Mini-Review

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Donor-recipient matching in adult liver transplantation: Current status and advances

Caterina Accardo[1], Ivan Vella[1], Duilio Pagano[1], Fabrizio di Francesco[1], Sergio Li Petri[1], Sergio Calamia[1], Pasquale Bonsignore[1], Alessandro Tropea[1], Salvatore Gruttadauria[1,2,*]

[1] Department for the Treatment and Study of Abdominal Diseases and Abdominal Transplantation, Istituto di Ricovero e Cura a Carattere Scientifico-Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione (IRCCS-ISMETT), University of Pittsburgh Medical Center (UPMC), Palermo, Italy;

[2] Department of Surgery and Medical and Surgical Specialties, University of Catania, Catania, Italy.

SUMMARY The match between donor and recipient (D-R match) in the field of liver transplantation (LT) is one of the most widely debated topics today. Within the cohort of patients waiting for a transplant, better matching of the donor organ to the recipient will improve transplant outcomes, and benefit the waiting list by minimizing graft failure and the need for re-transplantation. In an era of suboptimal matches due to the sparse organ pool and the increase in extended criteria donors (ECD), ensuring adequate outcomes becomes the primary goal for clinicians in the field. The objective of this mini-review is to analyze the main variables in the evaluation of the D-R match to ensure better outcomes, the existence of scores that can help in the realization of this match, and the latest advances made thanks to the technology and development of artificial intelligence (AI).

Keywords liver, transplantation, donor-recipient, matching, outcomes, allocation

1. Introduction

With the increasing number of liver transplant (LT) candidates and the sparse pool of available organs, the rationale for allocating a graft to a potential recipient on the list is now a lively topic in the field of liver transplantation. In addition, at a time in which marginal organs are increasingly available, to ensure a good post-transplant outcome it is necessary to find the most appropriate way to allocate these grafts to the most suitable recipients. Allograft allocation should and can be more precise and personalized, but D-R matching is really a problem of classification, in which some donor variables are combined with variables of the listed recipients, surgical considerations, and logistical factors; in short, it is a quite complex process (*1,2*).

In 2002, liver allograft allocation changed with the implementation of the Model for End-Stage Liver Disease (MELD) scoring system. Given its effectiveness in predicting short-term mortality, priority in this score is based on the "sicker first" principle (*3*). However, some of its limitations have been underscored over time. One of these is that some pathologies do not have an adequate priority (*e.g.*, hepatocellular carcinoma) because their prognosis is not directly related to the underlying liver function but to the risk of disease progression.

The MELD score system is not useful for predicting survival after LT in an era in which recipient and donor combinations can be suboptimal matches.

Another aspect that needs to be analyzed is the impact of the advent of extended criteria donors (ECDs). The use of ECDs has increased the donor pool but, on the other hand, it has also worsened its quality (*4*). Today, we have various organ preservation techniques that have allowed us to increase the pool of transplantable organs among ECDs, increasing and improving recipient outcomes (*5,6*). Despite this important goal, a good percentage of grafts remain non-transplantable (8.4% in a U.S. series) (*7*).

If, with an appropriate matching between the donor and the recipient, even organs defined as marginal can produce a good outcome in select patients (*8*) , an ideal prioritization system should be valid for all patients and diseases, and should be able to assign the organ to the patient with the highest risk of mortality, and at the same time with the best predictable post-transplant survival (*3*).

Various scores have therefore been developed over the years with the aim of guaranteeing an adequate donor-recipient match, and an improvement in post-transplant survival rates. Moreover, in the last decade, investments have been made in AI for the definition of the best D-R match, though we are still awaiting satisfactory results on its real clinical applicability.

The aim of this mini-review is to analyze the most widely used scores and the most studied variables in D-R matching, providing a snapshot of the current state of the literature, with an eye to new frontiers.

2. The most widely analyzed variables in the literature

The principal variables analyzed in donor-recipient matching are summarized in Table 1.

2.1. Donor-to-recipient age match

Considering the increase in marginal grafts, several studies have focused on the role of recipient and donor characteristics such as age match, seeking to identify predictive factors that reduce the risk of graft failure and patient death (*9*).

