Early graft dysfunction following adult-to-adult living-related liver transplantation: Predictive factors and outcomes

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RESULTS: A trend in favor of the non-EGD group (3-mo actuarial survival 98% vs 88%, \( P = 0.09 \); 3-mo graft mortality 4.7% vs 20%, \( P = 0.07 \)) was observed as well as shorter LOS (13 d vs 41.5 d; \( P = 0.001 \)) and smaller requirement of peri-operative Units of Plasma (4 vs 14; \( P = 0.036 \)). Univariate analysis of pre-transplant variables identified platelet count, serum bilirubin, INR and Meld-Na score as predictors of EGD. In the multivariate analysis transplant Meld-Na score (\( P = 0.025 \), OR: 1.175) and pre-transplant platelet count (\( P = 0.043 \), OR: 0.956) were independently associated with EGD.

CONCLUSION: EGD can be identified preoperatively and is associated with increased morbidity after LRLT. A prompt recognition of EGD can trigger a timely treatment.

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Key words: Small-for-size graft dysfunction; Living-related liver transplantation; Graft-to-recipient body weight ratio; Partial liver transplantation; Allograft dysfunction

INTRODUCTION
Small-for-size graft dysfunction (SFSGD) is one of the greatest limiting factors for the expansion of segmental liver transplantation from living donors\(^1\), and is characterized by: (1) onset within 2 wk after living-
related liver transplantation (LRLT); (2) a graft-to-
recipient body weight ratio (GRBWR) below 0.8%; (3)
total bilirubin higher than 5 mg/dL, and/or output of
ascites through abdominal drainages of more than 1 L/d;
and (4) exclusion of technical (e.g. arterial or portal
occlusion, outflow congestion, bile leak), infective (e.g.
sepsis) and immunological (e.g. acute cellular rejection)
complications.

By definition, SFSGD can be diagnosed only in the
presence of a GRBWR of less than 0.8%, or a ratio of
graft volume (GV) relative to the standard liver
volume (SLV) of the recipient (GV/SLV) of less then
30%[5-6]. However, despite a GRBWR above 0.8%, some
recipients of LRLT may have a worse clinical course.

The aim of this study was to analyze a group of
LRLT recipients in order to identify those who
developed a clinical picture of SFSGD in the absence of
a GBWR of < 0.8% and with a GV/SLV ratio highest
than 30%. Those patients were defined as affected by
early graft dysfunction (EGD).

MATERIALS AND METHODS

We evaluated the rate of EGD in 73 consecutive recipi-
ents of adult-to-adult LRLT performed at our institute
between July 2004 and September 2008, and whose
GRBWR was > 0.8% and with a GV/SLV ratio higher
than 30%. Follow-up in months was 27.34 ± 13.77.

There were 43 males and 30 females, with a median
age of 57 years (range 18-68 years). The etiology of the
liver disease was related to hepatitis C virus infection in
47 cases, to hepatitis B virus infection in nine patients,
to both B and C virus infection in three patients, and to
non-viral causes in 14 patients. Twenty-two patients had
hepatocellular carcinoma (HCC). Donor liver resection
resulted in 73 right heptectomies (liver segments 5-8).
Graft implantation was performed with the piggy back
 technique and, in all cases, with the use of veno-venous
bypass. Details of surgical procedures are reported
elsewhere[5,6]. Volumetric computed tomography (CT)
scan was used to calculate liver and spleen volumes.

The main measures of outcomes analyzed were
overall mortality, number of re-transplants and length of
stay in days (LOS).

In order to identify predictors of EGD, epidemiologic
pre-transplant variables such as age of the recipient and
donor, sex of the recipient and donor, recently reported
as markers of graft function[7,8], were evaluated (Table 1).

Furthermore, we analyzed other clinical pre-trans-
plant variables such as: serum bilirubin, serum albumin,
serum sodium, INR, platelets count, WBC count, Child-
Pugh score, MELD score, Meld-NA score, recently
described[9-10], percentage of donor liver steatosis, liver
volume and spleen volume evaluated using CT, spleen/
liver volume ratio (S/LVR), GBWR and GV/SLV
(Table 2).

Then we observed the following intra-operative
parameters: mean arterial pressure, systemic vascular
resistance, cardiac output, cardiac index, units of
transfused packed red blood cells, units of transfused
platelets, and units of transfused fresh frozen plasma
(Table 3).

Finally as post transplant data we looked at the LOS.

Statistical analysis

Survival analysis was performed using the Kaplan-
Meier analysis with SPSS (SPSS Inc., Chicago, III, United
States), and a descriptive analysis was used for the out-
come. Normality was tested with the Wilk-Shapiro test.
Differences between the two groups were tested using
the unpaired Student’s t-test, Mann-Whitney test, χ² test;
P < 0.05 were considered significant. Multivariate analy-
ysis was performed to identify independent determinants
for occurrence of EGD (logistic regression stepwise
backward procedure).

