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Extended Criteria Donors in Liver Transplantation: Definition and Impact in Liver Graft Function

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ÁREA CIENTÍFICA DE CIRURGIA GERAL

Trabalho realizado sob a orientação de:

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Abstract

Background: Liver transplantation (LT) is used worldwide in patients with end-stage liver disease. The concept of extended criteria donor (ECD) was introduced as an alternative strategy to respond to the increasing number of patients in waiting list. However, controversy exists related to the features considered to this definition.

Objective: The aim of this work is to review the state of the art concerning ECD in LT, whose features are implied in the risk of impaired liver graft function (LGF) and infer how their usage can be optimized.

Methods: Research was conducted in Pubmed and Embase between May and November 2018 and inclusion criteria were as follows: 1) studies that comprised ECD in LT; these could include – a) merely ECD in LT or b) ECD and other donors in LT and 2) research that assessed one or more features contributing to the characterization of ECD; 3) records relative to risks and improvement of LT, by using these ECD, were also briefly taken into account.

Results: Of the 1241 articles identified, 224 were selected after excluding the duplicates and reading their abstract. Inclusion and exclusion criteria were applied and further extensive reading of the articles was conducted. Secondary terms relevant to this topic were also used, which allowed the detection of additional 51 casuistic.

Discussion: The utility of ECD was assessed and the features related with risk of impaired LGF, were approached in the present work. Emphasis was given to donor age, steatosis, hemodynamic instability, inotropic and vasopressor drugs, hypernatremia and donation after cardiac death.

Conclusion: We concluded LT should take advantage of ECD. Despite the persistence of divergent considerations it seems that more recent published data supports their usage has justified and safe. However, it cannot be forgotten the complexity these donors convey, not only due to the variety of features that each donor can comprise but also thanks to the uncertain effect each feature has on LGF. Above all, the final decision of using a graft from an ECD or discarding it remains a challenge.

Keywords: liver transplantation, expanded criteria donors, marginal donors, liver graft function.

Resumo

Contexto: O transplante hepático é utilizado mundialmente em doentes com hepatopatia terminal. Com o intuito de responder ao número crescente de doentes que necessitam de um fígado foi introduzido o conceito de dadores de critérios expandidos. No entanto, existe controvérsia quanto às características a ter em conta nesta definição.

Objetivo: O presente trabalho pretende rever o estado da arte referente a dadores de critérios expandidos em transplante hepático cujos critérios estejam relacionadas com o risco de disfunção do enxerto hepático e inferir como o seu uso pode ser otimizado.

Métodos: A pesquisa foi realizada no Pubmed e Embase entre maio e novembro de 2018. Os critérios de inclusão foram os seguintes: 1) estudos que compreendiam o uso de dadores de critérios expandidos no transplante de fígado, sendo que estes estudos poderiam conter – a) apenas dadores de critérios expandidos em transplante hepático ou b) dadores de critérios expandidos e outros dadores em transplante de fígado e 2) investigação alusiva a uma ou mais características que contribuíssem para a caracterização do dador de critérios expandidos; 3) artigos relacionados com os riscos e aperfeiçoamento do transplante de fígado, usando estes dadores marginais, também foram, brevemente, tidos em conta.

Resultados: Dos 1241 artigos identificados, 224 foram selecionados após a exclusão de duplicados e leitura do seu resumo. Os critérios de inclusão e exclusão foram aplicados e uma leitura mais extensa dos artigos foi realizada. Termos secundários relevantes para este tópico também foram utilizados, o que permitiu a deteção de casuística adicional (n=51).

Discussão: A utilidade dos dadores de critérios expandidos foi avaliada e as características relacionadas com o risco de disfunção do enxerto hepático foram abordadas no presente trabalho. Foi dado ênfase à idade do dador, esteatose, instabilidade hemodinâmica, uso de inotrópicos e vasopressores, hipernatrémia e dadores de coração parado.

Conclusão: O transplante de fígado deve fazer uso dos dadores de critérios expandidos. Apesar da persistência de considerações divergentes parece que os dados publicados mais recentemente justificam e asseguram o uso dos mesmos. No entanto, a complexidade destes dadores não deve ser desvalorizada, não só pela variedade de fatores que cada dador pode apresentar, como também pelo efeito, ainda incerto, que cada um destes fatores poderá ter na função do enxerto hepático. Acima de tudo, a decisão final de usar um enxerto de um dador de critérios expandidos ou descartá-lo permanece um desafio.

Palavras-chave: transplante hepático, dadores de critérios expandidos, dadores marginais, função do enxerto hepático.

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List of Acronyms

ALT – Alanine Aminotransferase

AST – Aspartate Aminotransferase

ATP – Adenosine Triphosphate

BMI – Body Mass Index

BRB – Bilirubin

CI – confidence interval

CIT – Cold Ischemia Time

CNS – Central Nervous System

DBD – Donors after Brain Death

DCD – Donation after Cardiac Death

ECD – Extended Criteria Donors

ELTR – European Liver Transplant Registry

Emtree – Embase Subject Headings

HCV – Hepatitis C Virus

ICU – Intensive Care Unit

INR – International Normalized Ratio

IPF – Initial Poor Function

IRI – Ischemia Reperfusion Injury

LGF – Liver Graft Function

LT – Liver Transplantation

MELD – Model for End-Stage Liver Disease

MeSH – Medical Subject Headings

MP – Machine Perfusion

NHBD – Non-Heart Beating Donors

NMSC – Non-Melanoma Skin Cancer

OPTN – Organ Procurement and Transplant Network

OR – odds ratio

PNF – Primary Non Function

QoL – Quality of Life

RR – risk ratio

SCD – Standard Criteria Donors

WIT – Warm Ischemia Time

(-) – Negative

(+) – Positive

1. Introduction

Liver Transplantation (LT) is a therapeutic option in several hepatic diseases and in selected patients with end-stage liver disease it may even be the only curative option.[1]

In Portugal, the process of LT takes advantage majorly from cadaveric donors. However, the possibility of donation after cardiac death (DCD) became a reality as part of a pilot program since October 2016.

