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Review Article

Primary liver graft dysfunction and non-function: integrative literature review.

Disfunção e não função primária do enxerto hepático: revisão integrativa.

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ABSTRACT

Avoiding deaths in the waiting list for an organ is no longer the only focus of the transplant teams attention. Research and care in clinical practice has been increasingly focused on post transplant graft survival and functioning. In the present work, we performed an integrative literature review to identify the terminology used about liver graft dysfunction and non-function, as well as to investigate the incidence and risk factors of these clinical events. We chosen articles written in Portuguese, English and Spanish between 2012 and 2016, based on CINAHL, MEDLINE, Cochrane, LILACS, BDENF, IBECS, EMBASE and Web of Science. We selected 14 studies, in which we identified the incidence of hepatic graft dysfunction ranging from 7% to 27%. The terminology used to describe this clinical event was initial malfunction, graft hypofunction, marginal function or delay in function. The primary non-function of the liver graft was found in 1.4% to 8.4% of the patients, and the terminology used to describe the event was early dysfunction or graft loss. The risk factors found are related to donor, recipient, graft and transplant logistics variables. We conclude that knowledge of the different terminologies employed in the literature, of the incidence of dysfunction and primary non-function, and of their risk factors are fundamental to qualify the control of the events, aiming to improve patients' survival after liver transplantation.

Keywords: Primary Graft Dysfunction. Liver transplantation. Risk Factors.

INTRODUCTION

The most feared event by transplant surgeons is the graft non-functioning after implant[1-6]. To describe this condition, the literature uses different nomenclatures, especially in the case of liver transplantation[7]. Liver transplant initiates with withdrawal of the liver to be donated, followed by preparation of the graft and ending with the implant in the recipient. In the withdrawal, when the aorta is clamped, the graft is submitted to devascularization, with prolonged oxygen deprivation and consequent decrease of energy reserves in the tissues. Despite the lack of cellular nutrition, the organ exposed to cold ischemia (ice) maintains its macroscopic morphological aspect unchanged. However, when the aortic artery is unclamped in the recipient and the liver is reperfused, the so-called ischemia-reperfusion lesion occurs at the tissue and cellular levels. The resulting biochemical and morphological changes with persistent ischemia-hypoxia of endothelial cells cause the formation of free radicals that damage the endothelium and hepatic cells and activate Kupffer cells, resulting in changes in the levels of proteins associated with inflammatory and immunological events[5]. Histopathological findings include acute inflammatory infiltrate, hepatocellular damage such as coagulative necrosis and large neutrophil infiltrates, which characterize graft dysfunction[6]. After 14 hours of cold ischemia, this lesion is much more severe, and may contribute to the early graft failure.

Liver dysfunction is characterized by the presence of at least one of the variables: bilirubin =10mg/ml, International Normalized Ratio (INR) =1.6 during the first seven postoperative days, and aminotransferases >2000IU/l in the first week of the postoperative period. Early graft dysfunction (EGD) is described as early malfunction, graft hypofunction, marginal function or delayed function[7-10]. Its incidence occurs in about 8% to 24.7% of patients[11,12]. The primary non-function (PNF) is a severe clinical condition with coagulopathy or fibrinolysis, persistence of acidosis, hyperpotassemia with oliguria or anuria, hypoglycemia, absence of bile and wakefulness, hemodynamic instability, leading to retransplantation or death. This condition has been termed as early dysfunction or graft loss and can occur in 0.9% to 7.2% of patients[8,13].

In these situations, the literature describes risk factors related to the donor, recipient, graft and the logistics of the transplantation that interfere in the function of the hepatic graft. However, clinical practice has observed risk factors that need to be better investigated. In this sense, the present study aimed at identifying in the literature the nomenclature used for EGD and PNF of the hepatic graft, their incidence and risk factors.

METHODS

This is an Integrative Literature Review (ILR) carried out in six stages: formulation of the problem, establishment of criteria for sampling, categorization of studies, analysis, data interpretation, and results synthesis[14]. The guiding question established was: What is the nomenclature used, the incidence and the risk factors evident in the literature regarding EGD and PNF of the hepatic graft? The search in the literature used the following controlled descriptors available in MesH and DeCS in English, Portuguese and Spanish: "Liver Transplantation", "Delayed Graft Function", "Risk Factors", "Primary Graft Dysfunction" and "Hepatic Transplantation". We searched in the databases of the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medical Literature Analysis and Retrieval System online (MEDLINE), Cochrane Library, Latin American Literature in Health Sciences (LILACS), Nursing Database (BDENF), Spanish Bibliographical Index in Health Sciences (IBECS), Excepta Medica Database (EMBASE) and Web of Science, in addition to performing reverse search.