A single-center retrospective analysis of 849 deceased donor LTs by Gilbo *et al*. (*10*) shows that matching older donor livers with older recipients does not affect long-term outcomes because there is no exponential increase in age-related risks, provided that other risk factors are absent or minimized. Chapman *et al*. (*11*) also did not observe any difference in patient and graft survival in LTs matched or mismatched per age. Recently, Nakamura *et al*. found that elderly liver grafts showed slower recovery trajectories in the acute phase, but finally achieved acceptable outcomes (*12*). These results are in contrast with results from large

Table 1. The main variables analyzed in the literature on donor-recipient matching

Variable	Authors	Place and year of publication	Conclusions
Age	Vitale A. *et al*. (*9*)	Italy, 2011	**Donor age >70 y** among the criteria for defining a **suboptimal liver.**
	Pagano D. *et al*. (*14*)	Italy, 2013	**Age mismatch** is an independent **risk factor for patient death**.
	Chapman WC *et al*. (*11*)	U.S., 2015	**Comparable outcomes** in graft and patient survivals **using older donors** (> 60 y) without increased rate of complications.
	Gilbo N. *et al*. (*10*)	Belgium, 2019	**Older livers can be safely used in older recipients** if other risk factors are minimized.
	Nakamura T. *et al*. (*12*)	Japan, 2022	**Elderly liver grafts** exhibit slower recovery trajectories in the acute phase but **finally achieve acceptable outcomes**.
	Caso maestro O. *et al*. (*15*)	Spain, 2022	The results of **LT with nonagenarian liver grafts** are not significantly different from those obtained with octogenarian donors, with **satisfactory outcomes**.
Size	Levesque E. *et al*. (*21*)	France, 2013	Using **large grafts for recipient size did not impair liver function and did not modify graft and patient outcomes at one year**.
	Croome KP *et al*. (*22*)	U.S., 2015	Donors with a calculated **sTLV size ratio ≥ 1.25 have an increased risk of EAD**.
	KW Ma *et al*. (*20*)	China, 2019	**SFSG is associated with inferior medium-term but not long-term graft survival.**
	Reyes J. *et al*. (*19*)	U.S., 2019	In deceased donor LT, **the D/R body surface area ratio is a significant predictor of graft survival**.
	Kubal CA *et al*. (*24*)	U.S., 2021	**Significant donor-recipient body size mismatch did not have a negative impact on early and long-term outcomes**.
	Addeo P. *et al*. (*25*)	France, 2022	**Combination of anthropometrics of the donors with imaging of the recipients** can be **helpful in improving** the process of **donor-recipient matching** and avoiding complications.
	Kostakis ID *et al*. (*23*)	U.K., 2023	**Donor-recipient size mismatch affects the rates of portal vein thrombosis within the first 3 months** and overall graft survival.
Gender	Rustgi VK *et al*. (*26*)	U.S., 2022	**Gender-mismatched patients have a 6.9% increase in likelihood of graft failure**.
	Lehner F. *et al*. (*28*)	Germany, 2009	**Gender-incompatible LT is not a confounder in patient survival**.
	Schoening WN *et al*. (*27*)	Germany, 2016	The impressive **long-term graft survival benefit of gender mismatch** versus matched groups in LT may be caused by significant differences in donor quality and recipient characteristics, and **may not be related to gender itself**.
	Lai Q. *et al*. (*29*)	Italy, 2018	**Gender mismatch is a risk factor for poor graft survival after LT** (female-to-male mismatch represents the worst combination).
	Germani G. *et al*. (*30*)	Italy, 2020	**Donor/recipient gender mismatch in male recipients**, and the use of obese donors in female recipients are associated with **reduced survival after LT**.

registry studies from the past (*13*).

Our previous analysis (*14*) indicated that both recipient and donor ages were predictors of transplant outcome; patients of the same age were more likely to show better graft survival and longer lifespan.

Finally, there is currently no consensus on the donor age limit for liver transplantation, due mainly to recent improvements in outcomes with elderly donors (*15*).

2.2. Donor-to-recipient dimensional match

The impact of donor and recipient size mismatch in deceased whole liver transplantation has not been well studied. The consequences of size mismatch using whole grafts have been shown to increase the risk of developing "small for size syndrome", in which the transplanted liver is unable to ensure the functional and metabolic needs of the recipient.

On the other hand, a "large for size donor" can cause graft damage caused by vascular thrombosis or graft necrosis secondary to poor blood supply (*16*).

Body surface area (BSA) has proven to be an excellent indicator of metabolic mass because it is less influenced by fat mass, and therefore allows prediction with a good approximation the liver volume (*17*). The donor to recipient body surface area ratio (DR_BSAR = BSAdonor/BSArecipient) has been studied to determine its influence on graft survival (*18*).

Reyes *et al*. conducted a retrospective analysis of 79,704 liver transplants performed in the U.S., and found that in whole liver transplantation from deceased donors, DR_BSAR is a significant predictor of graft survival (*19*), thus demonstrating the importance of the correct dimensional match between donor and recipient.