Despite several advances in this area during the last decades, the increasing number of patients in waiting list was not accompanied by an equal increase in the donor pool. This imbalance implies a rise in the duration, worsening of clinical status and mortality rate in patients waiting for LT.[1, 2]

In order to overcome this reality and augment the donor pool, one of the applied strategies was the use of the so-called extended-criteria donors (ECD) or marginal donors. However, their use remains a controversial topic, with no clear agreement on the features considered to its definition and also a lack of consensus about the implications that each feature can have on the morbidity and mortality rates.[3]

Previous studies have shown influence of some features in liver graft function (LGF), although these features were not consistently determined, once the definition of ECD considered for each authors and thus, studies, is not the same.

The objective of the present work was to review the state of the art concerning ECD usage in LT by evaluating its definition, most common related features and its relation with impaired liver graft function in the post-LT period.

2. Methods

In order to prepare this review, a research was made regarding information present in scientific articles collected via PubMed and via Embase.

Medical subject headings (MeSH)/Embase subject headings (Emtree), specifically *liver transplantation* was the key component used. However, other terms such as *extended criteria donor* or *marginal donor,* were also taken into consideration due to their significance for this review. Therefore, the combination of these terms for PubMed and Embase, respectively – (*Liver Transplantation* AND *Tissue Donors* [MeSH] AND *Marginal* OR *Marginal Donor Liver Transplant** OR *Marginal Liver Transplant** OR *Extended-Criteria Donors*) and (*Liver Transplantation* [Emtree] AND *Donor* AND *Marginal* OR *Marginal Liver Transplant** OR *Extended-Criteria Donors*) – were the cornerstone of this research.

In both research equations, filters were defined concerning article types, text availability, language edition (English, Portuguese, Spanish and Italian) and publication date (between 1990 and 2018).

Inclusion criteria were: 1) research that comprised ECD in LT; these studies could include (a) merely ECD in LT or (b) ECD and other donors in LT and 2) research that assessed one or more features contributing to the characterization of an ECD. Records regarding risks in LGF and improvement of LT, by using these marginal donors, were also briefly taken into account 3).

Exclusion criteria were: 1) article types - letters to the editor, case reports, reviews and synopsis of congresses presentations not including new data on the field; 2) research that comprised ECD in LT merely in pediatric age.

According to this, primary selection of the most appropriate articles was conducted by title and abstract evaluation and secondary selection was made after careful reading of the previously selected articles, confirming the adequacy of the information provided.

Further research was made by using secondary terms and other search resources with the aim of uncover additional bibliography of potential interest for this topic.

3. Results

Using the research equation it was possible to obtain 1241 scientific articles. Then, by excluding the duplicates and reading the abstract it was possible to select 224 articles as appropriate to this literature review. As previously mentioned, other non-MeSH/Emtree key terms relevant to this topic were also used, which allowed the detection of additional 51 papers, resulting in a total of 73 articles used. The process is illustrated in Figure 1.

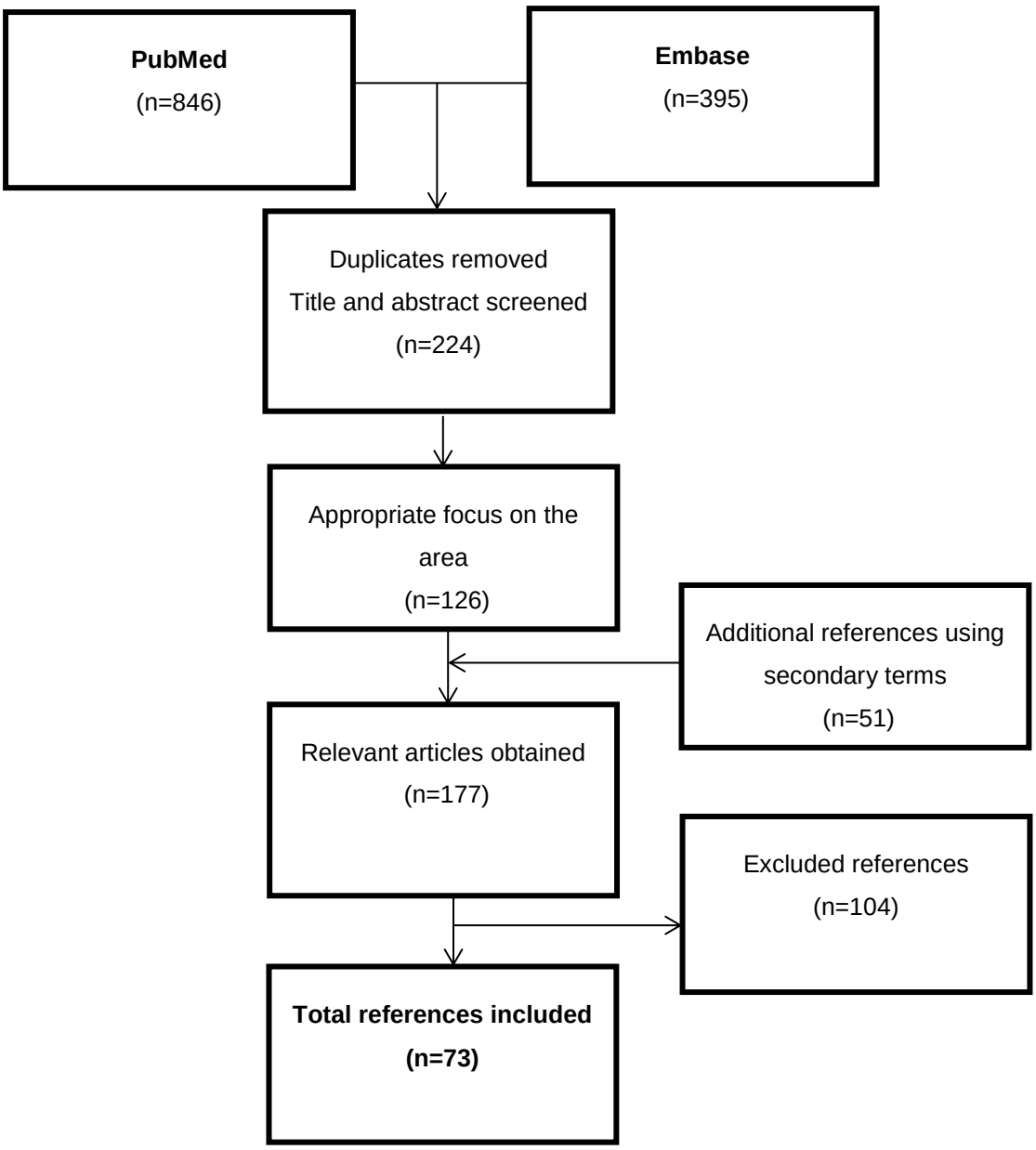

Figure 1. Flow-chart of the literature selection process for the present work.

