Transplant International

Transplant International ISSN 0934-0874

CONGRESS PAPER

http://www.D-MELD.com, the Italian survival calculator to optimize donor to recipient matching and to identify the unsustainable matches in liver transplantation

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Keywords
D-MELD, ethics, expansion of donor pool, marginal donors, MELD, outcome analyses, selection criteria.

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Conflicts of interest
All the authors of this manuscript have no conflicts of interest to disclose.

Received: 15 September 2011
Revision requested: 2 November 2011
Accepted: 12 December 2011
Published online: 23 January 2012

doi:10.1111/j.1432-2277.2011.01423.x

Summary

Optimization of donor-recipient match is one of the exciting challenges in liver transplantation. Using algorithms obtained by the Italian D-MELD study (5256 liver transplants, 21 Centers, 2002–2009 period), a web-based survival calculator was developed. The calculator is available online at the URL http://www.D-MELD.com. The access is free. Registration and authentication are required. The website was developed using PHP scripting language on HTML platform and it is hosted by the web provider Aruba.it. For a given donor (expressed by donor age) and for three potential recipients (expressed by values of bilirubin, creatinine, INR, and by recipient age, HCV, HBV, portal thrombosis, re-transplant status), the website calculates the patient survival at 90 days, 1 year, 3 years, and allows the identification of possible unsustainable matches (i.e. donor-recipient matches with predicted patient survival less than 50% at 5 years). This innovative approach allows the selection of the best recipient for each referred donor, avoiding the allocation of a high-risk graft to a high-risk recipient. The use of the D-MELD.com website can help transplant surgeons, hepatologists, and transplant coordinators in everyday practice of matching donors and recipients, by selecting the more appropriate recipient among various candidates with different prognostic factors.

Introduction

The World Wide Web represents an excellent tool for the real-time diffusion of knowledge. In medicine, it allows the interaction of all operators involved in the care of patients, making possible the sharing of protocols, data, and results. Besides medical communication, the Web may be particularly effective in transferring information with the purpose of allocating referred organs in organ procurement areas where several transplant programs are active. Nevertheless, the use of Web resources in organ transplantation, and especially in liver transplantation, is still confined to the diffusion of published studies and communication by e-mail. The implementation of allocation algorithms in internet websites may favor their broader use, their extensive testing and, hopefully, their further refinement.

The opportunity to achieve better survival results by means of an optimization of donor-recipient matching has been hypothesized in 2004 [1,2], and recently demonstrated with the introduction of the D-MELD. The D-MELD formula consists of the arithmetical product of donor age and recipient MELD score. It was developed by Halldorson in 2009 by using the North American UNOS-STAR database [3] and refined on the Italian Donor to Recipient Liver Transplant (D2R-ILTx) database with the identification of covariates with significant effect on the prediction of outcome (recipient age, HBV status, HCV status, portal thrombosis, re-transplant, volume of the transplant Center) [4]. The major strength of D-MELD relies on its easy calculation, which can be performed by the use of a basic calculator. However, a more precise representation of different survival scenarios can be better obtained through an electronic worksheet, thanks to which multiple combinations of the covariates lead to a better stratification of prognosis.

The aim of the http://www.D-MELD.com calculator is to offer transplant surgeons, hepatologists, and transplant coordinators a powerful instrument to obtain prognostic forecasts based on the D-MELD plus covariates approach. The web site was implemented to show, each time a donor is referred, individual graphic survival predictions for several alternative potential recipients.

Patients and methods

The data source

The calculator was developed using algorithms obtained from a population of 5256 donor-recipient liver transplant pairs. The database was filled with records of cases performed in Italy from July 1st 2002 to December 31st 2009, merging data prospectively collected by 21 Centers. Median follow-up was 36 months. Pediatric cases, split, living donor and multi-organ transplants were excluded. The characteristics of patients, the modalities of constitution, and audit of the database, the stratification of cases according to biennium and to volume of Centers, as well as the modality of organ allocation and of donor-recipient match, are reported in detail elsewhere [4]. Starting from a set of 25 primary and 20 calculated variables, algorithms of patients and graft survival were identified by logistic regression analysis. There were six determinants of patient survival (namely D-MELD, recipient age, HCV status, HBV status, portal thrombosis, re-transplant), and five determinants of graft survival (D-MELD, recipient age, HCV, HBV, portal thrombosis) (Fig. 1).