Most studies have concluded that a liver graft needs to have at least 0.8% of the recipient’s weight or 35% of his/her ideal liver volume (*20*), but not more than 2.5% of the recipient’s weight or 125% of his/her ideal liver volume (*21,22*). In a series by Kostakis *et al*. (*23*), in which 11,245 transplants were considered (the liver grafts were from donors after brain death (DBD) in 9,504 (84.5%) transplants and from donors after circulatory death (DCD) in 1,741 (15.5%) transplants, three distinct categories were identified: donor size of 85% of recipient size or less, donor size more than 85%, but up to 140% of recipient size, and donor size more than 140% of recipient size. There were statistically significant differences for overall graft survival among these 3 categories ($P < 0.001$): the first category had shorter overall graft survival (75th percentile: 4,514 days) than the second category (75th percentile: 5,721 days), while the third had much shorter overall graft survival than both of the others. The data was confirmed by multivariable Cox regression analysis. The findings of this study demonstrated that donor-recipient size mismatch affected the risk of developing portal vein thrombosis within the first 3 months after transplantation, and reduced the overall graft survival. These data were confirmed by other studies on the same topic (*19,24*).

Another useful dimensional parameter is that of the Strasbourg group: the maximum volume that a graft to be implanted in patients with cirrhosis can have is the sum of the volume of the recipient's liver and the dimensions of the right upper abdominal cavity. This overall volume correlates with the severity of portal hypertension (ascites, large direct portosystemic shunt) and right anteroposterior cavity diameter (RAP; measured above the hepatic dome). The RAP reflects the compliance of the right hypochondria and correlates linearly with the overall volume. This combination of donor anthropometry with recipient imaging can be helpful in improving the donor-recipient size match, according to Addeo (*25*).

2.3. Donor-to-recipient gender match

Gender match seems to be one of the aspects that influences outcomes after LT, though this association is controversial. In the past, some monocentric studies have underlined a correlation between donor gender and graft loss (*26*), especially in male recipients of female donors (*27*), in contrast to other studies (*28*). In recent times, a number of scores have been proposed with the aim of predicting the post-transplant outcome, though none has identified the donor gender as a risk factor for poor graft survival.

A more recent meta-analysis conducted in 2018 suggests a detrimental role of the female-male (F-M) mismatch in terms of graft survival (*29*). These results are absolutely in line with several experiences worldwide (*27*). Nevertheless, Lai's group argues that there are several confounding factors to consider in these analyses.

Also Germani *et al*. pointed out recently that donor/recipient gender mismatch in male recipients and use of obese donors in female recipients are associated with decreased survival after LT, highlighting the importance of associating an anthropometric evaluation with the gender mismatch in the allocation process to have better long-term outcomes (*30*).

In conclusion, the impact of gender mismatch on post-transplant outcomes is still much debated in the literature. Further large, well-calibrated studies are needed, with the aim of definitively clarifying the potential harmful role of gender mismatch in the liver transplantation setting.

3. Scores in the literature

Liver transplantation is today the most appropriate treatment for end-stage liver disease, and a myriad of factors, as we have seen, relating to the donor, the recipient, the anesthetic-surgical procedure, and the

Table 2. Main scores proposed for donor-recipient matching in the graft allocation process

Score	Authors	Place and year of publication	Variables
DRI (Donor Risk Index)	Feng S. *et al.* (*32*)	U.S., 2006	**Donor age, race, height**, death from cerebrovascular accident (**CVA**), donation after cardiac death (**DCD**), **cause of death classified as "other"** (excluding trauma, CVA, or anoxia), **split or partial graft, cold ischemia time and location of organs** based on donor service area.
P-SOFT (the Preallocation score to predict Survival Out-comes Following Liver Transplant Score) and **SOFT Score**	Rana A. *et al.* (*41*)	U.S., 2008	**Age, BMI, previous transplant or abdominal surgery, albumin < 2.0 g/dL, dialysis before transplantation, ICU pretransplant, MELD score, life support pretransplant, encephalopathy, portal vein thrombosis, ascites pretransplant.** **SOFT: P-SOFT + points awarded from donor criteria,** 1 recipient condition **(portal bleed 48-h pre-transplant)** and two logistical factors **(CIT and national allocation)** at the time of graft allocation.
D-MELD	Halldorson JB *et al.* (*42*)	U.S., 2009	The product of **donor age** and **preoperative MELD**, calculated from laboratory values.
BAR (Balance of Risk)	Dutkowski P. *et al.* (*33*)	Switzerland, 2011	**Donor age** (years), **recipient age** (years), **cold ischemia time** (hours), **retransplantation** (yes/no), **life support** (yes/no), and the **MELD score** at the time of liver transplant (true value without exception points).
ET-DRI (Eurotransplant-Donor-Risk-Index)	Braat AE *et al.* (*13*)	Eurotransplant region, 2012	**Donor age, cause of death, donation after cardiac death, split liver graft, organ location** (regional or national), **cold ischemia time, rescue allocation**, and **gamma-glutamyltransferase levels.**
ISO (Italian Score for Organ allocation)	Cillo U. *et al.* (*39*)	Italy, 2015	Based on principles of urgency, utility, and transplant benefit, the score considers in addition to pure **MELD**, **exceptions**, and **hepatocellular carcinoma**