4. Discussion

4.1. Definition of ECD

4.1.1. History and Evolution

History of LT dates back to 1963 when the world's first attempted LT in humans was performed by the surgeon Thomas Starzl. However, it was only in 1967 that this surgical procedure was successfully performed.[4]

In Portugal, the first LT took place in Coimbra on 26th October 1992, by the hands of the surgeon Linhares Furtado. Since then and owing to an improvement in surgical techniques, immunosuppressive strategies and patient management, LT was able to go from an experimental procedure to a valuable and widely practiced clinical treatment.[1]

Furthermore, in 1987, successful extensive use of livers from marginal donors was reported for the first time by *Makowka et al..*[4]

Nowadays, orthotopic LT is an effective treatment for end-stage liver disease[5] with a high survival rate and a good quality of life (QoL).[6] According to the European Liver Transplant Registry (ELTR), until 2015, the two main primary diseases leading to LT, in Portugal, were cirrhosis and metabolic diseases.[7]

During the 1980s and the first half of the 1990s, the ideal donor was a young male who sustained brain death from cerebral trauma, with hemodynamic stability, without infection or neoplasm and without chronic liver disease or macrovesicular steatosis. However, in recent years, the availability of these donors has diminished as a consequence of demographic changes and reduction in traffic and labor accidents, which added to the problem of organ shortage.[1]

Organ shortage has become a major limitation for transplant programs worldwide due to an imbalance in the supply and demand related to this procedure. This is explained, on one hand, by a limited number of available cadaveric organs and, on the other hand, by a constant increase in the number of patients on waiting lists for transplantation.[2]

In LT, several strategies have been developed to face this reality and increase the donor pool, such as the utilization of domino livers, which was developed in first hand by Linhares Furtado in Coimbra, Portugal,[8] living donors, split-liver grafts and extended-criteria donors (ECD) or marginal donors.[2]

ECD, introduced by *Renz et al.*[9], are mostly defined as donors who might be at risk for diminished transplant function, meaning, increased risk of short-term complications – initial poor function (IPF), primary nonfunction (PNF) – and long-term complications that may

cause graft loss.[10] In a last instance, these grafts may subject the recipient to greater risks of morbidity and mortality.[11]

However, what constitutes an ECD remains controversial.[12] There is no global agreement on the use of these terms and no univocal interpretation of this evolving definition.[11] Difficulties in establishing it could be related to the excess of univariate survival analysis, studies that comprise an insufficient number of ECD, an absence of evolutive studies and no consensus about uniform and defined cut-off points.[3]

Consequently, different transplant units have their own policies to distinguish which livers they will accept or discard and, despite the increased use of ECD throughout the years in many transplant centers, the differences between these policies can imply the acceptance of a graft in one transplant unit that was previously discard by another.[12,13]

4.1.2. Determining Factors

Evaluation of ECD is complex as it was not possible so far to establish a unique definition of this concept. This lack of homogeneity underlines that it is not compulsory to convey exactly the same factors to this definition and, furthermore, that the impact each considered factor may have is still uncertain.[11]

Several studies conducted on this area can demonstrate this disparity.

Through the analysis and reading of our casuistic it was possible to verify that different studies convey different factors to their own definition of ECD. Here, we corroborate this existing difference by presenting studies from several authors, their own definition of ECD and factors included in this definition, before presenting the factors that will be detailed in the present work.

Gruttadauria et al.[14] reported they never used an ECD until May 2003. After this period, statistics considering the number of transplants performed in their center in Italy just tripled per year thanks to the use of ECD donors. These were defined as: age >60 years, liver steatosis >30%, prolonged intensive care unit (ICU) stay (>7 days), prolonged hypotension with the need for inotropic drugs (dopamine >10 μg/kg/min), cold ischemia time (CIT) >12 hours, hypernatremia with serum sodium higher than 160 mEq/L, raised extrahepatic tumor values and viral infection, namely hepatitis B and/or C. This increment in ECD usage had successfully results as a consequence of optimal donor care, minimized CIT, usage of liver biopsy and good, improving understanding of the best donor-recipient match. In the end, they concluded ECD may be the simplest way to minimize the problem of organ shortage.

Barshes et al.[15], in 2007, developed a study to demonstrate that an increased use of ECD can be correlated with a decrease in waitlist mortality rates. In this study, the authors considered the following factors to define ECD: black donor with ≥60 years *or* donor with ≥60 years or ≥50 years (if black) whose cause of death was either anoxia, cerebrovascular accident or other non-trauma cause *or* donor after cardiac death with ≥40 years *or* donor after cardiac death with <40 years and black or dying from either anoxia, cerebrovascular accident or other non-trauma cause *or* CIT >12 hours. The study involved a total of 3555 ECD transplants and 11660 standard-criteria donors (SCD) transplants performed at more than 100 USA centers during 2002 and 2005 and concluded not only that ECD and SCD LT were both inversely correlated with waitlist mortality but also that ECD would be a feasible way to diminish waitlist mortality rates encouraging the increase of their use.

On another hand, *Blok et al.*[16] considered age >65 years, ICU stay >7 days, high body mass index (BMI), steatosis, hypernatremia and high-levels (non specified) of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum bilirubin (BRB) as factors contributing to the definition of ECD. Data from 5939 liver transplants performed in the Eurotransplant region (Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands and Slovenia) between January 1, 2003 and December 31, 2007 were analyzed. Their objective was to identify the potential use of the donor risk index (DRI) in the Eurotransplant Region, once the latter was created by *Feng et al.* based in data from Organ Procurement and Transplantation Network (OPTN) and, thus, in a different reality.

