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Is Marginal Donor an Efficient Solution for Expanding the Donor Pool for Liver Transplant?

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Rezumat

Este donatorul marginal o soluție eficientă pentru creșterea numărului de grefe pentru transplantul hepatic?

Odată ce tehnicile de chirurgie hepatobiliopancreatică s-au îmbunătățit, practicarea intervențiilor de transplantul de ficat s-a extins pe scară largă în diferite spitale; prin urmare, nevoia de grefe şi automat a donatorilor de ficat a raportat o creştere semnificativă în ultimul deceniu. În acest sens, atenția s-a concentrat pe creşterea fondului de donatori de ficat. Scopul acestei revizuiri este de a studia beneficiile utilizării grefelor marginale în transplantul hepatic. Odată cu apariția mai multor metode de conservare a ficatului, utilizarea grefelor considerate anterior necorespunzătoare a devenit posibilă. Astfel, au apărut criterii de alocare extinse. Cu toate acestea, alocarea acestor grefe trebuie luată în considerare şi analizată cu atenție în contextul factorilor legați de primitor şi donator.

Cuvinte cheie: donator marginal; transplant de ficat; fond de donatori

Abstract
Once the techniques of hepatobiliopancreatic surgery improved, liver transplantation widely extended in different hospitals; therefore, the need of grafts and automatically of liver donors reported a significant increase in the last decade. In this respect, attention was focused on increasing the liver donor pool. The aim of this review is to study the benefits of using marginal grafts in liver transplantation. With the advent of multiple methods of liver preservation, the use of grafts previously considered unsuitable has become possible. Thus, extended allocation criteria have emerged. However, the allocation of these grafts must be carefully considered and analyzed in the context of both recipient and donor factors.

Key words: marginal donor, liver transplantation, donor pool

Introduction

The main indications for liver transplantation are: end-stage liver cirrhosis - hepatitis C (HCV) liver related cirrhosis, hepatitis B ± D (HVB ± HVD) liver related cirrhosis, primary biliary cirrhosis-biliary cholangitis, biliary duct atresia, fulminant liver failure, metabolic diseases (Wilson's disease, amyloidosis, familial hypercholesterolemia), polycystic liver disease, primary unresectable liver tumors (hepatocarcinoma, hepatoblastoma) or Budd-Chiari syndrome (1,2). Therefore, liver transplantation remains the only chance of cure for patients with end-stage liver disease as well as for certain cases with advanced liver cancers or acute liver failure (3). However, there is an increasing discrepancy between waiting lists and available organs, the number of cases on the waiting list surpassing the number of available grafts. The lack of organs for transplant has made it necessary to expand the liver donor pool beyond the traditional criteria and to accept donors previously considered suboptimal, even if the risk for primary dysfunction or even nonfunction increases (4).

Although the availability of liver grafts increased in the last decade, the overall mortality on the waiting lists ranks between 5 and 10% due to the long waiting period (5). In order to decrease mortality and waiting time on these lists, currently marginal donors have been used, such as: advanced-age donors, steatotic grafts, non-heart-beating donors, HCV donors or HVB core positive antibody donors. In this respect, marginal donors have been traditionally proposed in high risk recipients (6).

An accepted definition of marginal liver donors has not been widely established within the liver transplantation community; however, cases with age over 70 years, macrovesicular steatosis >30%, moderate-to-severe liver preservation injury, high inotropic drug dose (dopamine >15 μg/kg/min; epinephrine, norepinephrine, or dobutamine at any doses), peak serum sodium >155 mEq/L, any hypotensive episode <60 mm Hg and >1 hour, cold ischemia time (CIT) >12 hours, intensive care unit (ICU) hospitalization >4 days, bilirubin >2 mg/dL, aspartate aminotransferase (AST) and/or alanyl aminotransferase (ALT) > 200 UI/dL are routinely included in this category (7).

