USE OF EXTENDED CRITERIA OF DONORS IN LIVER TRANSPLANTATION

UTILIZAÇÃO DE DOADORES COM CRITÉRIOS EXPANDIDOS NO TRANSPLANTE DE FÍGADO

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ABSTRACT

The use of marginal/extended criteria for organ donors is a solution to the problem of organ donors shortage, and since its use has become more common worldwide, concerns on the effectiveness of such organs and the outcomes of the liver transplantation (LT) have been raised. In spite of the importance of the term, there is no consensus on the features of the marginal donors. Some parameters related to the features of those donors were found to have negative consequences: increasing donor or recipient age, longer cold ischemia time, hypotension and inotropic support, gender mismatch, after cardiac death donation, hearts that stopped beating, non-heart-beating donors, and macrosteatosis. This paper discusses some controversial issues found in the literature, and shares our experience related to the use of marginal/extended criteria of donor in liver transplantation.

Key Words: Liver transplantation, Marginal Donors, Donor Risk Index

INTRODUCTION

In the last few years, orthotopic liver transplantation (OLT) has shown some of the most successful results among some medical areas. Consequently, it has become the standard treatment for several end-stage liver diseases. This phenomenon is partly due to improvements in surgical techniques, immunosuppression, and patient management.

However, this success created a wide gap between organs demand and supply. While demand of liver transplantation increases worldwide, many countries have observed a shortage of available deceased donors, resulting in an increasing death rate among patients on the waiting list.[1] Furthermore, because of the model of end-stage liver disease (MELD) scoring system to the liver allocation, which denies the waiting time, people on the list are likely to be in critical need of liver transplantation.[2]

Therefore, specialized transplant surgeons and centers in liver transplantation are interested in expanding the pool of donors in looking for suitable liver grafts and identifying new donor sources. Some strategies have been used to achieve such goals: split/partial and DCD (donation after cardiac death) liver transplant, living donor transplantation (LDT),[3] and the use of the so-called marginal donors. Currently, split and DCD liver transplants account only for 2% and 1.1% of cases, respectively. Despite the higher risk of graft failure in such cases, the amount of these transplants has increased. LDT[4] represents a natural evolution of the procedure, based on the segmental liver anatomy, as its size is reduced in deceased and split transplants. Although this transplantation is suitable and is frequently performed in many transplanting centers, it poses a lot of difficulties, thereby limiting the use of this technique.[5] The procedure is more complex, needing a strong donor motivation, and showing a relatively high amount of complications.

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As a result, the focus among the transplantation community has recently turned to the use of previously considered non suitable organs. Because of that, criteria of an acceptable liver donor are changing, in order to meet patients on waiting list's needs. In general, "marginal donors," "suboptimal donors," or "extended criteria donors" are the ones with specific features that could have an impact in terms of short- or long-term risks to the recipient.[4] The study that could predict the availability of these donors was first reported by Alexander and Vaughn in 1991.[6] Nardo et al.[7] was the first to demonstrate that octogenarian donors' livers presented similar outcomes as those which came from standard young donors. Salizzoni et al.[7] reported that low-grade macrosteatosis livers also showed good outcomes, whenever the cold ischemia time (CIT) was kept below 10h. Other reports also demonstrated also that livers with some traumatic lesions[9,10] and HBcAb-positive11 (prophylaxis with lamivudine and hepatitis B-immune globulins) could be safely transplanted.

Considering the suitability of the extended criteria donors, this study aims to make a review on the use of marginal liver grafts as an additional resource to increase the amount of liver transplantation, in accordance with its factors and patient's outcomes.

Features of Marginal Donors

Since the 1980s, liver transplantation has been confined to optimal condition donors, often the whole organ from a male less than 40 years old and hemodynamically stable donor, and not at risk of transmitting diseases, with sustained brain death from cerebral trauma or anoxia.[12] Such cause of death has been generally related to a better functioning donor liver, compared to the death caused by cerebrovascular accident or stroke.

During the transplantation, the liver is submitted to an interruption of the blood supply, characterized by cold and normothermic ischemia. After this period, the blood supply is restored and the liver is subjected to aggression, and the injury initially caused by the ischemia, is aggravated. The ischemic/reperfusion (IR) is related to the donor's preceding medical status. A history of donor's drug or alcohol abuse, low blood pressure after brain death, fatty liver, hypotension during the donor surgery and surgical trauma contribute to the increased IR-induced injury.