An interesting study developed by *Bruzzone et al.*[17], published in 2013, is a good example of the different policies used in several centers. They collected data from 35 centers, all of them considering ECD in LT. However, it was only in 2 centers (6%) that all the defining criteria were gathered. These were as follows: age up to 80 years in 15 centers (43%), steatosis in 33 centers (94%), ICU stay with ventilation >7 days in 17 centers (48%), serum sodium higher than 165 mmol/L in 25 centers (71%), AST >90 U/L in 6 centers (17%), ALT >105 U/L in 8 centers (23%), serum BRB >3 mg/dL in 15 centers (43%) and BMI >30 kg/m^2 in 19 centers (54%).

Halazun et al.[18], in 2017, presented a study including data from LT performed from January 20, 1998 to September 30, 2016, with 960 ECD being used. These authors considered the following criteria to the definition of ECD: donor age >70 years (n=219; 22.8%), CIT >12 hours (n=72; 7.5%) , liver steatosis >30% (n=37; 3.8%), grafts from DCD (n=44; 4.6%), grafts from hepatitis C virus (HCV) positive (+) donors (n=150; 15.6%), split liver grafts (n=101; 10.5%) and discarded grafts from other local/regional centers (n=649; 67.6%) were also comprised in this definition. From the 960 ECD, 276, 28.8% had more than

one of the set criteria. As seen, the most prominent criteria comprised in this study were donor age >70 years and discarded livers.

Thus, by reporting these studies it is possible to understand the intrinsic variability ECD definition has. Several factors can be used to determine what an ECD is, however, in order to simplify the approach to these donors, they can be divided into three major groups based on: 1) predispose to impaired LGF, 2) technical difficulties and 3) risk of infections or malignancy transmission to the recipient.[3] On the first group, factors such as donor age, liver steatosis, hypernatremia, hemodynamic instability and donation after cardiac death were included. On the second group, warm ischemia time, blood product use and technical variant grafts and complications can be considered. On the third group, donors with history of non-melanoma skin cancer (NMSC), low-grade (I and II) central nervous system tumors (CNS), bacterial or viral infections are comprised (Table 1).

Table I. Extended criteria and their associated risks to the recipient.

Impaired graft function	Technical difficulties	Risk of disease transmission
• **Advanced donor age** • **Donor liver steatosis** • **Hemodynamic instability, inotropic or vasodepressor drugs** • **Hypernatremia** • **DCD/NHBD**	• Warm ischemia • Technical variant grafts and complications • Blood product use	• Donors with active viral infection or positive serology (HBV, HVC, HIV) • Donors with active bacterial infections • Donors with malignancy (NMSC tumors, low-grade CNS tumors)

DCD, donors after cardiac death; NHBD, non-heart beating donors; HBV. hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NMSC, non-melanoma skin cancer; CNS, central nervous system

Given this information it is important to underline that the present work will not focus in providing a uniform, unique ECD definition. Instead, a review concerning factors related to impaired graft function will be the cornerstone of this work. Relevance was endorsed to these factors due to their vast contribution to ECD definition when in comparison with the other factors. Defining ECD with accuracy in order to be accepted worldwide remains difficult to achieve, however, we believe reviewing information in this area will be of major importance to make such progress.

4.2. Factors Associated with Risk of Impaired Function

4.2.1. Donor Age

Expanding donor age is the most used and appropriate practical measure to battle organ shortage and thus, to diminish the waitlist mortality.[19]

The age profile has evolved through the years, thanks to a stepwise approach, with donor age escalating from 50 to 80 years.[20,21] In Europe, in 1991, only 2% of donors had more than 60 years, 10% in 1996 and 20% in 2001, with this numbers tending to augment.[22] In the United States, according to OPTN, older adults and elderly donors (>50 years) accounted for a mean of 30% of deceased donor liver transplants since 1988 until 2018. Additionally, they showed, in 2005, a maximum value of 10.2% for donors with >65 years and 8.2%, in 2018, considering LT in all ages.[23]

In this context, liver aging is a process of particular interest in LT to better use the number of available older donors arising from the elderly population.[1]

Aging may disturb synthetic, excretory and metabolic functions of liver, though some authors have reported a bigger influence of it in the way liver reacts to extrahepatic factors, increased metabolic demands or diseases. These last aspects naturally affect more the elderly donors compared to the younger ones due to their intrinsic reduced capacity of response.[19]

In addition, the major age-related changes in the liver are a reduction in mass and blood flow, not evident in routine liver function tests.[24] These can somehow explain the higher vulnerability older grafts have when exposed to cold ischemia and reperfusion. Cold ischemia is capable of inducing injuries on endothelial cells while after reperfusion a decreased ability to produce adenosine triphosphate (ATP) is verified.[25]

Nevertheless, despite these modifications inherent to the course of getting older, the liver peculiar characteristics, namely its regenerative capacity, dual blood supply and good functional reserve, make it a suitable organ to consider in transplantation in older and even in extremely older donors.[19]

The Paris-consensus meeting, in 2007, that gathered experts from Europe, USA and Asia, reported there is no absolute limit of donor age for LT.[26]

In the beginnings of donor age widening, the risk of more pronounced impaired function, poorer patient and graft survival, superior amount of complications and transmission of occult tumors were considered the major fears of this extension.[27]

Since then, several studies regarding LT using donors with more than 50[28-30], 60[31-33], 70[34, 35] and 80[24,27,30,36,37] years have been published with divergent results. Some authors shared this same concerns, reporting a negative[31,33,34] impact, conversely, other transplant groups reported the use of these elderly donors as a safe measure with similar[27-30,35,36] results to younger donors.