Meanwhile, allocation policies for marginal donors aren't very clear, however, studies have shown that the Model for End Stage Liver Disease (MELD system)is not the most proper tool to be used due to the fact that it does not predict the quality of the graft (8).

Material and Method

Retrospective analysis of papers published on Pubmed, Embase, Cochrane Library and Google Scholar between 2015-2023 has been performed. A final number of 153 articles were found; however, this paper reviews only full text articles written in English and French, papers published in other languages or in which a full text version was not available being excluded. Finally, a number of 70 papers was reviewed.

Ethical Considerations and Patient Information

An ethical allocation practice is based on justice, equity, and utility. Candidates for transplantation must be informed about the possibility of allograft-specific risks. Moreover, a clear distinction between the risk of graft failure and the risk of disease transmission should also be emphasized as part of the informed consent process (9).

Along with the development of the new allocation criteria, a new ethical problem has arisen, that of informing the potential recipient about the quality of the graft which is to be transplanted. In this respect, certain institutions pay particular attention to this aspect and offer patients a separate consent form, which is strictly reserved for the allocation of marginal grafts.

Therefore, allocation policies must provide the best results both for each patient needs as well as for the population at risk.

Age

Elderly donors (>60 years) were the most important source of increasing donor pool. However, reports from various liver transplant registries have shown that donor age is a significant factor related to graft malfunction and patient mortality. Therefore, according to the European Liver Transplant Registry (ELTR) it seems that donor age > 60 years significantly increases the 3-month mortality rate (10). This aspect is explained through the fact that in contrast to other organs, liver may be more immune to senescence, particularly in otherwise healthy persons. This is possibly because of the liver's large functional reserve, regenerative capacity, and dual blood supply, which exceeds its metabolic needs. On the other hand, older donor livers tend to be smaller and darker-colored, and may have developed fibrous thickening of the capsule. The percent in which these morphologic changes impact on organ function after transplantation is still under investigation (10-11).

However, the subject of age is still widely debated; therefore, while certain authors sustain the fact that donors elderly than 60 years of age should be carefully selected (10), other authors came to demonstrate that harvesting a graft is a risk free procedure even in donors older than 70 years, no significant difference in patient and graft survival being observed when comparing the outcomes to those in which the liver donor was younger than 70 years. However, caution must be taken when using grafts from advanced-age donors because any additional risk factor in the donor such as steatosis or prolonged ischaemia may increase the incidence of organ dysfunction (12). Meanwhile, certain authors demonstrated that is rather preferable not to allocate elderly donors to HCV-infected recipients (11,12).

Gender

A multivariate analysis of United Network for Organ Sharing (UNOS) data conducted on patients between 1992 - 2000 showed that gender-mismatched liver transplant recipients had a higher likelihood of graft failure when compared with gender-matched liver transplant recipients (12.2% versus 11.3% respectively; p=0.013). Therefore, the study underlined the fact that a female recipient receiving a liver from a male donor had no increased risk of graft failure (11.5%). while in male recipients receiving female donor organs the graft failure risk was significantly higher (12.9%; p= 0.003) (13).

Steatotic Donors

Hepatic steatosis is a common finding, with a prevalence between 13% and 26% among both cadaveric and living donors. It is estimated that moderate to severe steatosis is encountered in approximately 20% of potential live donors. Given the steady increase in the average age of donors and the prevalence of obesity, an increase in the prevalence of hepatic steatosis is also expected (14-16).