The search in MEDLINE used the strategy ("Transplante de Fígado" OR "Liver Transplantation" OR "Trasplante de Hígado" OR "Enxerto de Fígado" OR "enxerto hepático" OR "Liver Grafting" OR " Liver Graftings" OR "Transplantação de Fígado" OR " Transplantação hepática" OR "Hepatic Transplantation" OR "Transplante Hepático" OR "trasplante hepático") AND ("Disfunção Primária do Enxerto" OR "Primary Graft Dysfunction" OR "Disfunción Primaria ri Injerto" OR "Não função primária" OR "primary non function" OR "primary non-function"). For the bases EMBASE, CINAHL, Web of Science and Cochrane were used the following strategy: ("Liver Transplantation" OR "Liver Grafting" OR "Hepatic Transplantation") AND ("Primary Graft Dysfunction" OR "primary non-function" OR "primary non-function") AND ("Risk Factors" OR "Risk Factor" OR Risk).

We included in the selection studies published in full in Portuguese, English and Spanish languages, with the time limit between 2012 and 2016, justified by the significant volume of publications in the last ten years. For the selection, we considered articles with level I of evidence (systematic reviews), level II (experimental) and level III (almost experimental, case control or historical cohort)[15]. We excluded from the sample theses, dissertations and articles repeated in the databases. For the information collection, we applied an instrument adapted to the search[16].

We identified 727 studies: 38 in PUBMED, five in Cochrane, two in CINAHL, 575 in EMBASE, ten in LILACS, 6 in IBECS, 23 in BDENF and 44 in the Web of Science, and 24 in reverse search. Of these, we excluded 680 after reading the title. We considered 47 papers eligible after reading the abstracts. We then excluded 33 articles: 27 for not addressing the topic and six without evidence quality. Fourteen studies addressing the nomenclature, incidence and/or risk factors of EGD and PNF of the hepatic graft remained at the end (Figure 1).

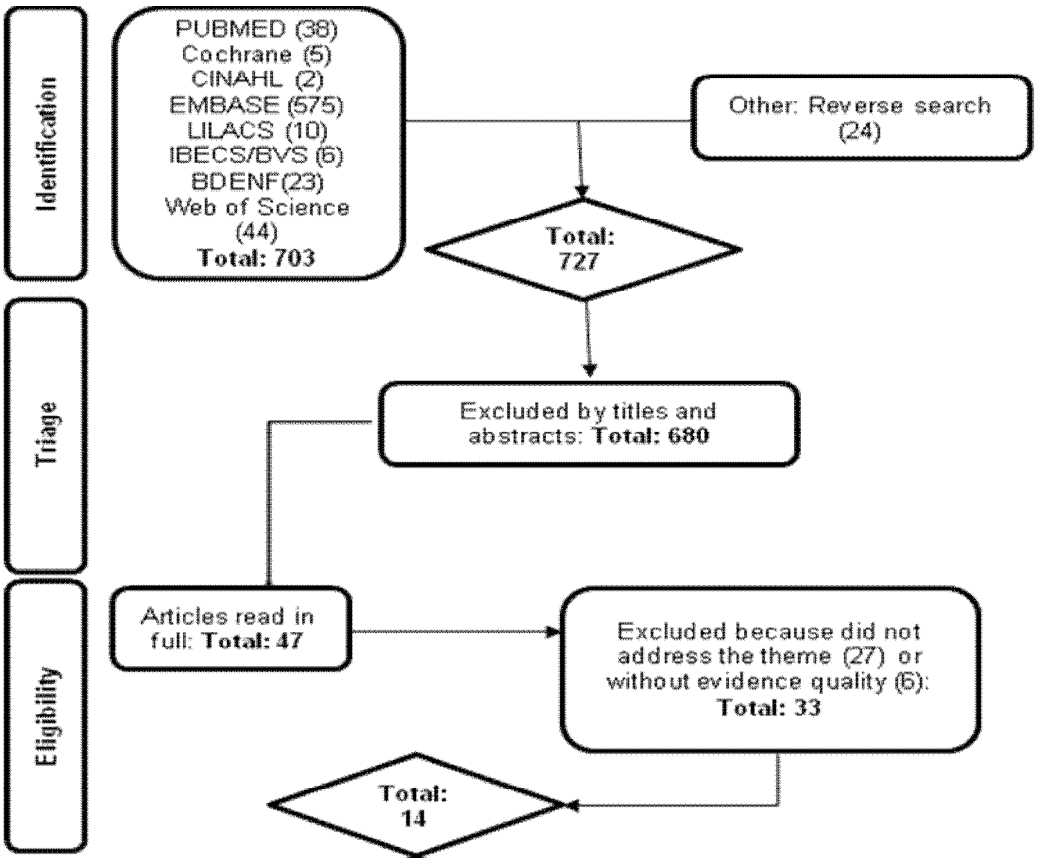

Figure 1. Flowchart of identification, selection and inclusion of the studies.

RESULTS

Among the 14 articles selected (Table 1), we observed a fragility from a methodological point of view, since the predominant level of evidence was III, in 12 studies (85.7%).

Table 1. Demonstration of the selected articles, contemplating objectives, risk factors and level of evidence.