To better clarify this topic, firstly, series comparing donors with <50 and >50 years emerged, which revealed no significant differences in what concerns rates of PNF, retransplantation and patient and graft survivals, establishing that LT with donors with >50 years were safe.[28-30]

Yerzis et al.[28] is one example of the performed studies. These authors compared 95 recipients that received liver grafts from donors older than 50 years (mean age 57.14±5.5, range 50-71) with 50 recipients that received liver grafts from donors younger than 50 years (mean age (24.6±3.1, range 20-30). PNF was defined as a non-recoverable hepatocellular function with the need of retransplantation within 72 hours. Delayed nonfunction was defined as a graft function in need of retransplantation within 1 month. LGF, immediate and long-term, as well as evidence of ischemic and reperfusion injuries up to one year after LT were compared between both groups. No statistically differences were found in LGF between both groups although older group was reported to display more profound ischemic/reperfusion injury. Yet, they concluded by that time that utilization of liver grafts from older donors is a calculated risk, resulting in an excellent post-perfusion function in the majority of the patients, without lowering patient survival when poor function is early recognized.

Regarding grafts older than 60 years, evidence of inferior 1-year graft survival rate was shown in the primary two comparative studies realized.[31]

Posteriorly, rates of patient and graft survival, graft dysfunction, PNF appeared to be similar to donors younger than 60 years.[32]

Rodríguez González et al.[32] have proven this similarity by developing a study in LT comparing 100 donors older than 60 years with 233 donors younger than 60 years. Donor characteristics were equivalent between both groups, with exception for age. They reported PNF, acute rejection and 1 and 5- year patient and graft survival to be similar in elderly and younger donors.

On another hand, *Serrano et al.*[33] reported a bigger risk of non-anastomotic biliary stricture in these sexagenarian donors. Their study included a prospective analysis of LT performed between February 2000 and June 2005 including only livers from deceased donors, which they divided into two groups (group A, from donors with <60 years, n=102 and group B, from donors with ≥60 years, n=47). Average donor age was 38.7±13.4 in group A

against 67.6±5.4 in group B. Other donor variables (such as ICU stay, sodium serum level and ischemia time), recipient factors and the technical procedure itself were similar between both groups. Results concerning 1-year graft survival were statistically inferior in group B (74.2% *vs.* 85.4% in group A). However, patient survival was statistically similar between both groups (89.5% in group A *vs.* 82% in group B). Acute rejection occurred in 16 patients in the older donor group against 27 patients in the younger donor group, while chronic rejection was present in 2 patients in group B and 3 patients in group A. The risk of anastomotic strictures was higher in group A although not statistically significant (8.8% *vs.* 8.5%). Contrary, the risk of non-anastomotic biliary strictures, has previously reported, was higher in the older donor group (17% *vs.* 4.9% in group A).

Furthermore, The Scientific Registry of Transplant Recipients considered donor age over 60 years as the strongest risk factor for graft failure.[1]

In relation to septuagenarian donors, some authors reported worse patient and graft survival.[34] Contrary, authors such as *Gastaca et al.*[35] showed similar patient and graft survival rate between donors with >70 years and younger donors.

Liver grafts older than 80 years became a reality after *Wall et al.*[30] reported the successful use of an 86-year-old liver graft.[24,27] *Nardo et al.*[27] in a retrospective multicenter study compared the outcome of 30 LT using octogenarian donors (mean age 82.7 years; range 80–93) with LT using 60 chronologically correlated donors with <40 years (mean age 27.6 years; range 13-40). Initially, 58 livers from octogenarian donors and 230 livers from donors aged <40 years were considered, however, from this amount, 28 livers (48.2%) *vs.* 33 livers (14.3%), respectively, were discarded, being this rate higher in the elderly group as shown here. There were also other donor characteristics that were statistically different between both groups, namely the cause of death and transaminases and total BRB levels. In the octogenarian group, the major cause of death was cerebrovascular (80%) while in the group of younger donors it was traumatic (65%). Favoring results were reported with the octogenarian group: acute rejection episodes in need for treatment and non-ischemic biliary stenosis were similar to control group; hepatic artery thrombosis, primary graft dysfunction, including both IPF and PNF, were not reported in this group; furthermore, patient survival was lower in these donors but graft survival was not significantly influenced.

A series considering donor age divided into 5 groups (<50, 50-59, 60-69, 70-79 and ≥80 years), reported donor age among 60-79 years, HCV+ recipients, Model for End-Stage Liver Disease (MELD) score ≥25 and emergency LT as predictors of poor graft survival.[37]

Further, important considerations can be made and apply in bigger or lesser grade to all these donor age ranges.

Firstly, it is important to underline that advanced donor age is not a contraindication by itself. The dilemma arises when graft protection and minimization of other risk factors are not fulfilled.[22]

For example, risk factors as severe atherosclerosis and fatty infiltration in the liver, significantly more common in elderly donors, have several implications when in association with extended donor age. Conversely, hypertension and diabetes mellitus do not have influence in LT outcomes.[38] Not only the presence of calcified plaques into liver vasculature might result in severe complications[39], the presence of moderate to severe steatosis is also strongly correlated with adverse recipient and early graft survival.[40] The latter, fibrosis, cholestasis and hepatitis can be histologically confirmed through a liver biopsy, which is highly recommended in this type of donors prior to LT.[24] Moreover, steatosis may potentiate cold preservation injury, that is why CIT should be kept to less than 8 hours in these donors.[28] A cholestatic pattern can also be present in recipients of older donor livers after LT, but the majority of this is able to recover normal liver function during the first weeks post-LT.[28]

Secondly, it is strongly recommended not to allocate elderly donors to HCV-infected recipients. This is explained by the fact that advanced donor age may be related with early recurrent liver disease in mentioned recipients.[41] Supporting these evidences, *Russo et al.*[41] found that 1-year graft survival in HCV+ recipients was 84% in donors with <40 years old *vs.* 73% in donors with ≥ 60 years and *Ghinolfi et al.*[42] showed 5-year graft survival was lower for HCV+ (62.4%) *vs.* HCV negative (-) (85.6%) recipients of old donor livers.