According to the pathology studies, liver steatosis can be classified as microvesicular - in which small vesicles of lipids are present and they do not dislocate the nucleus and macrovesicular in which there is a large lipid vacuole which dislocates the nucleus; the latter one is assocaited with alcohol consumption, diabetes and obesity (17-20). When it comes to the severity of the disease, three types of hepatic steatosis have been described: mild (<30%), moderate (30-60%) and severe (>60%). While mild steatotic grafts are associated with improved post-transplant outcomes, moderate steatotic liver is considered marginal graft and can lead to poor liver function, especially if associated with other factors such as advanced donor age and prolonged cold ischaemia time. Steatotic livers have an increased sensitivity to endotoxin, endothelial damage, decreased adenosine triphosphate (ATP) stores, sinusoidal swelling and congestion following preservation and ischemia/reperfusion. The steatotic liver is characterized by a decreased tolerance to ischemia/reperfusion. It has been observed that the accumulation of fat in the hepatocytes and the increased cell volume cause an impairment at the level of liver microcirculation. Steatosis is associated with a malfunction of ATP production and storage, increased lipid peroxidation, and an increased release of tumor necrosis factor α which can be responsible for the lung damage occurred sometimes after transplant. The detrimental effect of steatosis may be due to the increased resistance of the sinusoids due to the presence of ballooned hepatocytes and/or sinusoidal lining cells after cold preservation and reperfusion. Therefore, if a moderate to severe grade of hepatic steatosis is detected, other variables supporting the use of grafting should be considered (21). A study in this regard showed that immediate post-transplant survival was significantly reduced in high-risk patients with MELD score >20 who received marginal steatotic grafts (21).

In the literature, the use of steatotic livers has been associated with poor liver function or even primary allograft dysfunction. Tekin et al. created a system to classify the donor as marginal or non-marginal, depending on age and grade of steatosis (22). However, according to a retrospective study conducted in Brazil on a group of 177 patients transplanted between October 1995 and May 2006, the score suggested by Tekin et al. could not predict initial primary dysfunction (23).

Donation after Cardiac Death

Donors in cardiac death (DCD) were divided into four categories: dead on arrival, unsuccessful resuscitation, awaiting cardiac arrest with ventilation switched off and cardiac arrest while brain-dead. The first two categories are considered uncontrolled donation and the second two categories are considered controlled donation (19). Therefore, in controlled donation, organs undergo a period of prolonged warm ischaemia before cold perfusion, associated with severe ischemic damage, leading to increased incidence of primary non-function (NFP) and reduced graft survival. However, interesting outcomes have been reported by using normothermic extracorporeal membrane oxigenation which transforms the initial period of cardiac arrest into ischemic preconditioning. On the other hand, controlled donation takes place in intensive care units, which reduces the period of warm and cold ischemia (12).

In addition, a higher incidence of intrahepatic ischemic biliary strictures and arterial complications has been recorded after transplantation with DCD grafts. In a recent UNOS study comparing 117 controlled DCD grafts with a group of donors in brain death (DBD) grafts, it was observed that the

PNF was 11.8% versus 6.4%, (p >0. 008), while 1-year graft survival was 72.3% versus 80.4%, (p >0.056). The survival rate was similar, but the retransplantation rate was higher among the DCD group, 13.9% versus 8.3%, (p >0.04) (24). Several recipient-related factors leading to graft loss were identified, such as: history of previous liver transplant, being on life support, prolonged hospitalization, dialysis therapy, serum creatinine > 2mg/dl, age > 60 years.

Donors with Positive Virology

In Western countries, HCV cirrhosis remains the most common indication for orthotopic liver transplantation (OLT). Despite the high risk of recurrent infection, postoperative outcomes are favorable: the 5-year patient and graft survival are comparable to those with other indications. However, viral relapse is universal, so that most patients develop viral relapse with progression to cirrhosis in up to 30% after 5 years; therefore, certain cases are listed again for retransplantation (11). The use of marginal liver donors may affect liver transplant outcomes in patients with HCV infection, but there are no firm conclusions about the criteria for allocating marginal grafts to recipients with HCV cirrhosis. Due to the fact that HCV-positive donors almost always transmit HCV infection to the recipient, it has been widely aggreed that HCV positive grafts should be reserved for HCV-negative grafts (15).