The D-MELD was found to be the strongest prognostic index, and maintained its prognostic power at 3 months, 1 year, and 3 years. Two D-MELD models were developed. D-MELD proved predictive as a continuous variable and as a categorical variable after stratification in deciles and regrouping in three classes (class A: D-MELD <338, low risk; class B: D-MELD 338-1628, reference risk; class C: D-MELD>1628, high risk).

The web site

The http://www.D-MELD.com website was developed using PHP scripting language on HTML platform. All the code relevant to the development of the website is written in PHP language and is hosted by the largest Italian web provider Aruba.it (IP address 62.149.188.157). The access to the site is free. Registration and authentication are required (password: 'D-MELD123').

The http://www.D-MELD.com website has an opening page where the mission of the Donor to Recipient Liver Transplant (D2R-LTx) study group is declared and the links to 10 subpages are featured (Fig. 2). In the first subpage, the aims are illustrated and the list of members and their Institutions are reported. Links to the American and to the Italian D-MELD papers can also be found [3,4]. The following subpages illustrate the main match modalities currently used in the clinical practice of liver allocation, the D-MELD formula, the Italian study population from which the coefficients were obtained. The two D-MELD models (i.e. continuous and categorical) and the graphic representation of the coefficients found in the D-MELD study are also illustrated. The definition of the unsustainable match (i.e. donor-recipient match with predicted patient survival less than 50% at 5 years) and the graphic representation of patient survival according to the unsustainable match cutoff in HCV patients are illustrated in a dedicated subpage. The internal link to the prognostic calculator is then provided. A summary subpage concludes the web site.

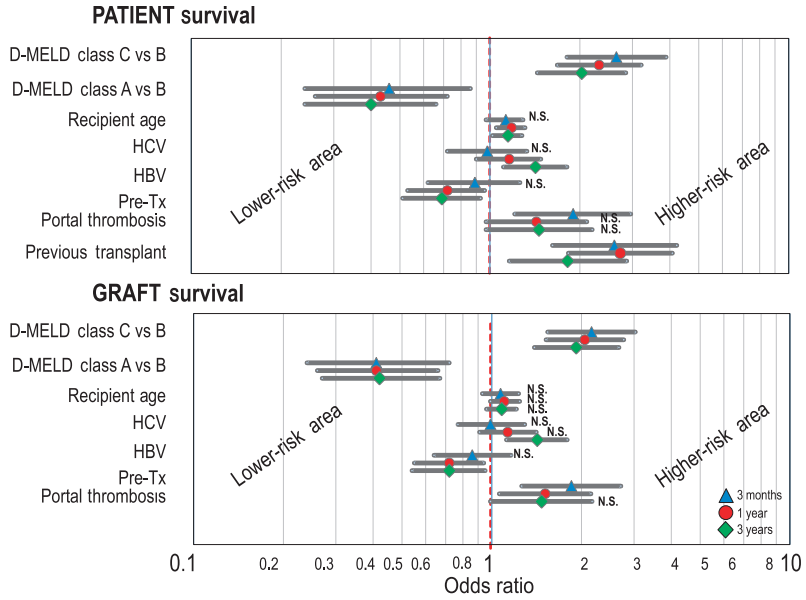

Figure 1 Odds Ratios and 95% confidence intervals of patient and graft survival determinants at logistic regression analysis. N.S. denotes absence of significance.