	Author, year and title	Kind of study	Goals	Risk factors	Level of Evidence
1	Chu, 2015. Donor Hepatic Steatosis and Outcome After Liver Transplantation: a Systematic Review.	Systematic review	To evaluate the impact of liver steatosis on the results of transplantation.	Graft: macrovesicular steatosis >30%.	I
2	Ghabril, 2016. Portal Vein Thrombosis Is a Risk Factor for Poor Early Outcomes After Liver Transplantation: Analysis of Risk Factors and Outcomes for Portal Vein Thrombosis in Waitlisted Patients.	Historical cohort	To determine the impact of portal vein thrombosis (PVT) on the patient after hepatic transplantation and graft survival, waiting list results and factors associated with PVT.	Recipient: pre-transplant portal vein thrombosis in.	III
3	Beck-Schimmer, 2015. Conditioning With Sevoflurane in Liver Transplantation: Results of a Multicenter Randomized Controlled Trial.	Randomized clinical trial	Examining whether volatile anesthetics have an effect on acute graft injury and clinical outcomes after liver transplantation.	Recipient: anesthetic propofol.	II
4	Maggi, 2014. Ischemia Time and Liver Transplantation, Today.	Historical cohort	To evaluate the impact of the time of ischemia and other clinical factors in the development of PNF.	Donor: age >60 years and female. Graft: time of ischemia >10h. Recipient: plasma consumption >30UI. Logistics: surgical time.	III
5	Lee, 2016. Early allograft dysfunction after liver transplantation: an intermediate outcome measure for targeted improvements.	Historical cohort	Use of EGD as an intermediate outcome measure and to identify donor, recipient and perioperative risk factors.	Donor: stopped heart.	III
6	Fukazawa, 2013. Crystalloid fl ush with backward unclamping may decrease post-reperfusion cardiac arrest and improve short-term graft function when compared to portal blood? Ush with forward unclamping during liver transplantation.	Historical cohort	To compare two methods of reperfusion: crystalloid infusion with retrograde depletion and infusion of portal blood with post-anastomosis de-flushing.	Graft: lavage technique and retrograde reperfusion.	III
7	Angelico, 2014. A Bayesian methodology to improve prediction of early graft loss after liver transplantation derived from the Liver Match study.	Historical cohort	Generate a robust predictive model of early graft loss after hepatic transplantation.	Donor: age >60 years, BMI and height. Graft: time of cold ischemia (TCI). Recipient: creatinine, bilirubin, disease etiology, previous surgery of the upper abdomen and portal thrombosis.	III
8	Cortes, 2014. Metabolomics discloses donor liver biomarkers associated with early allograft dysfunction.	Historical cohort	To investigate if there is a preoperative metabolic biomarker of the donor associated to EGD.	Graft: metabolic profile.	III
9	Silberhumer, 2013. The difficulty in defining extended donor criteria for liver grafts:the Eurotransplant experience.	Historical cohort	To analyze the impact of donor-specific risk factors, independent of the characteristics of the recipient.	Donor: Sodium >160mmol/l, gamma glutamyl transferase (GGT), stopped heart and gender (female). Graft: TCI>12h.	III
10	Hoyer, 2015. Donor information based prediction of early allograft dysfunction and outcome in liver transplantation.	Historical cohort	To evaluate donor predictive information for the development of EGD.	Donor BMI, GGT, macroesteatosis. Graft: TCI.	III
11	Dutkowski, 2012. The Use of Fatty Liver Grafts in Modern Allocation Systems Risk Assessment by the Balance of Risk (BAR) Score.	Historical cohort	To integrate the amount of hepatic steatosis in the modern liver allocation system.	Graft: liver macroesteatosis > 30%.	III
12	Lee, 2014. Early Allograft Dysfunction in Liver Transplantation with Donation After Cardiac Death Donors Results in Lower Survival.	Historical cohort	To investigate the incidence and ratios of EGD and its role in predicting morbidity and mortality in hepatic recipients from brain death donors.	Donor: stopped heart.	III
13	Taner, 2012. Events in Procurement as Risk Factors for Ischemic Cholangiopathy in Liver Transplantation Using Donation After Cardiac Death Donors.	Historical cohort	To determine the factors that cause graft loss and the development of ischemic cholangitis and compare the survival of patients with grafts from CPR and brain death donors.	Donor: stopped heart. Logistics: time elapsed between asystole and aortic clamping. Recipient: race: African-American.	III
14	Blok, 2012. Validation of the Donor Risk Index in Orthotopic Liver Transplantation Within the Eurotransplant Region.	Cohort	To validate the Donor Risk Index (DRI) in Eurotransplant.	Donor: DRI. Recipient: age, Model for End-Stage Liver Disease (MELD) and underlying disease (Viral Cirrhosis C).	III

We found the following nomenclatures in the literature for EGD[7,17,18]: poor graft initial function[19,20]; early allograft dysfunction, early graft failure[2,5,7,12,13]; delayed non-function and impaired primary function[7]. For the PNF of the hepatic graft, we found the following nomenclatures: early graft loss[3,4,12] and graft loss[3,13,21,22]. There was consensus regarding the concepts/definitions for EGD and PNF among the authors.