Moreover, recently it has been demnostrated that donor age plays an important role in the proper functioning of HCV+ grafts. Among HCV recipients, marginal grafts function was comparable to non-marginal grafts, except for those with steatosis >30%, especially when associated with prolonged cold ischaemia time (CIT). However, there are no sufficient arguments to contraindicate transplantation of a marginal graft in a recipient with HCV infection. What is certain is that in such cases aggravating factors for graft function, such as donor age, grade of steatosis and prolonged (CIT) exist (24-26).

Transplantation of grafts from donors previously exposed to hepatitis B virus (HBV), especially those with anti-HBc antibodies, to naïve recipients carries a risk for de novo HBV infection (33% to 78%). However, the use of prophylactic antiviral therapy (hepatitis B immunoglobulins and lamivudine), has been followed by low rates of de novo infection and acceptable graft and patient survivals (27).

Donors with Malignancies

Quantification of the true risk of donor transmitted malignancies has been difficult because of their underreporting. Neoplastic histologies with potentially high transmission risk include melanoma and choriocarcinoma (10). Data reported from a population-based cancer registry estimate that the risk of having a donor with undetected malignancy is 1.3% while risk of transmitting a malignant disease from such a donor is 0.2% (28-32). The cancer-free interval must also be considered on evaluation of donors with a history of malignancy. However, tumors that may possess the potential of unpredictable recurrence risk include breast, renal cell, lung, colon cancer and melanoma. Meanwhile, donors with previous histories of primary central nervous system (CNS) tumors, such as medulloblastoma and glioblastoma multiforme, have a higher risk of transmission and should be avoided unless the recipient needs urgent transplantation (2). However, we should not omit the fact that recipients of donors with malignancies should have their immunosuppression modulated because over immunosuppression reduces immune surveillance that can accelerate tumor growth.

Multiple Donor Variables and Donor Risk Index

Several studies have investigated the effect of multiple donor factors on graft survival. However, there is no agreement on the impact of each particular factor on OLT outcome. Several donor factors had a negative impact

on graft survival including: donor age over 50 years, stroke as a cause of death, body mass index over 25 kg/m^2, use of inotropes (Dopamine infusion more than 15 μg/kg/min), ICU stay >6 days, increase liver enzymes levels (ALT, AST or GGT >200 U/l), low bicarbonate level <18 mEq/l and history of hypertension >3 years and associated anti-hypertensive treatment (12). Moreover, it seems that extended CIT and warm ischemia time (WIT) were significant independent risk factors for mortality. Warm ischaemia beyond 55 min doubled the risk, while cold ischaemia greater than 10 hours substantially increased the risk of death. Meanwhile, the risk significantly increased when three or more factors were present (33,34).

A donor risk index (DRI) in OLT has been developed by Feng et al, who analyzed data from deceased donors reported to the Scientific Registry of Transplant Recipients. Those factors were: donor age over 70 years was the strongest risk factor, african-american donors, reduced donor height, cerebrovascular accident as the cause of death, DCD or split grafts, each additional hour of CIT beyond 8 hours, and a graft from another transplant area. Whereas a DRI of 1 or less was associated with a 87.6% 1-year survival, it was 76.9% for a DRI of 1.6 to 1.8 and 71.4% for a DRI > 2 (35).

The most important studies conducted on the issue of the impact of different risk factors on liver grafts and overall outcomes after liver transplantation are summarized in *Table 1.*

Allocation Decisions

Because of limited organ availability, the practice of using marginal donor livers has become arguably more accepted. There are no guidelines for the allocation of marginal donors, although we believe that the impact of donor risk factors on OLT outcomes may be modified by the correct choice of the recipient for these organs. Some recipient factors, including obesity, impaired renal function, or fulminant hepatic failure, may affect early graft function. Therefore, it is not recommended to use high-risk donors in high-risk recipients (43). There are centers who have assessed a scoring system that would determine the accumulation of donor risks on outcome of liver transplantation. Donor criteria including donor age >60 years, ICU stay >4

Tabel 1. Studies discussing the impact of different risk factors on liver grafts and overall outcomes

