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Poor initial graft function after orthotopic liver transplantation: can it be predicted and does it affect outcome?

An analysis of 125 adult primary transplantations

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Abstract

Donor liver shortage is a persistent problem in liver transplantation. A more liberal donor acceptance policy may be a possible solution. However, this might put recipients at risk for initial poor function or even non function of the graft. Therefore risk factors for initial graft dysfunction should be identified, preferably by using an uniform definition of primary graft dysfunction or non function.

We retrospectively analyzed 125 adult liver transplantations in order to identify risk factors for initial poor function and primary non function. Donor, recipient pretransplant and surgical parameters were evaluated. Since there is no consensus on the criteria of dysfunction we used two definitions known from literature. No risk factors for postoperative dysfunction could be identified for either of the two definition sets. Furthermore, the definition set that included ALAT, prothrombin time and bile production in the first 72 hours to identify poor graft function showed no relation with graft or recipient outcome. The other set, using ASAT and prothrombin time, determined from day 2 through 7, showed that patients with a primary dysfunction had significantly higher morbidity and mortality, compared to patients with a well functioning graft.

We conclude that initial poor function after liver transplantation remains unpredictable, irrespective of the way it is defined. Moreover, our analysis shows that initial poor function can also develop in recipients that receive “non-marginal” grafts without prolonged ischemia times. These results may support a more liberal selection of donor livers.

Introduction

Organ shortage remains an important problem in liver transplantation. In order to expand the available organ pool, a solution might be to accept so-called marginal quality donor livers. However this may result in an increase of morbidity or mortality. Selection of liver donors remains a continuing enigma about which many reviews have been written. Many potential risk factors for post operative graft dysfunction have been identified such as age, length of ICU stay, the cause of brain death and the use of vasopressors in donors. The data available so far are inconclusive for several reasons. First of all it is not just the
donor but also the operation and the condition of the recipient that influence 
etui early function of the transplanted liver. Only a few reports take all these 
variables into account. A second reason might be that end points in these studies 
differ. Some have looked at survival while others have looked at early graft 
(dys)function. Unfortunately no consensus exists on the definition of early graft 
dysfunction. A third reason might be that factors unrelated to the parameters 
included influence outcome. Factors such as, surgical technique, like split liver 
and reduced size liver transplantation and retransplantations could well be 
confounding variables in this respect. Even the type of preservation fluid may 
influence outcome.

It is for these reasons that an analysis of associated and perhaps prognostic 
factors was performed of all adult primary orthotopic whole liver transplantations 
in one center. Retransplantations, which are reported to be associated with 
increased morbidity and mortality were excluded. Also excluded were pediatric 
liver transplantations, because split liver and reduced size liver transplantation 
are commonly used, which in itself will influence postoperative graft function. 
Also, we included only livers that were perfused with University of Wisconsin 
solution. In that way, a homogeneous, well defined group of liver transplantations 
was selected.

Since it is not clear which definition should be used to evaluate post operative 
graft function, two definitions as described in literature were evaluated. First 
we applied the criteria of Ploeg et al. \(^5\) and secondly the definition of Gonzalez 
et al. \(^6\) for reason of validation and comparison.

Finally we compared morbidity and survival between groups with good and 
poor graft function using the same definitions for post operative graft function.

Patients and Methods

Design of the study

A retrospective cohort study was performed on 125 adults who received their 
first liver graft between September 1988 and March 1994. Inclusion stopped in 
‘94 in order to ensure a one year follow-up. The diagnoses leading to end-stage 
liver disease are shown in Table 1.
Patients were grouped according to graft function using two definition sets, i.e. that of Ploeg et al.\textsuperscript{5} and that of Gonzalez et al.\textsuperscript{6}. Within one definition set, groups were compared with regard to donor, surgical and recipient parameters. Morbidity and survival in each group was assessed and compared.

Donor selection criteria, operative technique and immunosuppressive regimen

Only donor livers that fulfilled the following criteria were accepted. Donors should not be over the age of 65, should have no history of liver disease, alcoholism or drug abuse. They should not have experienced hypotensive periods or should have recovered from a hypotensive period for more than 24 hrs. with normal or near normal liver function tests afterwards. They should not have received consistently more than 10 μg/kg/min. of dopamine. Liver function tests should be less than triple normal values. All livers were preserved in University of Wisconsin solution.