Thirdly, these grafts have an extreme sensibility to hemodynamic instability, which advises strict management of body temperature, diuresis (>1 mL/kg/h), hematocrit (>25%) systemic blood pressure (>100 mmHg) and central venous pressure (>10 cmH_2O) in order to establish a good perfusion and oxygen support to the liver graft.[43]

4.2.2. Steatosis

Liver steatosis, defined as lipid accumulation in hepatocytes, is the most prevalent underlying condition in liver grafts available for transplantation with a reported prevalence in deceased organ donors of 13 to 28%.[44] Some early studies considered graft steatosis as the most significant variable in multivariate analysis of factors determining graft function after transplantation.[45]

Despite the fact that nearly one third of donated livers get discarded for steatosis alone[46], with steady augment in the mean age of deceased donors and obesity worldwide, one has to expect a further increase in its prevalence in organ donors.[44]

Steatosis has a multifactorial etiology, namely obesity, present in more than 65% of obese patients, diabetes mellitus, alcohol abuse, hyperlipidemia and increased age.[44]

Furthermore, steatosis can be better defined according to a qualitative and quantitative classification based on histologic features.[47]

The qualitative classification divides steatosis in microvesicular and macrovesicular, although it is common that both are simultaneously present, still with different degrees, into the same liver.[47]

Microvesicular steatosis consists in a diffuse fat small-droplet vacuolization with centrilobular distribution into the cytoplasm. It is caused by diminished mitochondrial fatty acids' metabolization, usually reversible and related to parenteral nutrition, long hospitalization, sepsis, toxins and metabolic disorders.[48]

Macrovesicular steatosis consists in a large unique fat vacuole bigger than the nucleus, consequently, displacing it from its normal position to the periphery. The fat content is mainly triglycerides because excessive *de novo* synthesis or increased uptake of fatty acids from the adipose tissue occurs. This type is generally linked to diabetes mellitus, obesity, hyperlipidemia and alcoholism.[44]

Additionally, it is possible to quantify steatosis in three degrees: mild (<30%), moderate (30–60%) and severe (>60%).[49]

In order to optimize the use of these donors, two methods can be applied to determine the extent of steatosis: a macroscopically, gross examination by the surgeon during liver procurement or a liver biopsy. Even though the results of some studies, like *Marsman et al.*[50], showed good estimate of liver steatosis by the procuring surgeon, especially if steatosis is <30%, and despite the development of non-invasive techniques such as ultrasonic elastography, liver biopsy remains the gold standard, providing an objective assessment of the degree of liver steatosis.[49] Liver biopsy using hematoxylin-eosin stain and frozen section is difficult but preferred and its misinterpretation or observer variability is unlikely and should not be an obstacle to further ECD expansion.[47] Thus, liver biopsy is recommended in any case of steatosis' suspicion and some authors go further when they recommend it routinely at the time of the harvest.[49]

In what concerns microvesicular and mild macrovesicular steatosis, both were reported safe in LT as their outcomes were proven similar to nonsteatotic grafts.[48] *Urena et al.*[48] showed a slightly initial dysfunction after implantation of these organs however, the risk ratio (RR) between non steatotic grafts and grafts with mild steatosis were similar. Patient and graft survival were not decreased by using these donors.

On the contrary, moderate macrovesicular steatosis represents a challenge as rates of PNF and delayed graft function can reach up to 25% and 35%, respectively.[50] These grafts can only be used if restriction and careful selection of other donor and recipient factors is done. For example, younger donors, CIT <6 hours, total ischemia time <12 hours and HCV-recipients are preferred as steatosis seems to exacerbate the injury of hepatocytes inducing ischemia and an environment favorable to HCV virus.[51] The use of severe macrovesicular steatosis is being recently reported, however, its usage is still not advisable by the majority of the authors.[47]

McCormack et al.[47] analyzed patients receiving liver grafts with severe steatosis between January 2002 and September 2006. Primary end-points of this study were the incidence of PNF and graft and patient survival while secondary end-points included primary graft dysfunction, incidence of post-operative complications and steatosis assessed by follow-up biopsies. From 118 LT conducted, 20 liver grafts (17%) had severe steatosis (median amount of total steatosis of 90%). Of note, almost all (except 2 donors) presented one or more extended criteria. The recipients from these 20 liver grafts were then compared with a matched control group of 40 recipients. Liver support therapy was not applied in any recipient before or after LT. Early outcomes were promising with similar PNF rates between both groups. Only one patient in steatotic group (5%) developed PNF after receiving a liver graft that had four additional extended-criteria. This case required retransplantation but died after a few days due to a *Staphylococcus aureus* sepsis. CIT was similar for both groups but severely steatotic liver exhibited higher vulnerability to the same degree of ischemic insult, which was demonstrated by higher serum transaminases level. Incidence of primary dysfunction was significantly higher in steatotic group (30% *vs.* 10%, in control group). Graft and patient survival at 1 and 3 years was equivalent and greater than 80%.

Moreover, with this study and several other data we confirm that the more one progress in macrovesicular steatosis' degree the more severity and frequency of unfavorable outcomes, with risk of graft dysfunction or even nonfunction, succeed in LT.

Despite hepatocytes are undoubtedly susceptible to ischemic reperfusion injury (IRI) during LT, in steatotic grafts, IRI is extremely enhanced due to cellular edema caused by fat droplets' accumulation during cold ischemia which, consequently, induces a damage of

microcirculation with partial or complete reduction of sinusoidal spaces. Additionally, steatotic livers are more prone to lipid peroxidation, pro-inflammatory response and Kupffer cell dysfunction.[52]

In order to limit this ischemic graft damage new solutions are being proposed. One of the most promising innovations is the use of machine perfusion and/or preservation (MP), which consists of a pump creating a flow of blood or preserving solution through the organ.[53]

Several authors underlined that their usage might be more beneficial to optimally preserve ECD liver grafts in comparison to simple cold storage methods. This can be explained by better preservation of the microcirculation, removal of noxious metabolites and the ability to monitor the performance of the graft and to provide adjuvant substances. [54]

While with simple cold storage the sinusoids become constricted due to hypothermia, which induces a barrier to penetration of preservation solution into the tissues and may cause impaired microcirculation upon reperfusion, MP gives a metabolic support, evaluates the metabolic state of the graft before transplantation and is able to recover some liver grafts rejected on first-hand to LT. [54]

To date, different MP strategies have been proposed, which can be characterized by different: temperatures (hypothermic, subnormothermic or normothermic), flow regimens and pressures (pulsatile *vs.* unpulsatile), perfusion methods (single *vs.* dual) and oxygenation supply (oxygenated *vs.* non-oxygenated). Despite this variability and, consequently, divergent effects in the liver graft depending on chosen MP characteristics, no consensual results were obtained providing the best MP strategy in detriment of the others.[53-55]

