liver graft loss and including a larger number of patients are necessary to confirm the results of the present series.

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Alves RCP, Fonseca EA, Mattos CAL, Abdalla S, Gonçalves JE, Waisberg J. Fatores preditivos da perda precoce do enxerto hepático em transplante hepático intervivos. *Arq Gastroenterol.* 2012;49(2):157-61.

**RESUMO** – *Contexto* - O transplante hepático intervivos constitui alternativa para amenizar a falta de doação de órgãos. *Objetivo* - Identificar os fatores preditivos da perda precoce do enxerto hepático nos 3 primeiros meses após transplante hepático intervivo. *Métodos* - Setenta e oito adultos submetidos ao transplante de fígado intervivos foram divididos em grupo I com 62 (79,5%) doentes com sobrevivência do enxerto superior a 3 meses, e grupo II com 16 (20,5%) que faleceram e/ou apresentaram falha do enxerto até 3 meses após o transplante hepático. As variáveis analisadas foram: sexo, idade, origem da doença hepática, classificação de Child-Pugh, critério MELD, nível sérico de sódio pré-transplante e relação GRBW. O critério MELD foi categorizado em  $\geq 18$  e a relação GRBW em  $< 0,8$ . Na avaliação dos fatores de risco para perda precoce do enxerto hepático foi utilizada a análise uni e multivariada. *Resultados* - Critério MELD  $\leq 18$  ( $P = 0,001$ ) e nível sérico de sódio  $> 135$  mEq/L ( $P = 0,03$ ) foram maiores nos doentes do grupo II. A probabilidade de perda do enxerto no transplante hepático intervivos teve como variáveis independentes o índice MELD  $\geq 18$  e a relação GRBW  $< 0,8$ . *Conclusão* - Os valores de MELD  $> 18$  e GRBW  $< 0,8$  estão associados com maior probabilidade de insucesso no transplante hepático intervivos.

**DESCRIPTORIOS** – Transplante de fígado. Doadores vivos. Prognóstico. Disfunção primária do enxerto. Sobrevivência do enxerto.

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