Recipient hepatectomy and implantation of the donor liver were performed according to the techniques described by Starzl\textsuperscript{7,8} using a venovenous bypass with a portal\textsuperscript{9} or inferior mesenteric vein catheter\textsuperscript{10}.

Anesthetic techniques were standardized using vecuronium, midazolam and fentanyl for induction and fentanyl and midazolam for maintenance anesthesia. Immunosuppressive therapy consisted of methylprednisolone 1000 mg on the day of operation, cyclophosphamide for 7 days (100 mg), prednisolone 200 mg for
3 days, then 100 mg for 4 days and then tapered guided by liver tests and clinical condition. Azathioprine was given in a dose of 125 mg/day. Cyclosporine was started around day 3 aiming for a whole blood level between 200 and 250 ng/ml (determined by HPLC method). After 3 weeks trough levels were maintained between 100 and 150 ng/ml.

**Graft function**

In the first analysis patients were classified as either having immediate function or suffering from primary dysfunction using the criteria defined by Ploeg et al. Primary dysfunction was diagnosed if ASAT >2000 U/L and prothrombin time >16 sec on day 2-7 (initial poor function), or death or regrafting occurred on day 1-7 (primary non-function). All other patients were diagnosed to have immediate function.

The second analysis graded initial graft function using the parameters defined by Gonzalez et al (Table 2).

These parameters are obtained in the first 72 hours after transplantation. In each patient the score was calculated from the sum of the assigned values of each parameter. Patients were considered to suffer from severe graft dysfunction if the sum was 7-9, to have moderate graft function if the sum was 5 or 6 and to have good early graft function if the sum was 3 or 4.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Assigned value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ALAT (U/L)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>1</td>
</tr>
<tr>
<td>1000 – 2500</td>
<td>2</td>
</tr>
<tr>
<td>&gt;2500</td>
<td>3</td>
</tr>
<tr>
<td>Bile output (ml/24 hr.)</td>
<td></td>
</tr>
<tr>
<td>&gt; 100</td>
<td>1</td>
</tr>
<tr>
<td>40 – 100</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>3</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 60 while receiving FFP</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 60 despite receiving FFP</td>
<td>3</td>
</tr>
</tbody>
</table>

ALAT = alanine-amino-transferase  
FFP = fresh frozen plasma

Table 2 Criteria according to Gonzalez et al. for classifying graft function (after OLT)
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Potential risk factors

The qualitative donor parameters at the time of explantation are shown in Table 3. The cause of brain death was also included as a variable. Diagnoses were isolated head trauma, polytrauma with brain trauma, cerebral bleeding, brain tumor and other.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Ploeg Criteria</th>
<th>Gonzalez criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td>Age (yr.)</td>
<td>31(11-59)</td>
<td>32(12)</td>
<td>30(12)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75(48-95)</td>
<td>70(9)</td>
<td>72(10)</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>3(0-27)</td>
<td>3(5)</td>
<td>3(3)</td>
</tr>
<tr>
<td>ASAT (U/L)</td>
<td>43(1-139)</td>
<td>38(20)</td>
<td>44(32)</td>
</tr>
<tr>
<td>ALAT (U/L)</td>
<td>31(1-189)</td>
<td>29(18)</td>
<td>31(30)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>65(23-207)</td>
<td>71(50)</td>
<td>64(28)</td>
</tr>
<tr>
<td>α Glutamyl transpeptidase (U/L)</td>
<td>22(2-160)</td>
<td>14(6)</td>
<td>23(26)</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>16(3-93)</td>
<td>15(13)</td>
<td>16(13)</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>52(24-77)</td>
<td>54(7)</td>
<td>52(11)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>34(14-58)</td>
<td>34(6)</td>
<td>33(10)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>82(43-203)</td>
<td>71(24)</td>
<td>84(28)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>148(127-182)</td>
<td>147(14)</td>
<td>148(10)</td>
</tr>
</tbody>
</table>

Table 3  Donor variables at the time of harvesting

In the overall column values are median and range. In the other columns mean values are given whilst values in brackets are standard deviations. Group 1 according to the Ploeg criteria is suffering from initial dysfunction while group 2 has immediate function. Group 1 classified using the Gonzalez criteria is having good initial function while group 2 has moderate function and group 3 has severe graft dysfunction.

Perioperative variables analyzed were total ischemia time (cold ischemia time and warm ischemia time) and peroperative blood loss.

