Transpl Int (2000) 13 [Suppl 1]: S249–S252

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A proposal for scoring marginal liver grafts

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Abstract The aim of this study is to assess the effect of accumulation of marginal liver graft criteria on the immediate outcome of liver transplantation (LT). The last 325 consecutive LT performed in 293 patients were analyzed retrospectively with respect to donor acceptance criteria. A marginal liver score was elaborated on the basis of the following features: donor > 60 years, ICU stay > 4 days, cold ischemia times > 13 h, hypotensive episodes < 60 mmHg > 1 h, bilirubin > 2.0 mg/dl, ALT > 170 U/l, and AST > 140 U/l were scored with the value 1. The use of dopamine doses > 10 μ/kg per min and peak serum sodium > 155 mEq/l were labeled with value 2. The cut-off point at 6 months after LT revealed 42 deaths (14%), with 65 graft losses (20%) and 32 (9%) retransplants. Recipient survival was not affected by the combined effect of marginal criteria. However, recipients transplanted with marginal livers with score 3 or more showed a decrease in graft survival (log-rank 6.21; $P = 0.045$) and an increase in delayed non-function rate (10 out of 33 vs 4 out of 156; $P = 0.03$). The use of marginal liver donors with more than three risk factors must be carefully reviewed or refused because of the cumulative dysfunction of these grafts.

Key words Marginal liver donors · Primary non-function · Delayed non-function

Introduction

In recent years, the number of liver transplants performed has been increasing and the number of solid organ donors has remained relatively static. This last factor seems to be a distinct limit of liver transplantation (LT), and the current balance between transplantation and organ availability is characterized by its fragility [7]. The ominous consequences of this fact are the deaths in waiting list [8]. To meet current European requirements, as many as 50 donors per million population (pmp) may be required, but the best results in organ retrieval are around 14–27 donors pmp [6].

The use of marginal donors is a strategy used mostly in large LT units. It supposes to accept more donors at the expense of diminished quality of their organs. This reduction in standards has been termed "expanding the donor pool". Powerful voices are raised in support of marginal grafts for liver recipients, and the limits have been progressively broken. Donor age is the most expanded criterion [1, 10]. Other criteria such as fatty livers, hemodynamic instability, prolonged ICU stay, and non-heart-beating donors have been recently expanded [3]. We have also reported the impact of high-inotropic drug use and hypernatremic donors on graft survival, primary non-function (PNF), and delayed non-function (DNF) [2]. The basis for the procurement of these livers is that the risk of death in waiting list outweighs the risk of graft loss from a marginal liver donor. However, these organs are inferior, one way or another, and the clinical outcome of transplant is more likely to be poor [9]. Moreover, some authors have stated that the combina-

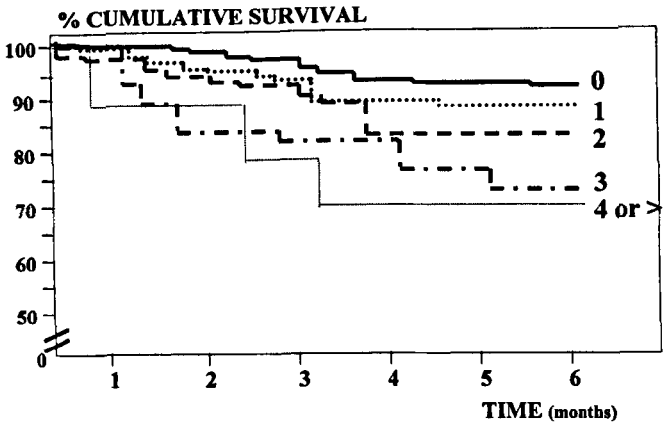

Fig. 1 Recipient survival at 6 months of follow up for each category of score. Survival functions are decreased with higher scores without reaching statistical significance

tion of significant factors should be avoided when possible [4]. The problem is the absence of a final consensus on the limits, and the single and cumulative impact of each criterion. The purpose of this study was to analyze the effect of the combination of marginal criteria in liver donors on the outcome of LT and to validate a scoring system for a "mathematical" acceptance of these poor-quality donors.