The D-MELD calculator

The D-MELD web calculator was developed using a previous in-house application built by means of EXCEL® worksheet (ver. 2007). The first template asks for the essential data which should be entered to allow a basic calculation of the risk according to D-MELD (donor age in years, recipient bilirubin in mg/dl, recipient creatinine in mg/dl, recipient INR). The web site was designed to allow the calculation of prognosis for three different potential recipients using the same given donor. On a scatter diagram, the software shows the coordinates (donor age and recipient MELD) of the three potential matches keeping the reference study population on the background, where the stratification of the risk according to deciles is shown (from green, indicating the lowest risk, to red, indicating the highest risk) (Fig. 3). After range control, the software calculates the MELD and the D-MELD values using the following standard formulas. MELD values were capped at 40 according to Kamath [5].

$$\begin{aligned}\text{MELD} = (&0.957 * \ln_{(\text{serum creatinine})} + \\ &+ 0.378 * \ln_{(\text{serum bilirubin})} + \\ &+ 1.120 * \ln_{(\text{INR})}) * 10\end{aligned} \quad [5]$$

$$\text{D-MELD} = \text{donor age (years)} * \text{MELD} \quad [3]$$

The patient survivals at 90 days, 1 year, 3 years are calculated including in standard survival formulas the coefficients obtained by logistic regression analysis at 90 days, 1 year, 3 years as follows:

$$\text{Patient Survival (PS)} = 1 - \frac{e^{[(K+\Sigma(\beta*\text{var})]}}{1 + e^{[(K+\Sigma(\beta*\text{var})]}}$$

$$\begin{aligned}&\text{90 days PS}, [(\text{K} + \Sigma(\beta * \text{var})] = \\ &= [-3.41 - 0.79(\text{if D-MELD} < 338) + \\ &+ 0.98(\text{if D-MELD} > 1628) + 0.01(R\,\text{Age}) + \\ &+ 0.02(\text{if HCV pos}) - 0.12(\text{if HBV pos}) + \\ &+ 0.64(\text{if PT}) + 0.96(\text{if reTx})]\end{aligned}$$

The donor to recipient italian liver transplant (D2R-ILTx) study group is a multidisciplinary group of physicians from 22 liver transplant centers, committed to analyze the factors (donor factors and recipient factors) predictive of survival after liver transplantation. The group includes hepatologists, transplant surgeons, anaesthesiologists, and transplant coordinators experienced in management of end-stage liver disease patients candidates to transplantation, in organ allocation and in post-transplant care.

- Background: match or mis-match & D-MELD
- Background: D-MELD
- Background: unsustainable transplant & unsustainable match
- Study population
- D-MELD stratification in deciles and classes
- Results logistic regressions
- Results cox regressions
- D-MELD calculator
- D-MELD prediction of unsustainable match in HCV recipients

Figure 2 The opening page of the http://www.D-MELD.com. website.