management of the intensive care unit are involved in the onset of complications, survival, and related costs. So with the aim of being able to analyze all these variables in the shortest possible time in the organ allocation process, various indexes have been developed (*31*), summarized in Table 2. The objective is to predict post-transplant outcomes.

3.1. Donor risk index (DRI)

Feng *et al.* (*32*) discuss the concept of the DRI, which objectively evaluates donor variables involved in transplant outcomes: donor age, DCD, and split/partial grafts are strongly associated with graft failure; African-American race, short stature, and cerebrovascular accident as the cause of death are modestly associated with graft failure. The DRI assessment offers an evidence-based D-R match. However, when DRI is assessed at the time of offering, D-R matching is not easily programmable, and the distribution of risks from donor and recipient is more dependent on the allocation scheme. By itself, DRI is a suboptimal tool for D-R matching.

3.2. Balance of risk (BAR) score

In 2011, Dutkowski *et al.* designed the BAR score, based on a combination of the principles of prognosis and justice. The main advantage is that it is based on objective factors available at the time of organ allocation, with the exception of cold ischemia time. The main disadvantage is that it does not consider other determinants, such as graft steatosis (*33*). Researchers, such as Schlegel, have proven that the BAR score is useful for finding good donor-recipient matches, but in other studies it showed a suboptimal ability (*34,35*). In the 336 patient sample of Lopez *et al.*, the BAR score was found to be inaccurate in predicting liver transplant survival (*36*), and unable to identify which of several D–R pairs will get the best result.

3.2. Eurotransplant Donor Risk Index (ET-DRI)

Braat *et al.* advanced the idea that the ET-DRI, a scoring system tailored for the Eurotransplant region, may be a useful tool for liver allocation in the future (*13*). In a retrospective single center study by Schoening (*37*) *et al.*, when combining donor (ET-DRI) and recipient factors (indication and/or lab-MELD), an estimation of long-term graft survival seems possible. This score was therefore considered to have a limited impact on the prediction of early outcome following LT in other series (38).

3.3. Italian Score for Organ allocation (ISO) system

The Italian Board of Experts in the Field of Liver Transplantation has developed the ISO system, incorporating a priority criterion for MELD exception conditions (*39*). In our previous monocentric case study (*40*), there was clearly a significant reduction in deaths while waiting for a liver, and an increase in the percentage of LT recipients with the application of the ISO score, though this would have to be validated prospectively to confirm its superiority compared to the MELD score.

3.4. Pre-allocation Survival Out-comes Following liver Transplant (P-SOFT) score and SOFT score

Another ambitious scoring system that predicts recipient survival after LT was proposed by Rana *et al*. (*41*): they identified 4 donors, 13 recipients, and 1 operative variable as significant predictors of 3-month mortality following LT. Consequently, two complementary scoring systems were designed: the P-SOFT score and the SOFT score, which are the result of adding P-SOFT points to points awarded from donor criteria, 1 recipient condition (portal bleed 48 hours pre-transplant), and two logistical factors (cold ischemia time [CIT] and national allocation) at the time of graft allocation. It seems that the SOFT and P-SOFT scores are adequate in predicting 90-day mortality. However, the inclusion of multiple variables, some of which are partially subjective and only semi-quantitative (*e.g.*, encephalopathy, ascites) and a complex underlying statistical model, limits its clinical applicability in pre-transplant decision-making (34,38).