We identified a large variation in the EGD incidences. A study with American and Italian population found incidences of 7.2% and 11.7%, respectively[3].Incidences of 14%[2], 14% to 27%[5], 21.7%[13], and 24.1%[9] were also described. However, when evaluating EGD studies involving donors with brain death (BD), we identified incidences between 21% and 26.5%, and for stopped heart donors, 39.5%[4,12]. On their turn, the incidences of PNF with BD donors were 1.4% to 8.4%[5], 2.3%[4], 3.6%[19], and 8.4%[13]. We found an incidence of 2.5%[22] and 1.4%[3] in cases with donors in cardiorespiratory arrest (CRA).

We identified risk factors for EGD and PNF relative to the donor. The use of hepatic grafts after cardiac arrest increased risk according to four articles[4,9,12,22]. Brazil and Italy are examples of countries where these types of grafts are not used. The age of the donor over 60 years was described as risk in two articles[3,9], as well as the female gender[4,19], body mass index (BMI) >30kg/m² [3,13], and mean gamma glutamyl transferase (GGT) values between 23 and 50 U/l[19,22]. We identified other isolated risk factors for graft dysfunction in only one article, namely: height[3] and the donor serum sodium levels above 160mmol/l[19]. The Donor Risk Index (DRI) is also an important risk factor, a DRI>1.45 increasing the risk of graft loss both for EGD and PNF[13,20,23].

The recipient-related risk factors identified in the literature were: pre-transplantation portal vein thrombosis (PVT) cited by two studies[2,21]. A historical cohort study showed that patients with PVT had a survival rate of 89.6% at three months post-transplantation, and without this comorbidity, a survival rate of 91.5% over the same period of time[21]. The underlying disease (viral C cirrhosis) was found to cause graft failure in two articles[3,23]. We identified the following risk factors in just one article: use of the anesthetic propofol appearing as increased risk for EGD[2]; consumption of fresh frozen plasma >30IU[9]; serum creatinine and bilirubin levels and previous abdominal surgery[3]; age of the recipient >60 years is still a controversial risk factor[23], and being African American[22].

We verified that the MELD index, although still used in clinical practice as one that establishes the priority in the queue for transplantation, should not be the isolated indication for the transplant. Both donor and recipient data should be considered when deciding whether to transplant, for increased patient survival[8,23].

Regarding the risks related to the graft, we found: time of cold ischemia (TCI) >10 hours in four articles[3,9,13,19], since time below this parameter is considered safe for graft quality. A prospective study of great relevance showed that this factor associated with female gander, donor age >60 years, and infusion of more than 30 fresh frozen plasma units were statistically significant predictors of graft PNF[9]. Macroesteatosis >30% was a risk factor in three studies[7,13,20]. A liver with mild (<30%) steatosis is considered safe to be used for transplantation; a liver with severe steatosis (>60%) should be discarded, and in cases of moderate steatosis (between 30 and 60%), it cautious use is recommended in cases where the recipients have low MELD and low TCI[7].

It was also observed that the metabolic profile of the graft may be associated to its post-implant functioning, since the concentration of metabolites reflects the functional phenotype of an organism. The gene expression profile was checked for ischemia and changes in lipid biosynthesis were identified. There was a strong association between some genes and the oxidative stress and apoptosis in liver grafts, by favoring the proliferation of toxic metabolites. It was concluded that these genes reinforce the marker potential of lipid-related injury and that this fact is important in evaluating graft quality before transplantation[5].

Regarding the risks related to **transplantation logistics,** the surgical time and the time between donor asystole and aortic clamping were described in two articles[9,22]. A study by Taner *et al*. comparing grafts from BD and PCR donor showed that the time between asystole and aortic clamping was related to a higher incidence of ischemic cholangiopathy, responsible for EGD and PNF[22]. Surgical time includes removal of the graft from the donor, preparation of the ex-situ graft (back table surgery), hepatectomy of the recipient's native liver, orthotopic graft implantation, and venous anastomosis. After reperfusion of the graft with portal blood, anastomoses of the hepatic artery and biliary tract are performed. Patients with prior surgery in the upper quadrants of the abdomen and with a high degree of portal hypertension are more prone to intraoperative complications due to the greater risk of bleeding. Thus, longer surgical time implies higher TCI. Moreover, the time of venous anastomoses is considered as a time of hot ischemia (THI). Thus, the surgical phase of transplantation with higher TCI and THI is considered a risk factor for graft function[9,22].

The technique of lavage and reperfusion of the hepatic graft was a risk for graft function according to one article[17]. Two methods were compared: crystalloid infusion with retrograde lavage through the donor portal vein and infusion of 250-500ml of recipient blood, with post-anastomotic declamping of the hepatic and portal veins. In this technique, the portal vein is declamped while the suprahepatic donor remains occluded. The first technique was considered superior in relation to the second one, since it allows gradual

reheating of the organ submitted to cold ischemia, without recipient blood loss. The ischemic biliary lesion rate in the group that received the crystalloid technique was 1.8%, while in the group receiving the recipient's blood it was 8.6%[17].

Knowledge of these risk factors for graft injury and, consequently, EGD and PNF made it possible to draw up a conceptual map to facilitate understanding of these events (Figure 2).