Recipient variables assessed at the time of transplantation were divided into two groups. The quantitative variables are shown in Table 4.
In the overall column values are median and range. In the other columns mean values are given whilst values in brackets are standard deviations.

Group 1 according to the Ploeg criteria is suffering from initial dysfunction while group 2 has immediate function. Group 1 classified using the Gonzalez criteria is having good initial function while group 2 has moderate function and group 3 has severe graft dysfunction.

The qualitative variables included were: the presence of insulin dependent diabetes mellitus, hepatorenal syndrome (defined as creatinine clearance < 90 ml/min and signs of sodium and water retention), previous abdominal surgery, pretransplantation treatment with antibiotics, lactulose or immunosuppressive drugs before transplantation, Child-Pugh score, Karnofsky score, UNOS score and gender.

### Table 4 Recipient variables at the time of transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Ploeg Criteria</th>
<th>Gonzalez criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44(18-64)</td>
<td>42(12)</td>
<td>43(11)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>29(18-72)</td>
<td>29(4)</td>
<td>30(7)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>43(27-125)</td>
<td>43(8)</td>
<td>45(13)</td>
</tr>
<tr>
<td>AT III (%)</td>
<td>43(4-109)</td>
<td>46(21)</td>
<td>50(25)</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>139(9-796)</td>
<td>170(165)</td>
<td>228(219)</td>
</tr>
<tr>
<td>Cholinesterase (IU/L)</td>
<td>785(149-3972)</td>
<td>1036(654)</td>
<td>885(574)</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>2.3(0.5-7.4)</td>
<td>2.4(1.1)</td>
<td>2.5(1.3)</td>
</tr>
<tr>
<td>Creatinine (g/L)</td>
<td>1.8(36-655)</td>
<td>85(34)</td>
<td>125(124)</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>5.2(1.3-21)</td>
<td>5.8(4.7)</td>
<td>6.5(3.7)</td>
</tr>
<tr>
<td>ASAT (U/L)</td>
<td>105(15-2529)</td>
<td>99(64)</td>
<td>173(265)</td>
</tr>
<tr>
<td>ALAT (U/L)</td>
<td>72(12-6931)</td>
<td>63(49)</td>
<td>218(725)</td>
</tr>
<tr>
<td>PTT (sec)</td>
<td>19(10-92)</td>
<td>20(6.0)</td>
<td>22.7(12.9)</td>
</tr>
<tr>
<td>Thrombocyte count (x10^9/L)</td>
<td>91(13-600)</td>
<td>125(93)</td>
<td>120(94)</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>5.6(0.9-49.2)</td>
<td>6.0(4.4)</td>
<td>8.6(8.5)</td>
</tr>
</tbody>
</table>
Group 1 according to the Ploeg criteria is suffering from initial dysfunction while group 2 has immediate function. Group 1 classified using the Gonzalez criteria is having good initial function while group 2 has moderate function and group 3 has severe graft dysfunction.

Assessment of morbidity and survival
Morbidity was assessed by length of ICU stay, number of days on the ventilator, length of hospitalization, the need for relaparotomies, the occurrence of gastrointestinal or abdominal bleeding needing interventions, peak creatinine levels in the first week after transplantation and the occurrence of bacterial infections in the first 3 months after transplantation. Pneumonia was diagnosed if the clinical pulmonary infection score was ≥ 7. Cholangitis was diagnosed in case of fever, chills, contaminated bile and obstruction of the biliary system. Abdominal infection was present in case of fever > 38°C and a positive ascites culture or when an abdominal abscess was surgically drained.

Follow up was one year, during which cumulative graft and patient survival probability was assessed.

Statistical analysis
Statistical analyses were performed using SPSS® for Windows. If two groups were compared, continuous variables were tested using the Student t-test for
normally distributed variables. In case three groups were compared a one-way ANOVA was performed. If the F-value was significant the Bonferroni test for multiple comparison was performed. Quantitative variables were evaluated using the Pearson chi-square test. If expected cell frequency was < 5 Fisher exact test was used. Significance was reached if p<0.05. Logistic regression was performed with those variables associated with outcome parameters with a p-value <0.1 in a stepwise backward manner. Patient and graft survival were compared with the log rank test (Kaplan-Meier).