Risk Factors	Mirza (36)	Agnes (37)	De Carlis (38)	Tekin (22)	Cuende (39)	Busuttil (40)	Cameron (41)	Feng (35)	Burroughs (42)
Year	1994	1996	1999	2004	2005	2005	2006	2006	2006
Age (years)	>55	>55	>55	>60	>60	NR	>55	>60	>60
Afroamerican race	NR	NR	NR	NR	NR	NR	NR	NR	Yes
Inotropes	Yes	NR	Yes	NR	NR	NR	NR	NR	NR
Hypotension	<90 mmHg, >15 min	<50 mmHg, >60 min	>60 min	NR	NR	NR	NR	NR	NR
ICU stay	>3 days	>7 days	>5 days	NR	>6 days	>6 days	>5 days	NR	NR
Death by CVA	NR	NR	NR	NR	Yes	NR	NR	Yes	NR
NHBD	NR	NR	NR	NR	NR	NR	NR	Yes	NR
Obesity	>100 kg	NR	NR	NR	BMI>25kg/m^2	NR	NR	NR	NR
Metabolic acidosis	NR	NR	NR	NR	NaHCO3<18mEq/l	NR	NR	NR	NR
Liver enzymes	AST>150 ALT>100	AST>150 ALT >150	NR	NR	ALT >200UI/l	NR	NR	NR	NR
Split grafts	NR	NR	NR	NR	NR	NR	NR	Yes	Yes
Cold ischaemia	NR	NR	NR	>12h	NR	>10h	>10h	Yes	>13h
Warm ischaemia	NR	NR	NR	NR	NR	>55 min	>55 min	NR	NR

CVA- cerebrovascular accident; NHBD – non- heart beating donor; BMI – body mass index; NR – not reported

days, CIT >13 hours, hypotensive episodes, elevated bilirubin level, and elevated transaminase level was given a score of 1. Dopamine doses >10 μg/kg/ min and serum sodium > 155 mEq/L were given a score of 2 (30). Recipients with a score of at least 3 showed a decrease in graft survival at 6 months (92% liver score of 0 versus 60% liver score of 3; p=.012) and an increase in the rate of delayed function (2% liver score of 0 versus 26% liver score of 3; p = .03) (42).

In a recent paper conducted by Schaubel et al cases with MELD score <2 reported a higher mortality when transplanted with higher DRI grafts while cases with MELD SCORE>20 reported a significant survival benefit regardless the graft DRI (44). In this respect, it would be reasonable for transplant centers that use marginal donors to establish a "secondary list" of recipients who would be suitable for a marginal graft, but at present this is only done for HVB +_and HCV+_donors, in some centers (45).

Liver Preservation and Procurement

Several clinical measures can be taken to increase the liver's tolerance to ischemia reperfusion injury. The use of improved preservation solutions allows extended ischemia and rewarming times. University of Wisconsin (UW) solution, considered the gold standard of preservation solutions, prevents the classic effects of hypothermia that include cell swelling, intracellular acidosis, impaired energy metabolism, and the accumulation of reactive oxygen intermediate precursors (44). UW has been used throughout the world for more than 20 years but is now challenged by 3 other solutions - Celsior, histidine tryptophan ketoglutarate (Bretschneider solution), and IGL-1, which are less expensive and potentially superior for organ preservation. No difference in short-term or long-term outcomes has been observed for each of these 3 solutions in comparison with UW (46).

Machine Perfusion

Multiple new machine perfusion preservation technologies have been developed, in order to assess graft viability, by reducing cold ischemia time and therefor improving outcomes in recipients of suboptimal (47). This machines are hypothermic oxygenated machine perfusion (HOPE or DHOPE), normothermic machine perfusion (NMP), controlled oxygenated rewarming, and normothermic regional perfusion (NRP) (48).