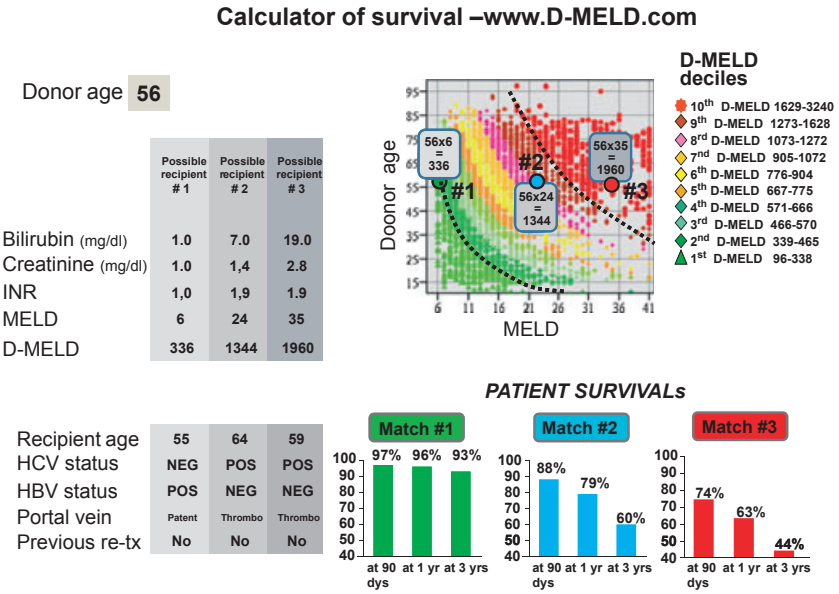

Figure 3 The http://www.D-MELD.com survival calculator. **Step 1:** After keyboard input of donor age and recipient bilirubin, recipient creatinine, recipient INR of three potential liver transplant candidates, the calculator reckons the values of MELD and D-MELD for the three donor-recipient matches. The positions of the three donor-recipient matches appear on a scatter diagram where all the matches of the reference study population are shown in the background, stratified according to their risk (green, lowest risk; red, highest risk). **Step 2:** After keyboard input of recipient age (years), HCV status (positive/negative), HBV status (positive/negative), portal vein status (patent/thrombosis), previous transplant (yes/no), the calculator shows the percentages of patient survival at 3 months, 1 year, 3 years for the three donor-recipient matches.

$$\begin{aligned}
&1\text{yr PS}, [(K + \Sigma(\beta * \text{var})] = \\
&\quad = [-2.96 - 0.84(\text{if D-MELD} < 338) + \\
&\qquad + 0.84(\text{if D-MELD} > 1628) + 0.02(R\ \text{Age}) + \\
&\qquad + 0.14(\text{if HCV pos}) - 0.34(\text{if HBV pos}) + \\
&\qquad + 0.36(\text{if PT}) + 1.00(\text{if reTx})]
\end{aligned}$$

$$\begin{aligned}
&3\text{yrs PS}, [(K + \Sigma(\beta * \text{var})] = \\
&\quad = [-2.10 - 0.92(\text{if D-MELD} < 338) + \\
&\qquad + 0.71(\text{if D-MELD} > 1628) + 0.02(R\ \text{Age}) + \\
&\qquad + 0.35(\text{if HCV pos}) - 0.37(\text{if HBV pos}) + \\
&\qquad + 0.38(\text{if PT}) + 0.60(\text{if reTx})]
\end{aligned}$$

where K is constant, var is variable, PS is Patient Survival; R Age is recipient age; HCV pos is HCV positive patient; HBV pos is HBV positive patient; PT is patient with portal thrombosis; reTx is patient at the second transplant.

The calculator was written in PHP and HTML, using JpGraph, Object-Oriented Graph creating library for PHP, to display the graphs. Specifically adapted applications for Symbian, iOS and Android-based smartphones are under development.

Discussion

Liver transplantation is not a finished product [6], and probably will never be. However, over the last 38 years many changes have taken place. Today, organ shortage is more critical than before, and efforts to sustain the demand urge transplant surgeons to shift forward the limit that characterizes 'extended criteria' grafts. The prevalence of elderly donors is increasing all over the world, and particularly in Italy, where the use of grafts from donors aged 80 and over represents a routine [7,8]. Much evidence has been gathered in support of the opinion that poor organ quality represents a risk factor, and that donor and recipient risk factors can be balanced by using 'ad hoc' developed formulas [4,9,10]. However, the implementation of complex prognostic algorithms requires the access to computer facilities, which is not always easy in everyday (and every night) clinical practice.

The success of the World Wide Web relies on the easy circulation of information. The system is now robust, secure, and potentially omnipresent. It is also fully accessible on several platforms, as well as on smartphones, and it does not need specific training since instructions are usually self-explanatory. However, the use of the Web in medicine is less common than in other fields, such as business (e.g. trading online, bank communication, web market) or other branches of science (physics, mathematics, engineering). Nevertheless, several calculators have been developed concerning nutrition, cardiovascular diseases and cancer [11–14]. They are currently used by physicians and often accessed by patients too. Among

medical operators, those who visit the web calculators for curiosity or interest of knowledge should be kept apart from those who work with them in everyday practice. Although the latter are the only final users, we should not disregard the other two categories. This is one reason why prognostic calculators should adopt a straightforward lexicon potentially accessible to everybody, including non-medical web surfers.