Results

**Graft Function**

Sixteen out of 125 patients (13%) were classified as suffering from initial dysfunction according to the Ploeg criteria. Six of these 16 patients (5% of the total population) were suffering from primary non function, i.e. these patients died or were regrafted within days 1-7. One patient died because of a ruptured splenic artery aneurysm, another died of a subarachnoidal bleeding, while having normal clotting factors, in the third patient treatment was terminated after 2 days because of irreversible brain damage during transplantation, and a fourth patient died of septic shock while having a severe rejection. The other two patients suffered from hepatic artery thrombosis for which they were regrafted. The remaining 109 (87%) were classified as having immediate function.

If the criteria defined by Gonzalez were applied, 23 (18%) patients were suffering from severe graft dysfunction, 41 (33%) were classified as having moderate graft function and 61 (49%) were having immediate good function. Table 6 shows the distribution of the patients using the 2 definitions.

<table>
<thead>
<tr>
<th>Gonzalez criteria</th>
<th>Ploeg criteria</th>
<th>Immediate function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good graft function</td>
<td>Primary dysfunction</td>
<td></td>
</tr>
<tr>
<td>Moderate graft function</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Severe graft dysfunction</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

*Table 6*  Relation between the two definitions used to identify dysfunction
Potential risk factors
The mean values of the quantitative donor variables in different groups are shown in Table 3. No differences were found between the groups, identified within each definition set.
For the whole study population, the mean perioperative blood loss was 11.8 liters (range 1.9-90). The mean total ischemia time was 12 hrs 24 min (range 6 hrs - 21 hrs 15 min).
In the group with initial dysfunction (Ploeg criteria) these values were 14.6 liters (±9.6) and 11 hrs 32 min (±4 hrs), respectively. In the group with immediate function the mean blood loss was 11.4 liters (±11) and total ischemia time was 12 hrs 31 min (±4 hrs). This did not differ significantly (Student t-test). If patients were grouped according to Gonzalez, mean blood loss was 11.3 liters (±12.6) in the group with good early function, 11.5 liters (±8.7) in the group with moderate graft function and 14.1 liters (±9.4) in the group with severe graft dysfunction. Total ischemia times were 12 hrs (±4 hrs), 13 hrs 40 min (±4 hrs) and 11 hrs (±4 hrs) respectively. Nor blood loss nor ischemia time differed between any of the three groups (ANOVA).
The mean values of the quantitative recipient variables are shown in Table 4. No differences were identified between the groups of either classification.
The qualitative variables are shown in Table 5. Using either definition, none of the variables differed significantly between the groups.

Morbidity and survival
If the Ploeg criteria are applied, patients with initial dysfunction compared to those with immediate function were longer ventilator dependent (13 versus 4 days, p<0.05) and had higher postoperative peak creatinine levels (250 versus 141 mmol/l, p<0.001) (Student t-test).
Patients with initial dysfunction had pneumonia more often (25 versus 8%), experienced more often periods of septic shock (31 versus 6%, p<0.006), had post-operative abdominal bleeding more frequently (44 versus 17%) and underwent more relaparotomies (63 versus 26%) when compared with patients with immediate function (Pearson chi-square test). All other monitored complications did not differ between the two groups.
Figure 1 shows survival in the groups identified using the Ploeg criteria. Survival is significantly lower in the group with initial dysfunction (log rank test, p=0.0001).
In case of classification according to Gonzalez et al., severe graft dysfunction resulted in the same morbidity as moderate or good early graft function with two exceptions. Peak creatinine levels (241 versus 127 and 147 mmol/l, p<0.05) (One way ANOVA) and the frequency of pneumonia (26 versus 10 and 5 %, p<0.02) (Pearson chi-square test) were higher in the group with severe graft dysfunction. Survival (Fig. 2) in the three groups did not differ (log rank test).

Discussion

This study focussed on the identification of risk factors for poor liver graft function and on the impact of initial post-operative graft dysfunction on morbidity and survival.