Furthermore, improvements in surgical techniques and critical care management can expand situations which would provide optimal conditions. So, in order to avoid death of patients due to acute liver failure, nonstandard livers have been eventually transplanted, being achieved a great level of success. Some transplantation programs began using higher aged female donors with high serum sodium. Due to the increasing success attained by using nonstandard livers, the concept of marginal donors has not been established until now by the transplantation community. At this time, they can be inferred as "expanded criteria donors" presenting some risk factors that could lead to initial poor function (IPF) or primary nonfunctioning (PNF). However, some authors believe that such concept must be extended to donors also causing late graft loss.

The definition of marginal donors related to patient's outcomes also depends on the condition of the recipient. As an example, the incidence of post-transplant PNF due to sudden hepatic failure is higher than that observed in other indications. In addition, obesity (body mass index > 30 kg/m^2), renal insufficiency, and longer ICU stay in recipients are also related to the increased risk of postoperative complications.[2]

Among all features related to the recipient, donor and transplant, some can be highlighted: increasing donor or recipient age, longer CIT, hypotension and inotropic support, donation after cardiac death (DCD), heart that stopped beating, non-heart-beating donors (NHBD), macrosteatosis and gender mismatch.[2] **(Table 1)** There are specific combinations in which the donor and recipient match shows unfavorable outcomes: liver from a female donor transplanted to a male recipient or liver from an older than 65 years old donor transplanted to an HCV-positive recipient.[5] Renz et al.[13] reported that the use of livers which were previously rejected by other centers because of low MELD scores yielded similar results as using deteriorating liver transplanted from standard donors. Indeed, "nonstandard donors" presented even lower rates of postoperative complications.

The increasing knowledge of suboptimal grafts has allowed the expansion of some criteria, as, for example, donors at risk for HBV and HCV (to HBV- or HCV-positive recipient). Particularly, using HBV-positive organs the availability of both lamivudine and passive immunoprophylaxis is an adequate measure to prevent viral replication and disease in the recipient.[5]

Donor risk index

Analysis on liver transplantation risks have been based solely on the qualitative effects of individual donor variables, as well as the recipients' features by the MELD scoring system. Feng et al. recently proposed a donor risk index (DRI) combining the association of several donor factors into a single continuous rating. It can be used to compare the relative risk of graft loss for an organ with a specific set of donor and transplant parameters as reference case.[36] By the DRI, it was demonstrated that some donor's features previously identified as risk factors did not attain any significance, such as female sex, obesity, elevated aminotransferase, serum sodium levels, and hypotension. [36] However, macrosteatosis[40, 41], CIT, DCD, and split grafts are still related to graft failure.

It has been stressed that the OLT outcome is related to the status of the recipient. Because of this, livers at lower risk of failure have been directed toward patients at higher risk of waiting-list mortality. In contrast, it has been thought that low-MELD patients should tolerate OLT using livers recovered from extended criteria donors. Nevertheless, recent studies suggest that for low-MELD patients, the risk of death following OLT is higher than the risk of remaining on the waiting list. Lack of survival benefit for liver transplantation at low to medium MELD score is reinforced when high DRI livers are used, and even when high DRI livers were used for those with highest MELD scores, there was a significant survival benefit. Patients with higher MELD score face the major death risk without transplantation, having the greatest survival benefit from transplantation, even using the extended criteria donor.37,38 Recent data show that grafts with increased DRI seems to be preferentially transplanted in older candidates (>50 years of age) with moderate disease severity. Insights from DRI studies should lead to modifications of the liver allocation system.

Outcome of Extended Criteria Liver Grafts: the Oswaldo Cruz Hospital Experience

Between 1999 and 2006, 178 consecutive liver transplants were performed at Hospital Oswaldo Cruz; 137 transplants using marginal grafts were eligible for the study. A liver donor was

Table 1. *Correlation of factors underlying LT and Extended Criteria Donors*

Factors	Findings	References
Age	Donors with age > or < 50 yr have similar outcomes	14
	Liver recipients from donors > 70 yr are related to poorer survival rates	2, 15
	Elderly donors have more probability to develop endothelial cell injury due longer CIT	2
	Livers from elderly donors have increased incidence of steatosis	16, 41
	Livers from aged donors (50yr) can be safely transplanted	17, 18
Steatosis	Most common condition in liver grafts	19, 20, 21
	Common causes: older age, obesity and diabetes mellitus	24, 25, 32, 40
	Classification	26, 27
	. Mild (<30%*): no affection on long-term graft function and patient survivals	30
	. Moderate (30%-60%*): use remains controversial	29
	. Severe (>60%*): steatosis lead to 80% more chances to PNF	28
	. Macrosteatosis (single, bulky fat vacuole in the citoplasm of the hepatocyte)	22
	Considered a major cause of liver dysfuction in the posttransplantation period	41
	. Microsteatosis (diffuse accumulation of tiny lipid vesicles in the hepatocyte)	23
Serum	Hypernatremia is related to graft failure	31
Sodium	Liver grafts from donors with Na+ > 155 mEq/l have greater incidence of graft loss	32
Need for inotropic drugs	Use of norepinephrine and dopamine (10mg/kg/min) increase risk of graft poor fuction	33, 34
CIT	CIT > 14 hours is related to postoperative complications and decreased graft survival	35