Hypothermic Machine Perfusion

In situations where the decision has been made to transplant a liver donated after circulatory death or donated following brain death, end-ischaemic HOPE will provide superior clinically relevant outcomes compared with static cold storage (SCS) alone (49-58). In HOPE procedure, the device enables liver perfusion via both the hepatic artery and the portal vein. The perfusion pressure is set at 3-5 mmHg for portal vein and 18-25 mmHg for hepatic artery. The pressure settings must provide a flow rate of at least 50-200 mL/min in the portal vein and 20-80 mL/min in the hepatic artery. The temperature of the perfusion fluid is about 10°C (59).

A number of studies showed that HOPE provided three different protective mechanism to allograft during preservation: therefore, it seems that HOPE determines up-regulation of Kruppel-like factor 2 (KLF2) and endothelial nitric oxide synthase (eNOS) which provide cellular protection from ischemic injury and it reduces damage associated molecular patterns (DAMPs) released by hepatocyte during early reperfusion. Meanwhile, low temperature and oxygen rich perfusion allows intracellular ATP regeneration, limits reactive oxygen species (ROS) accumulation, and reduces lactate production (24). HOPE or D-HOPE can also be performed for at least 15 h, shifting the recipient transplant surgery to the next morning if required for logistical reasons (60).

Normothermic ex situ Machine Perfusion (NMP)

Another perfusion machine is NMP, which creates the physiologic conditions by perfusing the organ at 34-38°C with oxygenated blood, nutrients, and medications. It was first clinically applied in 1984 to preserve heart and lung grafts during distant procurement, and the, in 2007, Steen et al. first used it as a method to assess viability in deceased donor lungs that were rejected for transplantation (61). They managed to maintain the graft for 17 h on ex vivo perfusion with successful overcome (62). Adequate oxygenation of the organ, via an oxygen carrier in perfusate, is necessary for NMP, whether is human blood products (very expensive and limited products) or acellular oxygen carriers such as Hemopure (bovine hemoglobinmultimer) (63). NMP does appear to improve utilization of grafts that would otherwise be discarded with SCS; however, the reasons for this, and whether this effect is specific to NMP, is not clear.

Normothermic Regional Perfusion

The advantage of NRP is the absence of any cold ischemia at the time of initial normothermic reperfusion in the donor, lower cost compared to other perfusion techniques, and the ability to simultaneously treat several abdominal organs. NRP is consequently used to procure and evaluate DCD all over the world. The role of this technique in prolonging liver preservation and enabling additional treatment of organs (25,64-69).

Conclusions

Marginal grafts are now encountered in about 50% of livers that are available for liver transplantation in the climate of increased requirement for liver grafts combined with the rising mortality on recipients waiting lists. It has been shown in several studies that the use of marginal grafts is safe, although is must be very carefully chosen. The criteria of considering a graft as suitable for transplantation are continuously extending, and differ from country to country and center to center. What is certain is that grafts otherwise discarded are now allocated for transplantation. When it comes to the perioperative management, this will take into account the donor age reserves, the degree of decompensation of chronic diseases. There have been imagined different scores to better evaluate the donor and the recipient, such as DRI, D-MELD, and organ patient index, but there aren't yet frequently used. Significant advances over the last decades in procurement, preservation, surgical technique, and post-transplant immunosuppression have enabled liver transplantation to be an effective therapeutic option throughout the world. Still, there remains an 8.4% of donated livers that are recovered and not used. It seems clear that machine perfusion methods are promising approaches in the field of organ preservation in order to increase the pool of available organs by including marginal livers.

Conflicts of Interests

The authors declared no potential conflicts of interest.

Ethics Statement

Fundeni Clinical Institute Ethics Committee approved the study (no 22/2024).

Authors' Contributions

Conceptualization: S.P.; M.Se.; methodology: L.P.; validation: N.B.; formal analysis: A.H.; investigation: C.M.; resources: I.B.; data curation: G.P.G.; writing — original draft preparation: M. Se.; writing — review and editing: I.B.; visualization: B.G; supervision: I.P.; project administration: M.St. All authors have read and agreed to the published version of the manuscript.

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