RESULTS

Ten out of 73 patients (13.7%) fit our criteria for EGD.
No statistically significant differences were found
between EGD and non-EGD recipients in terms of
3-mo patient and graft mortality (one patient out of ten
(10%) vs one patient out of 63 (1.6%), P = 0.13; two
patients out of ten (20%) vs three patients out of 63
(4.7%), P = 0.07], number of re-transplants during the
first 3 mo after LRLT [one patient out of ten (10%) vs
two patients out of 63 (3.2%), P = 0.33] and 3-mo and
1-year actuarial patient survival (88% vs 98%; P = 0.09
by the log-rank test; 80% vs 94%; P = 0.12 by the log-
rank test).

The 4-year actuarial patient survival was 77.78%
vs 88.01%, (P = 0.201 by the log-rank test) (Figure 1).
Although the statistical analysis doesn’t indicate any
statistical significance, probably due to the small size of
the sample examined, the survival analysis points out a
lower survival rate (77.78%) on the EGD patient vs non-
EGD patient (88.01%); this is clinically relevant.

In the EGD patients, we observed two deaths: one
because of sepsis and the second one due to multiorgan
failure. In the non-EGD group, we observed six deaths:
three because of neoplastic recurrence of HCC and
due to multiorgan failure. HCC recurrence could be
explained by the advanced stage of the tumor at the
pathologic examination, although the patients were
classified within Milan criteria.

We did observe a significant difference between the
two groups in terms of LOS, with the EGD group having
a longer median LOS (13 d vs 41 d, \( P = 0.001 \)) and greater median number of units of plasma transfused during surgery (4 vs 14, \( P = 0.036 \)).

At univariate analysis of the variables collected, INR, platelet count, serum bilirubin and Meld-Na score, were identified as predictors of EGD (Table 3).

In the multivariate analysis (logistic regression, backward stepwise procedure), we analyzed INR, platelet count, serum bilirubin and Meld-Na score. Meld-Na score (\( P = 0.025 \), OR: 1.175) and pre-transplant platelet count (\( P = 0.043 \), OR: 0.956) were the variables independently associated with occurrence of EGD (Table 4).

In conclusion, the main clinical outcomes of the two groups were not statistically significant in terms of both early and late patient survival, probably because of the small size of the sample. In fact, as the survival rate was 77.78% vs 88.01% for EGD and non-EGD patients, we can hypothesize that survival rate acquires a statistically significant difference by enrolling a larger number of patients.

**DISCUSSION**

A GRBWR below 0.8% is considered mandatory for the diagnosis of SFSGD. Despite these findings in the literature, there are few patients who fully develop SFSGD by classic definition.

On the other hand, there are many patients who do not do well immediately after LRLT. We observed a clinical picture similar to that of SFSGD in patients who received partial livers that could not be described as small (GRBWR > 0.8).

In this study, the relevant clinical impact of EGD is suggested by the reduced 3-mo and 1-year patient survival and the increased graft-loss rate in the group of patients with this condition, even though there was no statistically significant difference, which is probably
due to an insufficient sample size (and a small number of events). The increased LOS in the EGD group reflects the increased time of recovery. Those patients who developed EGD were in fact those with worse INR, platelet count and total bilirubin. In addition, as previously reported by Yoshizumi et al, we noted that patients with a higher MELD score, higher Child Pugh score and hyponatremia, tended to have a worse outcome.

In fact, in the EGD group (Table 3), these parameters were higher than in the non-EGD patient.

Our data, although not significant in accordance to others, are clinically relevant especially at the time of selection of donors and recipient.

Our study was also aimed at finding objective criteria for identifying those patients who had a worse clinical course in the 2 wk after LRLT, and with a GRBWR above 0.8%. Our data support the hypothesis that SFSGD and EGD have a multi-factorial genesis in which the combination of the donor’s factors (GV and quality of the graft) and the recipient’s factors (portal hypertension and stage of liver disease) lead to allograft dysfunction after partial liver transplantation.

The clinical variables identified at the univariate analysis as predictors of EGD confirmed the relevant roles of liver disease and portal hypertension in graft dysfunction.

Serum bilirubin, INR, and Meld-Na score are markers of liver function and platelet count is a marker of portal hypertension. However, at the multivariate analysis, the only variables independently associated with occurrence of EGD were Meld-Na score and pre-transplant platelet count.

The transplant community is now focused on the possibility of detecting predictive factors based on simple biochemical and imaging assessments which could allow physicians to treat those patients at risk of EGD immediately after surgery.

It has been demonstrated that in patients with cirrhosis and severe portal hypertension, the occlusion of the splenic artery causes a significant reduction in portal pressure, which is directly related to the spleen volume and indirectly related to the liver volume. This concept is at the center of our strategy for performing early splenic artery embolization for the treatment of SFSGD following LRLT.

EGD can be identified preoperatively and is associated with increased morbidity after LRLT. Obviously, a prompt recognition of EGD can trigger a timely and appropriate treatment.

REFERENCES


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