Patients and methods

The most recent of 325 consecutive LT performed in 293 recipients were reviewed retrospectively. Exclusion criteria for donor acceptance in this program included: sepsis, previous history of liver disease, tumors, and non-heart-beating donors. Marginal liver donor criteria were considered as follows: older than 60 years, a prolonged ICU stay (> 4 days with ventilatory support), a prolonged cold ischemia time (> 13 h), a high inotropic drug use (dopamine doses > 10 μ/kg per min, or any doses of other amines), prolonged hypotensive episodes > 1 h, < 60 mmHg, a peak serum sodium > 155 mEq/l, and high levels of bilirubin (> 2 mg/dl), SGOT (> 170 U/l), or SGPT (> 140 U/l).

We have scored our marginal criteria in two groups with respect to our previous report [2]: high-risk criteria (high inotropic drug use and hypernatremic donors) were scored with the value 2. Both these criteria showed a more than twofold risk increase in postoperative graft losses. The remaining criteria (low-risk group) were scored as 1. For each donor, a final score was computed as the sum of single scores. PNF was defined as non-recoverable hepatocellular function necessitating emergency retransplantation (ReLT) within 72 h. DNF was defined as a graft function necessitating ReLT within 1 month. Survival curves for each category of score were computed by the Kaplan-Meier method and compared with the exact log-rank test with confidence set at the 95% level. Frequency of PNF and DNF in each score was compared with the chi-squared test.

Results

The cut-off point of follow up of this study was 6 months. In this period, 42 deaths were reported (14%), 65 graft losses (20%), and 32 ReLT (9%). The distribution of donors in each score was: score 0 (no marginal criteria) = 156 donors, score 1 = 101 donors, score 2 = 35 donors, score 3 = 23 donors, and score 4 or more = 10 donors.

Recipient survival

Recipient survival in each group was computed at 1, 3, and 6 months, and compared with the control group (score 0). Recipient survival with score 0 was 98, 96, and 92%, respectively. Recipient survival with score 1 was 95, 92, and 88% (log-rank = 0.61; $P = 0.89$). Recipient survival with score 2 was 96, 90, and 84% (log-rank = 0.03; $P = 0.87$). Recipient survival with score 3 was 92, 82 and 74% (log-rank = 0.12; $P = 0.72$). Finally, recipient survival with score 4 or more was 90, 80, and 70% (log-rank = 0.12; $P = 0.71$). Even though survival curves are worse with higher scores, the accumulation of marginal criteria in this analysis did not reach statistical significance with respect to recipient survival. Survival curves of each category are depicted in Fig. 1.

Graft survival

Conversely, graft survival depended on the liver donor score. Graft survival with score 0 at 1, 3, and 6 months was 98, 96, and 92%, respectively. Graft survival with score 1 was 96, 91, and 86% (log-rank = 0.14; $P = 0.71$). Graft survival with score 2 was 89, 86, and 83% (log-rank = 4.23; $P = 0.12$). Graft survival with score 3 was 71, 66, and 60% (log-rank = 6.21; $P = 0.045$). Graft survival with score 4 or more was 60, 50, and 50% (log-rank = 6.32; $P = 0.012$). Accumulation of three or more criteria is accompanied with a dismal prognosis in graft losses. Survival curves for each score are depicted in Fig. 2.