The frequency of poor graft function in our series is comparable to reports from other centers if the criteria that are known, are applied. However, none of the tested donor, recipient or peroperative parameters was identified as a risk factor, in contrast to other reports.
The fact that we could not identify so-called marginal donors might be because of our strict donor acceptance protocol. However, it is clear from Table 3 that donor data at the time of harvesting were not always within the limits of our protocol. A possible explanation is that donors deteriorate in the time between acceptance and harvesting, or that in case of urgent transplantations, acceptance criteria tended to be more liberal. In our study steatosis of the liver was not included. We did not routinely perform liver biopsies, but only if during explantation severe steatosis was suspected. Therefore we did not take into account steatosis as such but just donor weight, as was done in another study. In contrast to the report by Mor et al. we did not find donor weight a risk factor. Reports have shown that recipient parameters such as UNOS status and age were risk factors for survival or initial graft function. In accordance to the study by Ploeg et al. we did not find these factors to be related to primary dysfunction. In contrast with Ploeg et al., we could not confirm the relation between recipient renal insufficiency and primary dysfunction. This might be due to a difference in study design: we looked for correlations using creatinine as a variable, while in the Ploeg study renal insufficiency (defined as creatinine >2.5mg% and urine output <500 ml/24 hrs) was used as the endpoint. Since we
used hepatorenal syndrome instead of renal insufficiency, it certainly will have led to different groups. As only four patients were on continuous venovenous hemofiltration at the time of transplantation, this small number does not justify any conclusion on a potential relation between recipient renal replacement therapy and primary dysfunction.

Blood loss has been identified as a perioperative risk factor. Our study does not confirm these findings. The reason might be that an increase in blood loss is a sign of technical and peroperative problems and not in itself a reason for decreased post operative graft function, when adequate peroperative and postoperative treatment was possible. Ischemia time was also reported to be associated with early post-operative graft dysfunction. Our results did not confirm this. Since all our donor livers were preserved in UW solution and no extreme preservation times were necessary, this is not an unexpected finding. Another explanation for the discrepancy between our and other studies is perhaps the more heterogeneous groups that were studied.

We also investigated the clinical impact of poor graft function as identified by the two definitions. Our data confirmed that livers showing primary dysfunction (Ploeg criteria) tend to do less well with regard to patient morbidity and mortality (Fig. 1). This finding was not unexpected because death on day 2 through 7 was an endpoint which was included in the definition described by Ploeg. A second reason was that in two patients a hepatic artery thrombosis occurred leading to regrafting in the first week. This was indeed graft failure. We think hepatic artery thrombosis should be excluded from the evaluation since these two livers showed no abnormal liver tests for the first 5 days. If in our study patients were excluded who died from causes unrelated to initial graft function (4 patients) or had hepatic artery thrombosis (2 patients), with initially normal liver function, initial dysfunction as defined by the Ploeg criteria was no longer related to survival. In contrast to the findings reported by Gonzalez, in our series outcome between the three groups did not differ. A possible explanation for this discrepancy might be the time of follow up. Evaluation was restricted to one year. It is highly unlikely that a graft that fully recovers from initial poor function still differs from any other liver after one year.

An even more interesting point in our study is that if two definitions were applied on the study group to identify livers with initial graft dysfunction, only 10 patients were having poor initial graft function in both grading systems. Table 6
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shows that 13 of 23 livers (57%) which were identified by Gonzalez as suffering from severe graft dysfunction were identified as immediate functioning using the Ploeg definition. This means that most livers with initially elevated liver tests will recover normal liver function within two days. In our study 23 (19%) patients had high transaminases and prolonged prothrombin time in the first 2 postoperative days (i.e. belonged to the group with severe graft dysfunction using the Gonzalez criteria). Our data show that not all of these grafts with severe dysfunction developed graft failure. Graft survival in this group is 70% after 3 months while it was 80 and 83 % in the other 2 groups. No statistical differences were found here.

On the other hand 6 patients identified by Ploeg as suffering from initial poor graft function were not suffering from severe graft dysfunction using the Gonzalez criteria. These six patients were the same as mentioned before, i.e. those that were included in the initial dysfunction group because of death or hepatic artery thrombosis on day 1 through 7, while having normal post-transplantation liver function. These findings stress again that postoperative classification of graft function is difficult and that consensus is needed in order to compare risk factors and outcome of poor initial graft function.

In conclusion, in a homogeneous group of donor livers and recipients no risk factors for initial graft function or primary non function could be identified. Concordance between the definitions of initial graft dysfunction by Ploeg and Gonzalez was low: only 34 %. Moreover, if initial graft function was not optimal, the postoperative course was not different from patients with good initial graft function. Since in this series no pretransplantation risk factors could be identified and the frequency of primary dysfunction was as high as in other reports, efforts should be made to look for new and better tests. Until better tests are available a less restrictive donor acceptance protocol is justified, which might decrease donor liver shortage.
References

18. Alexander JW, Carey MA. The use of marginal donors for organ transplantation: the older and
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Initial graft function after OLT
Zo is het vreemde

Ik zie en ben begonnen