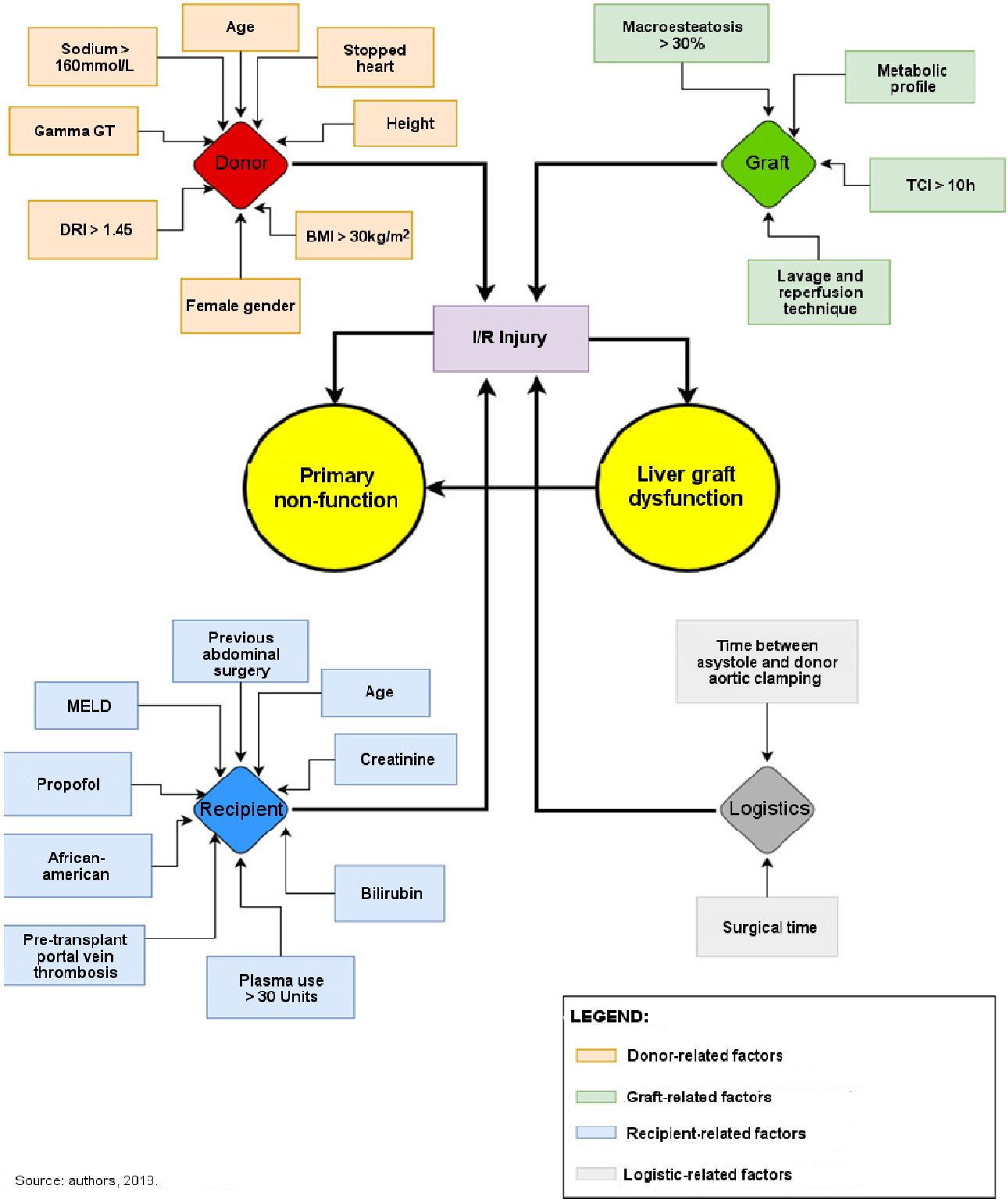

Figure 2. Dysfunction and non primary function of the liver graft.

DISCUSSION

This study identified the nomenclatures used in the literature, the incidence and risk factors associated with EGD and PNF. It is interesting to note that, although the nomenclatures used to describe EGD are diverse, there is a consensus in its definition as the presence of at least one of the variables: bilirubin =10mg/ml, INR=1.6 during the first seven postoperative days, and aminotransferases >2000IU/l in the first postoperative week[11,12]. Graft loss, i.e., PNF, should be considered as a complete failure of graft function, with rapid clinical worsening of the patient and requiring immediate retransplantation.

Donor-related risk factors for PNF and EGD were: stopped heart, age, female gender, BMI>30kg/m², GGT>55U/l, height, sodium >160mmol/l, DRI>1.45[3,4,9,12,13,19,23]. With regard to the use of the stopped heart donor, the justification is to increase the number of donors, access to transplantation, waiting list reduction, and pre-transplant mortality. In Brazil, Italy, and other countries, livers from such donors are not used[4,19,24]. However, this is common practice in countries in Europe and in the United States. In this donation modality, organ damage can occur during the donor's rapid progression to death in a context of low perfusion. It is emphasized that the donor hypoxia time impacts on graft function. Thus, the survival of the grafts and of the recipients of organs from stopped heart donors are smaller compared with the results of brain death donors. Therefore, the choice of the ideal recipient for the graft from this donor is important, since the risks of EGD and PNF are very high[4,19,22].