*% of fatty infiltration; yr = years old

defined as marginal if it would meet at least one of the following criteria: over 55 years old donor, over 30% macroscopic steatosis; below 90 blood pressure hypotension in need of inotropic drugs (noradenaline at any dose or over 10 µg/kg/min dopamine); over 155 mEq/l hypernatremia; above 4 d stay at Intensive Care Unit (ICU); over 14 h CIT, high values of transaminase (over 170 U/l ALT or over 140 U/l AST), over 30 body mass index (BMI), cardiopulmonary arrest prior to donation or NHBDs. The optimum liver donor was considered whenever presenting none of the above criteria. There were six NHBD in our series.

Six-month-patient survival values for normal vs. marginal donors were 82% and 72% (P = 0.30). Six-month-graft survival figures for normal vs. marginal donors were 80% and 71% (P = 0.31). One-year patient graft survival values for normal vs. marginal donors were 79.5% vs. 67.9% (patient, P = 0.23), and 80% vs. 68.8% (graft, P = 0.23), respectively. The 6-month analysis and 1-year-patient survival curves for patients who received liver from ideal vs. marginal donors showed no statistically significant difference (P = 0.90 and 0.13 respectively, log-rank test, **Figure 1**). There was no significant difference between the 6-month-graft and 1-year-graft survival curves (Kaplan-Meier) for ideal vs. marginal grafts (P = 0.22 and P = 0.13 respectively, log-rank test, **Figure 1**).

These observations recommend the use of more tolerant marginal grafts, including grafts from NHBDs.

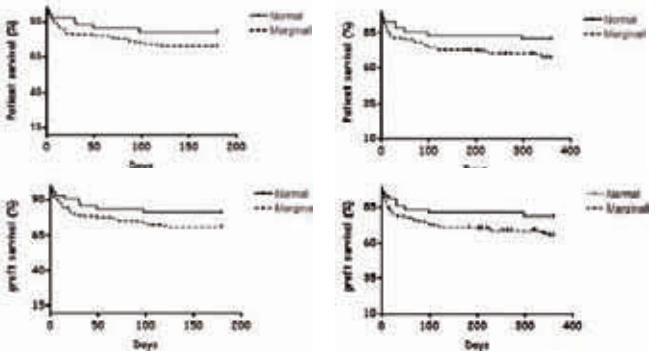
Limitations

Marginal donor livers have been used in a non-standardized way. There are no guidelines to the allocation of such organs, and the specific allocation policies have not yet been systematized. Up to this moment, there is not a ranking to the acceptance and rejection of a potential marginal organ. It was recently reported39 that several mistakes in the clinical assessment made by explanting surgeons result in discarding many potential marginal organs. Therefore, further in-depth investigation of the accuracy of clinical evaluation of marginal donor livers as well as their correlation to the histology is being proposed.

CONCLUSION

The use of extended criteria donors appears as an extraordinary resource to attend the needs of patients on waiting list. It has been proven to be an indispensable option to every transplant center. Donor risk index-based systems should regulate the national liver allocation policy in the future.

Figure 1. *Six-month (upper left) and one-year-patient (upper right) survival curves, and six-month (bottom left) and one-year-graft survival curves for patients (bottom right) and graft of patients who received liver from ideal donors vs. marginal donors showed no statistically significant difference (P > 0.05, Kaplan-Meier survival curves, log-rank test).*



RESUMO

Desde que o uso de doadores marginais, ou doadores com critérios expandidos tem se tornado mais comum como estratégia para enfrentar a carência de órgãos para transplante de fígado, há preocupações a respeito da segurança do uso desses órgãos e os resultados do transplante de fígado. Apesar da importância do assunto, ainda não há perfeito entendimento sobre a definição do termo doador marginal. Alguns parâmetros estão relacionados a uma pior função do enxerto, entre eles: idade avançada do doador ou do receptor, tempo prolongado de isquemia fria, hipotensão, sexo, doação após morte cardíaca e esteatose hepática. Este artigo discute os pontos controversos na literatura e apresenta nossa experiência com o uso de doadores marginais no transplante de fígado.

Descritores: Transplante hepático, Doadores marginais, Índice de Risco do Doador

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