In an attempt to maximize the number of potentially usable donor livers, including steatotic livers, which already were told to be more prone to IRI, several centers are exploring the role of MP. Although the favorable, safe and feasible results recently reported, the costs concerning their use and maintenance seem to limit its widespread applicability, with Portugal being an example of this latter reality, as the use of MP is not yet available in the majority, if not all, the hepatic transplantation centers.[55]

4.2.3. Hemodynamic Instability and Inotropic or Vasopressor Drugs

It is believed that ECD donors predispose their recipients to a more pronounced hemodynamically unstable pattern than patients allocated to “good quality” grafts. Moreover, LT is known as a surgical procedure with significant hemodynamic instability itself caused by clamping of the inferior vena cava, absence of liver function in anhepatic phase, reperfusion syndrome, surgical stress and manipulation, bleeding and so on.[56]

Furthermore, data suggest that systemic blood pressure should be maintained above 90-100 mmHg in ECD as prolonged hypotension was reported to intensify preservation injury. Conversely, other studies show absence of significant increase in the rate of graft loss related to prolonged hypotension.[3]

Milan et al.[56] analyzed hemodynamic profile in a beat-to-beat monitoring basis between marginal and standard grafts. However, authors could not prove statistically significant hemodynamic instability in the case of ECD.

In what concerns inotropic or vasopressor drugs, *Briceno et al.*[3] reported a disturbance of early LGF when donors received norepinephrine and/or dopamine. The study conducted by these authors had the aim of comprehend if liver preservation injury could be predicted based on donor and graft extended criteria. In fact, they concluded that the accumulation of marginality factors is correlated with an increased effect in liver preservation injury and one of the considered factors in this study was the high use of inotropic drugs. Dopamine dose >15 μg/kg/min accounted for a risk of 1.56 for severe liver preservation injury. Furthermore, a dopamine dose of 2-5 μg/kg/min increases the mesenteric and renal flows while a dopamine dose of >15 μg/kg/min can cause renal impairment, being for that reason considered an extended criteria.[57]

Lucidi et al.[2] stated high vasopressor use, ICU stay >4 days and BMI >30 kg/m^2 as risk factors in, respectively, 44%, 27%, and 16% of the donors. They concluded that bad initial function was mainly related with ICU stay >4 days and donor peak serum Na+ >160 mEq/L.

Another concern is temporary cardiac arrest. *Hoyer et al.*[58] identified 77 donors with reversed cardiac arrest of 884 OLTs from donors after brain death (DBD) and determined there were no differences in patients and graft survival between the ones suffering from cardiac arrest and the ones non suffering from it.

Despite the controversy of provided data so far, it is majorly accepted that hemodynamic instability control is of major importance when faced in elderly donors as previously mentioned in this work.

4.2.4. Hypernatremia

Hypernatremia is a common condition among donors and is considered to have negative effects on graft function and mortality[59,60], although the mechanism by which it causes injury to hepatic cells is not clearly established. Proposed physiopathology for high sodium levels is that a derangement of fluid balance occurs due to a change in extracellular osmolality, consequently, causing intracellular water accumulation and swelling of the cells.[59]

Donor hypernatremia was found to have a correlation with recipient liver enzyme levels (AST and ALT), high BRB levels and prolonged coagulation times post-LT. Moreover, plasma sodium level >155 mmol/L was related to graft loss, diminished survival rates and higher needs for retransplantation.[59,60]

Totsuka et al.[61] developed a study with the aim to determine whether donor hypernatremia was associated with early graft dysfunction after LT and the effects of its correction. LT were performed using 181 donors, which were divided into three groups according to serum sodium concentration: group A (n=118; Na^+ ≤155 mEq/L), group B (n=36; peak Na^+ ≥155 mEq/L and final Na^+ ≤155 mEq/L) and group C (n=27; final Na^+ >155 mEq/L). Results concerning graft loss were reported to be 12.7% in group A, 11.1% in group B and 33.3% in group C. Furthermore, improvement of previously mentioned parameters (liver enzyme levels, BRB and coagulation times) and reversibility of hypernatremic damage in hepatocytes were demonstrated as long as correction of donor hypernatremia (<155 mEq/L) and appropriate donor management were fulfilled.

Another study conducted by the same authors[60] analyzed which donor or recipient characteristics were able to affect 30-day graft loss after LT. A sample of 186 liver grafts was used and 28 grafts (15.1%) were in fact lost within 30-days. Hypernatremia (>155 mEq/L) was encountered in 18 of the 158 grafts that were not lost (11.4%) and in 10 of the 28 grafts lost within 30-days (35.7%). By reporting these results they concluded donor sodium was an independent predictor of early graft loss (odds ratio (OR) 3.03; 95% confidence-interval (CI)).

On the other hand, recent studies have shown no correlation between donor hypernatremia and graft function or loss.[9,10,62,63]

Akoad et al.[62] reported that recipients of grafts from donors with serum sodium levels >160 mEq/L had similar rates of PNF, early graft failure within 30 days and 1-year patient and graft survival as recipients from donors with reference sodium levels.

Goldaracena et al.[10] compared recipients from extended-criteria liver grafts (serum sodium levels >155 mEq/L) with recipients of optimal donors and concluded that there was no significant difference in the 30-day and 1-year mortality rates.

Cywinski et al.[63] also showed hypernatremia did not affected early recipient survival or early graft function, not even liver function tests (AST, ALT, and total BRB), length of hospital stay and length of ICU stay.

4.2.5. Donation After Cardiac Death

Donors after cardiac death (DCD) or non-heart beating donors (NHBD) were considered a medically effective alternative to overcome the problem of organ shortage. Because of these promising results, their use enhanced through a decade and nowadays, DCD accounts for 20% of LT in the United Kingdom.[64]

Despite their effectiveness, DCD cannot be considered optimal donors because they are exposed and more sensitive to prolonged warm ischemia time (WIT), defined as the time at which the liver graft remains at body temperature after its blood supply has been diminished/cut off but before cold preservation or reconnection to a blood supply is done.