The donor's age is also considered a risk factor for graft function[3,9,25]. However, there is disagreement among the authors regarding the age range acceptable for donation or the cutoff for organ discarding. One study showed worse results with recipients whose donor age is greater than 49[10], and another, that this threshold would be over 60 years[9]. However, Brazilian guidelines for evaluation and validation of the potential donor for transplantation recommend discarding of livers from donors over 90 years old[25]. On her turn, the female donor was identified as a risk factor for PNF[9,19].

Hepatic steatosis is classified in the literature as macro and microesteatosis[7,13,20]. Donors with BMI=35kgm/m$^{2\ 3}$ may present severe steatosis and, therefore, should not be accepted for liver donation[7]. However, macroesteatosis up to 30% is safe for use in transplantation[7,20]. Estimates of the steatosis degree, however, are observer-dependent and, in most cases, histological examination for determination of steatosis percentage is not available for timely evaluation before transplantation[13]. In addition, other authors did

not find statistically significant association of steatosis with graft dysfunction[4,12], evidencing that the sum of risk factors should be more important than an isolated one.

Mean donor GGT values of 23 to 50U/l have been pointed as a risk factor for injury[13,19]. Although the evaluation of an organ based on isolated laboratory data is controversial, a study showed an association of this parameter with graft failure, since the presence of donor comorbidities such as type II diabetes, chronic cardiovascular and renal disease, alcoholism or use of total parenteral nutrition alter the result of the exam[13,19]. Donor height =150cm[3] and serum sodium >160mEq/dl[19] were also isolated risk factors for graft PNF. The latter, although controversial, was related to irreparable damage to hepatocytes due to the change in intracellular osmolarity[19].

The donor risk index was developed by Feng *et al*.[26] in an American context and validated in the European community by Blok *et al*.[23]. This index provides an important quantitative evaluation of the relative risk for each potential graft, based on characteristics of the donor and graft at the time the organ is made available. The parameters used in its calculation are age, race, height, cause of death, donation of bipartite livers, origin (local, regional, national) and time of cold ischemia. In this ILR the cause of death and the donation of bipartite livers were not impacting factors in EGD and PNF. However, the other parameters for the DRI calculation were confirmed. Donor origin is directly related to the TCI of the graft, since in Brazil, for example, given the territorial extension, a donor being regional or national can certainly impact the time in which the graft will be submitted to low tissue perfusion, with risk of delayed function or post-implant dysfunction.

A DRI>1.45 is the identified cutoff for predicting dysfunction in the American population[26], the same threshold in Europe being >1.71[23]. Studies in Brazil that determine cutoff values of this index for EGD and PNF are not known. Thus, one should consider, from the present study, that a DRI cutoff of 1.45 be safe. Clinical studies should be developed to test identified donor risk factors, such as GGT level and BMI. The laboratory examination is simple, inexpensive and available at the time of evaluation of the potential donor, as well as data on the height and weight to calculate the BMI. These studies can broaden the predictive power of DRI and greatly assist transplant surgeons in choosing the ideal donor.

Regarding the risk factors of the recipient, age is still controversial. Some authors consider that younger recipients are at higher risk of death because this population is selected to receive bipartite livers[10]. In addition, recipients with a body mass index >25kg/m² are prone to a higher incidence of PNF and EGD[3,13]. Race has presented significant differences in survival in some populations. American researchers conducted a

study to determine the factors that cause graft loss and the development of ischemic cholangiopathy (IC) and to compare the survival of patients with grafts from CRA and BD donors. In the multivariate analysis, the African American race was a significant predictor of IC or hepatic necrosis 5.37 times more than the Caucasian one[22].

Portal hypertension is part of the natural course of chronic liver disease. The incidence of portal vein thrombosis among patients who are candidates for liver transplantation ranges from 4.5% to 9.7%[3,12,21]. Survival on the waiting list is slightly lower among patients with portal venous thrombosis (89.6%) compared with patients without thrombosis (91.5%) within 90 days. A study showed that the presence of steatosis, cryptogenic liver disease as etiology of liver disease, obesity, diabetes mellitus and the presence of ascites are risk factors for the development of portal thrombosis in patients on the waiting list[21].

Portal vein thrombosis may be a determining factor for post-transplantation evolution due to both its association with thrombophilia and the formation of hepato-fugal shunts. Only part of portal vein thromboses in cirrhotic patients is due to the change in coagulation, since thrombophilia implies a higher incidence of new thrombosis with low graft perfusion and graft dysfunction. On the other hand, the formation of hepato-fugal shunts from the portal circulation is extremely frequent in portal hypertension and, mainly, portal vein thrombosis. Their relation with graft dysfunction resides on blood flow theft to the collaterals, reducing the graft's portal perfusion, even when the portal trunk has free flow[3,21].

The standardization of the anesthetic agent for the liver recipient has been investigated[2,18]. Both propofol and sevoflurane are safe for use in liver transplant surgeries[18]. However, propofol has a higher risk for graft dysfunction compared with sevoflurane[2].