PNF and DNF

PNF was an uncommon event in our series. Only three grafts with score 0 (2%), one graft with score 1 (1%), no grafts with score 2 (0%), one graft with score 3 (4%), and no grafts with score 4 or more (0%) fell into the category of PNF, without statistical differences between groups. However, a great number of grafts showed DNF and were lost with increasing score scale. DNF was presented in 4 grafts with score 0 (2%), three grafts with score 1 (3%), four grafts with score 2 (11%;

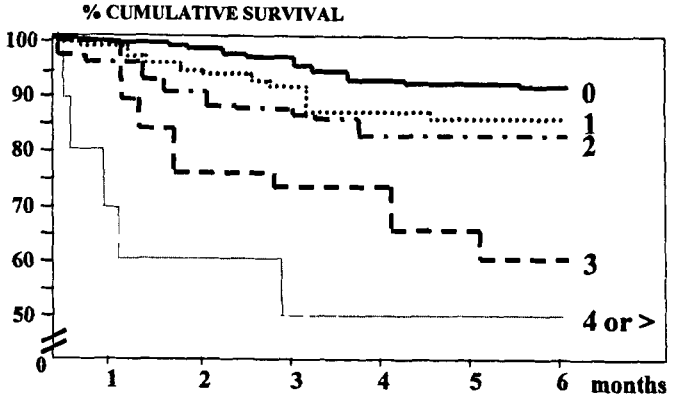

Fig. 2 Graft survival at 6 months of follow up for each category of score. Score 3 or more presents a worse graft survival than low scores

$P = 0.047$), six grafts with score 3 (26%; $P = 0.03$), and four grafts with score 4 or more (40%; $P = 0.02$).

Discussion

The current selection criteria for liver donation are the subject of controversy as they are of little value in the prediction of recipient and graft survivals. Since there is a great discrepancy between the increasing number of candidates for LT and the number of liver donors procured, the imbalance resolves in a rise in deaths in waiting list. To remedy this deficit, many LT teams have considered widening their list of liver donor acceptance criteria. The consecuence of this policy is to reduce the percentage of livers with a prompt recovery after grafting. An increase in PNF, DNF, and initial poor function are results expected of this controversy. LT units around the world are opening their minds with regard to the efficient use and proper administration of this very precious resource. The use of high-risk donors, also called "marginal" or "expanded" donors may be the most short term means to boost the organ donor supply. However, critical voices are raised in support of several parameters to be considered in a marginal liver donor for acceptance. The first of them is the fact that a marginal liver has to provide a similar recipient outcome as a good liver. In other words, the use of marginal donors in LT must outweigh the risk of death in waiting list. The second is to obtain acceptable graft survivals, with similar PNF and DNF rates. Finally, another concern is to establish predefined (and objective) limits to consider a potential donor. The data base of large series emphasizes that the first of these principles is generally obtained. However, acceptance of marginal donors increases the risks of primary dysfunction and negatively influences the results of LT. In this way, their discharge may reduce about 30% of the actual transplantation rates with unacceptable increasing of mortality in waiting list [4]. Another concern is relative to the design of the studies performed to assess these results. Most of them are retrospective and use univariate analysis with heterogeneous results. For obvious ethical reasons, it is difficult to put in place a prospective, randomized trial with donors and recipients of very different conditions, or without interaction of variables between one and another.

On the other hand, marginal donors include usually more than one liberalized criterion and the impact of cumulative effects must be defined. The present study is pointing to a cautious use of marginal liver donors with more than three criteria because of the worse graft survival and the increase in DNF rate. The question is if we can assume these risks or if they outweigh the risk of deaths in waiting list. The potential effect of the combination of some marginal factors on LT outcome have been studied in other reports. In this way, the negative addition of donor age and steatosis has been underlined by De Carlis and colleagues [4]. Similarly, steatotic livers seems to be more susceptible to cold ischemic injury [5]. Probably, the definition of score scales in each institution may facilitate the acceptance of these "high-marginal" liver donors.

In conclusion, an increase in the number of marginal criteria in the same donor correlates positively with the DNF rate and negatively with graft survival with respect to those liver transplants with "good" donors. At the end of the 90th, two positions can be assumed with respect to these donors: refusing them, or reviewing carefully recipient outcome with these organs and performing a ReLT when necessary.

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