Based on Maastricht classification, whose pillars are cardiopulmonary criterion for death rather than neurologic criterion, organ retrieval from DCD can be divided in uncontrolled and controlled.[65,66]

In uncontrolled DCD, death is unplanned and results of sustained circulatory arrest related to unsuccessful cardiopulmonary resuscitation (Maastricht type II) and/or inexistence of life-support equipment in place with death on arrival to the hospital (Maastricht type I). [65, 66]

Controlled DCD (Maastricht type III) undergo planned withdrawal of circulatory support and consequently, circulatory arrest, commonly occurring in the operating room with a surgical medical team prepared to start the procurement process.[65,66]

There is no doubt that the usage of DCD, principally controlled DCD, seems to be beneficial to augment the donor pool. Controversy tends to persist if controlled DCD have equivalent or non-equivalent results (such as graft failure and biliary complications) to donors after brain death (DBD), with studies showing divergent results.

Several studies had been developed in uncontrolled and controlled donors. Uncontrolled DCD are subject to more pronounced ischemic time and insult. Consequently, they present difficulties in recovery and inferior outcomes when transplanted. A study developed with these donors revealed higher incidence of IPF, PNF (25%) and biliary complications when compared with heart-beating cadaveric donors and a graft and patient survival at 2 years of 55% and 80%, respectively. Its authors recommended a maximum WIT of 130 minutes while cardiopulmonary resuscitation or support is being done if these organs were to be used in LT.[65]

On another hand, controlled DCD have acceptable results, with comparatively superior post-LT function because they are far less prone to ischemic insult than the uncontrolled

group. A study using controlled DCD showed 1 case of PNF, patient and graft survival at 15 months of 87% and 84%, respectively, and 9.4% of biliary complications.[66]

In this context, it is also important to convey additional comparative information between DCD and DBD livers.

An interesting study developed by *Foley et al.*[67] compared controlled DCD livers with DBD livers. In the DCD group WIT was 17.8 minutes; the incidence of PNF was considered similar between both groups, although, the incidence of biliary strictures at 3 years and the frequency of hepatic artery stenosis, hepatic abscess and biloma were greater in DCD than in DBD group; furthermore, graft and patient survival at 3 years was inferior in the DCD group.

Another relevant study identified controlled DCD grafts (n=117) and uncontrolled DCD grafts (n=11). By comparison between controlled DCD and DBD livers, the authors reported the following: DCD group had inferior graft survival (72.3% *vs.* 80.4%), higher rates of PNF (11.8% *vs* 6.4%) and retransplantation (13.9% *vs.* 8.3%) but similar patient survival. Furthermore, prolonged CIT and use of life support in the recipient at time of transplantation were considered as predictors of early graft failure within 60 days.[68]

Jay et al.[69] compared the impact of undergoing DCD transplantation with remaining on the wait-list until death or DBD liver transplantation. In patients with a MELD score <15 or with hepatocellular carcinoma receiving MELD exception points inferior survival was reported. Nonetheless, DCD provides a survival benefit to patients with a MELD score >20 or with hepatocellular carcinoma without MELD exception points.

Earlier, the common policy was not to associate DCD with other factors. Recently, studies aimed to examine the impact of DCD in HCV+ recipients.

Yagci et al.[70] analyzed data of 14 DCD and 188 DBD livers transplanted in HCV+ patients. DCD patients had a significantly lower patient and graft survival and a higher recipients' incidence of liver abscess with ischemic-type biliary stricture (42% *vs.* 2%). The incidences of hepatic artery thrombosis, portal vein thrombosis and PNF were similar between both groups.

Another study approached the impact of DCD in the severity of HCV recurrence. They concluded DCD grafts constitute a risk factor for earlier HCV recurrence at one year post-LT (DCD donors/HCV+ recipients 47% *vs.* DBD donors/HCV+ recipients 10%).[71]

Mawardi et al.[72] took in account DCD grafts transplanted in HCV+ and HCV- recipients. While a lower rate of biliary complications was seen in the HCV+ group, a much higher rate of patient and graft survival was observed in the HCV- recipients (100 and 92% *vs.* 78 and 67%, respectively). Additionally, 33% of the HCV+ recipients suffered graft loss caused by fatal aggressive fibrosing cholestatic HCV or ischemic cholangiopathy.

Caution must be taken not only when allocating DCD to HCV+ recipients but also when association is made with other donor factors, such as increased age, steatosis, prolonged CIT or WIT. A recent study considering UNOS database recommended optimal values for risk factors in DCD, namely, CIT <8 hours, WIT <20 minutes, and a younger recipient (<50 years) with international normalized-ratio (INR) <2 and albumin >3.5 mg/dL.[73]

5. Conclusion

Since the beginning of LT that the donor concept implied in this surgical procedure has suffered several changes. The primarily considered ideal donor sooner became replaced by the ECD due to the disproportion between potential recipients and available donors.

According to more recent data, the use of ECD is becoming growingly accepted, with its benefits supplanting the risks. Despite these encouraging results, the controversy that still exists concerning this topic cannot be omitted.

Guiding principles associated with the management of these donors were not yet published, but in the meantime, we are able to report the following: 1) the use of aged donors is, nowadays, relatively common and caution should be especially taken when moderate macrosteatosis is also present; 2) when using steatotic donors, CIT should be kept as short as possible; 3) hemodynamic and sodium levels' control should be achieved, more importantly, in elderly donors and 4) there is still doubt whether DCD results can be equivalent to DBD ones and so far DBD should be seen as first-line.

Limitations of this work were: 1) the need to use non-MeSH/Emtree terms and secondary terms so that a more adequate bibliography could be obtained; 2) the different population data presented in selected studies, making difficult to compare them on the same ground and to perform a quantitative analysis and 3) highlighting only the most common criteria presented in the selected studies implied in LGF.

In conclusion, the use of ECD is justified and safe as long as proper allocation is conducted in order to diminish the risk of impaired function of the liver grafts.

In the future, further research should be conducted so that a generalized and consensual definition of ECD could be achieved. With these advances, it is expected a more reliable, uniform and reproducible experience among national and international liver transplantation centers. So far, the decision of using these donors remains a challenge.

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