MELD has been useful for predicting the individual's chance of dying if not transplanted[8,10,23]. It evaluates the recipient's severity through laboratory tests such as creatinine, INR, and bilirubin. Such results undergo periodical updates, which reposition the patient in the list, so that the most serious ones have priority for transplant. The best survival results was observed with a MELD<18. Values above this limit constitute a statistically significant factor associated with post-transplant death[22,23]. When the DRI was validated, it was suggested that age, MELD and the recipient's underlying disease should also be taken into account when deciding whether to transplant. Much is discussed about the allocation of grafts with a high risk index. Low-risk recipients (low MELD) are the ones with the best reserve to tolerate an initial graft dysfunction. However, these recipients also

can wait longer for a better quality graft. Thus, transplanting low-risk recipients with donor grafts with high DRI may cause them injury. Medium or high risk (higher MELD) recipients may succumb to delayed graft function, but for these recipients, the worst risk may be of not achieving transplantation, since the severity of the disease imposes a risk of death[23].

Patients with severe portal hypertension and pre-transplantation thrombosis have a greater demand for perioperative transfusions and, consequently, a greater risk of bleeding and shock, with graft injury. In these, fresh frozen plasma consumption greater than 30 units is a risk for EGD and PNF[3,9].

Laboratory tests are also used to evaluate the function of organs. The recipient's elevated creatinine and bilirubin levels are predictors of hepatic graft PNF[3].

The graft risk factors for injury and its dysfunction are TCI > 10 hours, macroesteatosis >30%, metabolic profile and lavage and reperfusion technique[5,7,9,13,17,19,20]. TCI starts at the time the donor aortic clamping occurs, followed by the perfusion of the graft with the preservation solution recommended by the service. It ends with declamping of the recipient's portal vein, when the reperfusion of the graft begins. This time greater than ten hours is strongly associated with EGD and PNF of the hepatic graft[9,10,13,19]. In Brazil, this time has to be well addressed, especially due to the country's territorial extension. The National Transplantation System (SNT) legislation prescribes the organ allocation according to the states in a network organized in regional subsections, seeking the optimization of the donation-transplant process and of time. However, the allocation may occur from one region to another, impacting TCI, which must be taken into account, since it is directly related to graft quality[24].

Hepatic steatosis is already established as a risk factor for EGD and PNF of the hepatic graft[7,13,20]. It is classified in macro and microsteatosis, and graduated in mild, moderate and severe. Due to the shortage of organs for transplantation, the criteria for their use have been expanding. There is a worldwide trend of using livers from older donors, which, associated with increased weight of the general population, increased the finding of steatosis. Studies show that grafts with macroesteatosis greater than 30% constitute a risk for transplantation, with a recommendation for organ rejection with steatosis above 60%[7,13,20,25].

The findings on the evaluation of the metabolic profile of the graft are promising, since the possibility of evaluating the potential of developing perfusion injury is fundamental to the decision to use or discard a graft for transplantation. However, in the Brazilian reality, there is no study that evaluated the functional phenotype with the needed speed, at the critical decision moment. In addition to this lack of scientific evidence, the

structural and logistic limitation available in the Brazilian context makes it difficult to use this data in the decision on the disposal or acceptance of a graft for transplantation.

From the point of view of the surgical technique, graft portal lavage before reperfusion has been considered a protective factor against liver dysfunction. The goal of graft "lavage" would be to remove potassium, leukocytes and thrombi, with improvement of the sinusoidal microcirculation. Classically, ice-cold solutions of 4% albumin diluted in saline are employed. Others consider the Ringer cold solution or even heated solutions[27]. Reperfusion techniques with retrograde graft lavage have also been described, with better results compared with the classic portal lavage[17].

Regarding the stopped heart donor, the time between asystole and aortic perfusion also appears to be associated with graft dysfunction[4,22]. The US Institute of Medicine recommends waiting two to five minutes after the suspension of the artificial support and declaration of death by the physician so that the transplant team has access to donor[22]. This type of donation exposes the organ to increased THI and may result in increased incidence of graft PNF, hepatic artery thrombosis and IC. This, in turn, can cause abscess and hepatic necrosis, leading to graft loss[22]. Patients who received grafts with a mean time of 24-minute hot ischemia had 2.5% PNF rates, 3.5% hepatic artery thrombosis, 1.5% hepatic necrosis, and 12% IC[22].

Regarding the risks related to transplantation logistics, literature findings point to surgical time, particularly at the interval between asystole and donor aortic clamping. In the Brazilian reality, several factors are limiting to the use of the organ form this donor. Among the difficulties, the care of the potential donor is limited by problems such as the low number of intensive care beds, restricted access to diagnostic technology in several peripheral hospitals, and the lack of priority and commitment of intensive caregivers[24,25]. Infrastructure shortages also make it impossible to use the risk assessment criteria for an EGD and PNF, and lead to the choice of low quality grafts and donors. Thus, some graft quality evaluation scores evidenced in the present study cannot be applied now for transplant decisions in most Brazilian scenarios.