With regard to organ transplantation, and in particular to liver transplantation, the number of websites remains limited [15,16]. The reasons for such delay can be identified in the small number of cases compared to other diseases (e.g. diabetes, hypertension, cancer), and in the higher complexity of the procedure, which remains still circumscribed to a limited number of experts. In addition, support from institutions and from sponsors is lacking, owing to the smaller number of patients compared to other 'social' diseases. Nevertheless, several calculators dealing with liver transplantation can be accessed on the Web. A large part of them has been developed for calculating the MELD score [16] and very few offer a prediction of prognosis according to the characteristics of the recipients [17,18]. Similar calculators are available for kidney [19] and lung transplant patients [20]. Other applications offer the calculation of the risk of death according to donor characteristics [21] or stage of neoplasm in the recipients [22]. More complex calculators have been developed for research purposes, but they are not available on the web [23,24].

Today, to the best of our knowledge, only one prognosis calculator able to quantify the risk of death of the recipient according to both donor and recipient parameters has been implemented on the Web [25]. The calculator was developed in 2005 and it can be downloaded from the website of the European Liver Transplant Registry (ELTR). It requires installation on the user's computer to perform forecasts. It is based on five variables (namely donor age, donor-recipient blood group match, recipient age, UNOS status, Center size) and it was developed following a cornerstone study on liver transplantation conducted on European Liver Transplant data relevant to 1988–2003 [9]. It allows the calculation of the probability of death only at 3 and 12 months, without providing any graphical representation. In addition, survival was not correlated to MELD, as MELD had not been introduced yet in the clinical practice when data were entered. As a matter of fact, reports relying on its use are lacking.

The D-MELD is a formula able to balance donor and recipient risk factors with easy calculation. Its application works particularly well in the identification of high-risk and low-risk matches, for which the implications concerning organ allocation are stronger [4]. The http://www.D-MELD.com prognostic calculator adds significant value to the D-MELD formula. First of all, it contributes to the dissemination of the practice of balancing donor and recipient risk factors by using the D-MELD algorithm in liver transplantation. In addition, it offers a more precise tool for individualizing the prognosis according to the recognized risk factors and to their interactions. Better than D-MELD alone, the use of D-MELD covariates (recipient age, HBV status, HCV status, portal thrombosis, re-transplant, center effect) is effective in reducing the risk of an elderly donor graft previously considered hazardous, by matching it to a recipient with low-risk features. Finally, the strongest value of the D-MELD calculator relies on the direct graphical representation of survival according to different match possibilities. Although the website has not been jet routinely adopted for the graft allocation in the all Italian liver transplant Centers, it has been extensively tested in several liver transplant programs and developed according to requests from physicians and non-medical operators specifically involved in liver allocation.

An additional function of the http://www.D-MELD.com calculator allows the identification of donor-recipient combinations with 5-year patient survival <50%. When the recipient is HCV-positive and the D-MELD exceeds the 1750 cutoff, the calculator gives warning with a flashing alarm signal. In this case, it suggests a change in the allocation from an HCV to a non-HCV recipient, following the principle that the allocation of an organ with a potentially high risk should be shifted from a patient with high risk to another patient with a lower risk, to balance the overall risk.