3.5. Donor age × recipient Modified for End-stage Liver Disease [MELD] score (D-MELD score)

In 2009, Halldorson *et al*. (*42*) proposed a simple score, D-MELD, combining the sickest-first principle (lab-MELD) and DRI (donor age). The product of these continuous variables produces an increased risk of mortality and complications, calculated as length of hospitalization. A D-MELD cut-off score of 1600 defines a subset of D-R matches with worse outcomes. The positive aspects of this system are simplicity, objectivity, and transparency, but the prognostic ability of the D-MELD is lacking in LT centers using a more complex D-R matching policy (*9*).

The difficulty in identifying an effective score is due to the myriad of variables to be considered in the match between donor and recipient in each transplant.

4. Artificial intelligence (AI)

The ideal D-R matching system remains a chimera. Unfortunately, to date, the scores available are not statistically robust enough. Arguably, the human mind may not be precise enough to put so many interacting variables in order.

In this context, new technologies that exploit AI have been developing recently.

AI is a branch of computational science that studies computational models capable of performing activities similar to human ones based on two characteristics: behavior and reasoning. Machine learning is defined as a branch of AI that focuses on using data and algorithms to mimic how humans learn, and gradually improve the accuracy of the algorithms (*43*).

Today, AI is revolutionizing the field of hepatology and liver surgery, and its application is becoming frequent in the clinical setting (*44*).

In the D-R match, different variables (donor, recipient, and logistics) are combined to obtain two possible outcomes: graft survival or graft loss at different endpoints (3 and 12 months are the most commonly used). However, no current allocation system is capable of achieving an ideal match. This means that these systems are unable to identify the candidate on the waiting list with the highest probability of death, and identify, among all available grafts, the one with the highest probability of post-transplant success for this candidate (*43*).

How does AI fit into the complex match between donor and recipient?

Clinical decisions have both an objective and a subjective component (*45*): scientific data, memory, and previous experiences serve as the basis of mature clinical reasoning, while other considerations, such as intuition or emotions, constitute the subjective component.

Therefore, clinical decisions in D-R matching have an inherent emotional bias; furthermore, a single D-R match may include about 100 parameters between donor and recipient characteristics and logistics to take into consideration.

The principal AI model used in D-R matching is artificial neural networks (ANN).

Deep learning classifiers use several previous experiences based on objective data (database) to be able to make the best decision for which they have been programmed. The subjective sphere of the decision is removed, and large amounts of data are managed in a short time, which is why AI and, in particular, deep learning classifiers represent an interesting alternative to traditional scores today (*46*).

Briceño *et al*. (*47*) were the first to apply a neural network combined with a system of rules to create a donor-recipient allocation model (M.A.D.R.E model). This multicenter study included a total of 1,003 liver transplants performed between 2007 and 2008, using 64 donor and recipient variables. The probability of graft failure at 3 months was the endpoint variable. The authors demonstrated the superiority of ANNs in donor allocation over biostatistics-based prioritization scores (MELD, D-MELD, SOFT, P-SOFT, DRI, and BAR).

A second study was performed with a dataset of 858 D-R pairs from liver transplants at King's College Hospital, in London. The authors found that the model obtained with this database achieved excellent results at 3 months and 12 months, and when compared with other scores such as MELD and BAR, had 15% more favorable results (*48*).

Indeed, in clinical scenarios, neural networks are very useful in processing complex patterns because they can generate near-perfect predictions by analyzing multiple data rapidly, which is crucial in the allocation process (*49*).

The implementation of AI in the field of liver diseases has grown exponentially, but the number of clinical studies addressing D–R matching is small. Most of the studies mentioned are observational, and very few cases of clinical validation of the model are available (*48*). We are also starting to have studies that do not see the superiority of these complex deep learning systems when applied to larger databases, such as that of the United Network for Organ Sharing (UNOS) (Organ Procurement and Transplantation Network (OPTN). United Network for Organ Sharing (UNOS); 2020. Available from: *https://www.unos.org/*.) (*50*)

Therefore, they are not useful with large databases due to the extreme number of decision trees they would generate, making them impractical.

5. Conclusions

The match between donor and recipient in the delicate process of allocating grafts is a highly debated topic in the field of liver transplantation. The objective of the scientific community is to find a system that facilitates the match process in terms of speed, costs, and global outcomes.

In clinical practice, we do not yet have scores that are robust and effective in large databases.

The progress made in the application of deep learning to the field of liver transplantation bodes well for a future in which marginal grafts will increase, and the maintenance of adequate outcomes will increasingly depend on our ability to guarantee an adequate match between the donor and the recipient.

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**Address correspondence to:*
Salvatore Gruttadauria, IRCCS-ISMETT, University of Pittsburgh Medical Center (UPMC), 90127 Palermo, Italy.
E-mail: sgruttadauria@ismett.edu

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