As for using liver from stopped heart donors, it is clear in the literature that liver damage can be reduced in a fast process from a donor with cardiac arrest, compared with the graft exposure to a prolonged low perfusion, while awaiting the entire diagnosis of BD[22]. Considering the potential of Brazil to use this type of donor, it is necessary to develop well-established protocols for the withdrawal of organs in such cases, in a contextualized way to guarantee safety in their use. To that end, it is imperative that investments in public policies and resources unique to research become available, besides

improving the infrastructure in the area of transplants, to obtain results similar to those reported in developed countries.

From the knowledge of the donor, graft, recipient and transplantation logistics risk factors, evaluation scores were developed in order to assist the health team with the provision of a liver for transplantation. Some models associate data from the donor-recipient *(*Balance of Risk – BAR – and the Donor Model for End-Stage Liver Disease – D-MELD), from the recipient (Early Allograft Function – MEAF –, the Survival Outcome Following Transplant – SOFT –, and the Charlson Comorbidity Index – CCI-LT) and from the donor-graft *(*Donor-Recipient Allocation Model – DReAM*)*[3,4,8,13,14,20,28].

Among the pre-transplant evaluation models, in addition to the MELD and DRI[23,26], the BAR stands out because of the possibility of associating the data from donor and recipient in the search for an ideal graft for each recipient. It uses the following data: MELD of the recipient, TCI, recipient and donor age, previous transplantation, and pre-transplant intensive care unit need. The score ranges from 0 to 27 points, a BAR>18 displaying 98% specificity to identify patients at high risk of post-transplant mortality[8,20]. The score is a tool that rescues ethical principles related to transplantation, such as utility and fairness in the allocation of grafts for transplantation, that is, the ideal graft for each patient.

Regarding the post-transplant evaluation models, the early graft function (MEAF) uses data from INR, bilirubin and alanine aminotransferase on the third postoperative day. The MEAF stands out by helping to standardize the concept of early graft dysfunction and to compare the clinical outcomes of recipients, interventions and clinical outcomes within and between the different transplant centers. According to its authors, the model allows evaluating the results of graft and patient survival, according to the score of each recipient. A MEAF>7 points to increased risk of PNF and the need for an early retransplantation[28].

The transplant team's care in the donation-transplant process involves systematic and judicious evaluations for transplant candidates and potential organ donors. The monitoring and identification of risk factors of the donor, the recipient, the graft and the logistics of the transplant are of paramount importance for their control. Data from this monitoring should be shared with all team members. In this context, it is important that the transplantation surgeons and the whole team know the risk factors of EGD and PNF of the hepatic graft, in order to identify and intervene early in the face of these diseases, with a view to better survival of the grafts and, consequently, the patients.

CONCLUSION

The present ILR had some limitations, such as the fragility of the evidences of the identified articles and the lack of a standardized language referring to the subject, with a great variation of descriptors, which made the selection of the studies difficult. However, the proposed objectives were achieved, with the identification of various nomenclatures related to EGD and PNF, and their incidences. Risk factors related to donor, recipient, graft and transplantation logistics were also identified.

This study may contribute to the care of the transplantation team, especially liver transplant surgeons, in the implementation of actions to control the risks of EGD and PNF. The evidences produced may also corroborate with the teaching of transplant assistance and point to the need for well-designed clinical studies that aim to explore the pathophysiology of the ischemia-reperfusion injury responsible for liver graft dysfunction.

An important aspect in increasing awareness of these risks and evaluation scores is the legal requirement to provide information to the recipient about the expected results with a possible transplant. The law that regulates transplants already states that the transplantation or graft risks identified in the tests performed on the donor should be candidly clarified to the recipient, assuring that the patient understood the information and favoring his/her participation with greater autonomy in the decision about the completion of his/her own transplant.

RESUMO

Evitar mortes na fila de espera por um órgão não é mais o único foco de atenção das equipes de transplantação. As pesquisas e cuidados na prática clínica têm sido cada vez mais voltados para o funcionamento do enxerto pós-implante. O objetivo desse estudo foi identificar a nomenclatura utilizada na literatura para disfunção e não função de um enxerto hepático, bem como, investigar as incidências e fatores de risco. Trata-se de uma revisão integrativa da literatura de publicações na íntegra em português, inglês e espanhol, entre 2012 e 2016, nas bases: CINAHL, MEDLINE, Cochrane, LILACS, BDENF, IBECS, EMBASE e *Web of Science*. Foram selecionados 14 estudos em que se identificou incidências variando entre 7% e 27% e a nomenclatura utilizada para descrever o evento foi mau funcionamento inicial, hipofunção do enxerto, função marginal ou retardo na função. Foram encontradas incidências de não função primária do enxerto hepático entre 1,4% e 8,4% dos pacientes e a nomenclatura usada para descrever o evento foi disfunção precoce ou perda do enxerto. Os fatores de risco encontrados são relacionados às variáveis do doador, receptor, enxerto e logística do transplante. Conclui-se que o

conhecimento das diferentes nomenclaturas empregadas na literatura, das incidências da disfunção e não função primária e seus fatores de risco são fundamentais para qualificar as intervenções de controle dos eventos na perspectiva de melhorar a sobrevida do paciente pós-transplante hepático.

Descritores: Disfunção Primária do Enxerto. Transplante de Fígado. Fatores de Risco.

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