This innovative approach in organ allocation introduces the concept of the 'unsustainable match'. We consider unsustainable a donor-recipient match when the calculated patient survival is less than 50% at 5 years. The maximization of organ procurement in the elderly age, and the attention to avoid organ wasting, are two complementary strategies that can be adopted to address the disparity between patient's needs and resource availability. Given the same high D-MELD value, an organ from an elderly donor is likely to fail in an HCV recipient, but not in an HBV one. This approach follows the previous definition of the minimal outcome requirements in liver transplantation, first enunciated by Neuberger[26] and refined later on by other authors [27,28]. It refers to a utilitarian approach, aimed to optimize the use of organs and logistic resources. We are well aware that this point of view is finalized to maximize the use of resources and it is not in line with the principle which postulates to transplant the sickest patient on the list independently from the quality of the referred donor (sickest first principle)[29,30]. However, the poor prognosis predicted in the high-risk matches, particularly when recipient etiology is HCV cir-

rhosis, should suggest us to skip the sickest recipients to transplant the second or even the third recipient in a rank based on MELD score. This approach was adopted to guarantee an efficacious use of high-risk grafts. We believe indeed, that in the present era of 'extended criteria' grafts the issue of maximizing resources and to use them in a sustainable way deserves paramount attention.

The http://www.D-MELD.com calculator suffers from some limitations. Since pediatric cases, splits and multi-organ transplants are excluded from the study population, the algorithms are not applicable to such cases. For statistical reasons, they are also not applicable to other very selected conditions not specifically investigated for their low prevalence (i.e. AB blood group donor, low weight recipient, HBV-HCV co-infection). [31] Also in these cases we do not have enough statistical power to calculate the risk. Lastly, the calculator does not consider the number of patients on the waiting list, nor the time they spent during the wait. Those data are crucial for the quantification of the survival benefit (SB), particularly in patients with liver neoplasm, among whom a variable percentage of drop-out from the list exists [32,33]. After stratification for MELD, the SB model was developed to quantify the survival gain between undergoing transplantation and staying on medical care. Unfortunately, national Italian data on survival benefit are lacking. Nevertheless, reports on SB from single institutions lead us to hypothesize that the prognosis calculator can be ameliorated considering the SB and the risk of death related to the drop-out during the waiting list period [34,35].

In conclusion, the development of the first MELD-based donor-recipient survival calculator represents a simple instrument to guide donor allocation in liver transplantation. Its implementation on the World Wide Web platform offers the transplant community the demonstration that prognosis depends on the donor-recipient match. It facilitates the work of hepatologists, transplant surgeons and transplant coordinators in everyday practice of matching donor and recipient factors when choosing the recipient. Finally, it gives the opportunity to researchers from other countries to perform an external validation.

The questions that a few years ago were put forward as a gateway to future development 'Are we ready to match donor and recipient in liver transplantation? [36] And, how can we do this? [37]' are now starting to receive a meaningful answer. Algorithms, instruments, and technology are there. It is up to us to utilize and improve them.

Contributors

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Authorship

AWA: designed the study, performed the research study, developed the software, wrote the paper and approved the final version. SA: tested the software, revised the paper and approved the final version. UC: designed the study, wrote the paper and approved the final version. MCL: tested the software, revised the paper and approved the final version. RR: tested the software, revised the paper and approved the final version. UB: collected the data, revised the paper and approved the final version. FZ: collected the data, revised the paper and approved the final version. DN: collected the data, tested the software, revised the paper and approved the final version. MD: collected the data, revised the paper and approved the final version. AP: collected the data, tested the software, revised the paper and approved the final version. GME: revised the paper and approved the final version. MR: collected the data, revised the paper and approved the final version. NM: collected the data, revised the paper and approved the final version. GV: collected the data, tested the software, revised the paper and approved the final version. CdW: tested the software, revised the paper and approved the final version. SF: tested the software, revised the paper and approved the final version. PB: tested the software, revised the paper and approved the final version. AC: performed the research study, developed the software, wrote the paper and approved the final version.

Funding

Lazio Transplant Agency (LTA), Rome, Italy, and Liver Transplant Center, Catholic University, Rome, Italy.

Acknowledgements

The LTA had no role in study design, data collection, software development or writing the article. The corresponding author had final responsibility for the decision to submit for publication. The authors would like to thank Mr. Simone Mieli, a biomedical webmaster, for the development of the http://www.D-MELD.com website.

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