Retransplantation for Recurrent Hepatitis C in the MELD Era: Maximizing Utility

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Key Points

1. Retransplantation (re-LT) for hepatitis C virus (HCV) recurrence is controversial. Although re-LT accounts for 10% of all liver transplants (LTs), the number of patients requiring re-LT is expected to grow as primary LT recipients survive long enough to develop graft failure from recurrent disease.

2. Utility, as applied to the medical ethics of transplantation, refers to allocating organs to those individuals who will make the best use of them. The utility function (U) of liver transplantation is represented by the product of outcome (O = 1-year survival with LT) times emergency (E = 3-month mortality without LT), i.e., U = O × E.

3. For primary LT, maximal U is achieved by allocating organs at the highest model for end-stage liver disease (MELD) score (i.e., "sickest first"). No significant differences exist between HCV and non-HCV diagnoses.

4. For re-LT, maximal utility for HCV and non-HCV diagnoses are achieved at MELD scores of 21 and 24, respectively. Utility starts to decline at MELD scores above 28.

5. The current allocation system (MELD) fails to maximize utility with regard to re-LT. (*Liver Transpl 2004;10: S59–S64.*)

Hepatitis C virus (HCV)-related liver disease is currently the leading indication for liver transplantation (LT) throughout the world. Infection of the allograft after LT is universal. Fibrosis develops at a faster rate in the allograft than in the native liver and allograft cirrhosis may develop in 20% to 40% at 5 years, compared to 3% to 20% at 20 years in non-LT patients.[1–3] The development of allograft cirrhosis is associated with a 40% decompensation rate within 1 year compared with 3 to 5% in non-LT patients with cirrhosis.[2,4] Half of these patients do not survive an additional year.[4] Treatment of recurrent HCV after LT has proven difficult due to toxicity and limited effect on outcome.[5,6] For many patients with allograft failure, the only chance of long-term survival is derived from retransplantation (re-LT).

Re-LT for HCV accounts for about 40% of re-LTs performed annually in the United States.[7,8] Re-LT for HCV might be expected to increase in the future, as more patients are transplanted for HCV and develop allograft failure from HCV recurrence. However, re-LT in HCV-positive patients has been associated with poorer outcome compared to non-HCV diagnoses.[7,9] Regardless of the indication, re-LT is controversial due to issues of poor outcome, cost, and resource utilization.[10] Numerous factors have been identified as influencing survival following re-LT (Table 1). Despite these data, a recent survey revealed that a minority of transplant centers feel that a model for end-stage liver disease (MELD) score over 30 should be an exclusion criterion for patients being considered for re-LT for recurrent HCV.[23]

The aim of our study was to develop a model to determine what MELD score is associated with the greatest utility in re-LT for recurrent HCV. We hypothesized that the MELD score associated with maximal utility for re-LT due to recurrent HCV would be lower than the MELD score associated with maximal utility for primary LT due to HCV cirrhosis.

Materials and Methods

Utility as applied to the medical ethics of transplantation refers to allocating organs to those individuals who will make the best use of them, in accord with the "Final Rule" set forth by the Organ Procurement and Transplantation Network in 1998.[24] Issues of utility are balanced by concerns for justice that, in this context, refer to allocation of organs to those patients in the most immediate need. An example would be whether a potential recipient facing imminent death without a transplant (i.e., emergency [E]), but with a poorer chance of long-term survival (i.e., outcome [O]) should be given a transplant in preference to another individual with less immediate risk of death but a better long-term prognosis.

Abbreviations: MELD, model for end-stage liver disease; re-LT, retransplantation; HCV, hepatitis C virus; LT, liver transplantation.

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Table 1. Studies Evaluating Prognostic Criteria With Retransplantation

Reference	No. Patients	Time Period	Patient Type	Population	Poor Prognostic Factors	Comments
Doyle et al., 1996[11]	418	1987–1993	All diagnoses	Univ. of Pittsburgh	Donor and recipient age, mechanical ventilation prior to re-LT, creatinine, and bilirubin levels	
Wong et al., 1997[12]	70	1987–1994	All diagnoses	King's College	Recipient age, UNOS status, inpatient status, creatinine, and bilirubin levels	1-year patient survival 54%
Markmann et al., 1997[13]	299	1984–1996	All diagnoses	UCLA	Recipient age, interval to re-LT, UNOS status	1- and 5-year survival 62% and 47%
Rosen and Martin, 1998[7]	207	1990–1996	HCV; PNF and HCC excluded	UNOS	HCV-positive patient undergoing re-LT for non-PNF: creat >2.0 mg/dL and bili >10 mg/dL	HCV was risk factor for mortality
Markmann et al., 1999[14]	150	1992–1996	All diagnoses	UCLA	>18 years, Mechanical ventilation, cold ischemia >12 hours creat > 1.6 mg/dL and bili >13 mg/dL	17% pediatric patients: 1-year survival 27% if 4–5 factors
Rosen et al., 1999[15]	1,356	1990–1996	All diagnoses except HCC	UNOS	Recipient age, UNOS status, non-PNF diagnosis, creatinine, and bilirubin levels	HCV and donor age significant factors by univariate analysis
Kim et al., 1999[16]	447	Late80s–late 90s	PBC and PSC	Multicenter	Time to re-LT (>30 days)	
Facciuto et al., 2000[17]	48	1987–1997	All diagnoses (44% HCV)	Mt. Sinai	Recipient age >50, creat >2 mg/dL, use of intraoperative platelets	1- and 5-year survival 60% and 42%; excluded pts with re-LT <6 months
Azoulay et al., 2002[18]	139	1986–1999	All diagnoses, only 1st re-LT	Villejuif, France	Recipient age, urgency of re-LT, creatinine level, non-PNF diagnosis	1- and 5-year survival 71% and 58%
Watt et al., 2003[8]	2,129	1996–2002	All diagnoses	UNOS	MELD >25—<60% 5-year survival; MELD >30—20–40% 5-year survival	Limited to evaluate MELD in re-LT 1- and 5-year survival 67% and 52%; excluded pts with re-LT < 30 days
Rosen et al., 2003[19]	281	1986–1999	All diagnoses	Multicenter, International	Recipient age, 15–60 days post-LT, creatinine, and bilirubin levels	Validation of 1999 UNOS model; MELD predictive of survival; excluded pts with re-LT <15 days
Roayalie et al., 2003[20]	116	1989–2001	HCV only	Mt. Sinai	Donor age, prothrombin time	Excluded pts with re-LT <90 days
Ghobrial et al., 2003[21]	3,172	1990–2000	All diagnoses	UNOS and UCLA	Donor and recipient age, ischemic time, PT, creatinine, and bilirubin levels	
Yoo et al., 2003[9]	4,189	1987–2001	All diagnoses, PNF included	UNOS	PNF, HCV infection, donor and recipient age, African-American race, UNOS status, creatinine	Analyzed re-LT for PNF and all other diagnoses separately
Yao et al., 2004[22]	40	1988–2002	All diagnoses, (25% HCV)	UCSF	CTP ≥10, hepatic encephalopathy, ICU status, HCV diagnosis, creatinine level, MELD >25	1- and 5-year survival 69% and 62%; excluded pts with re-LT >90 days

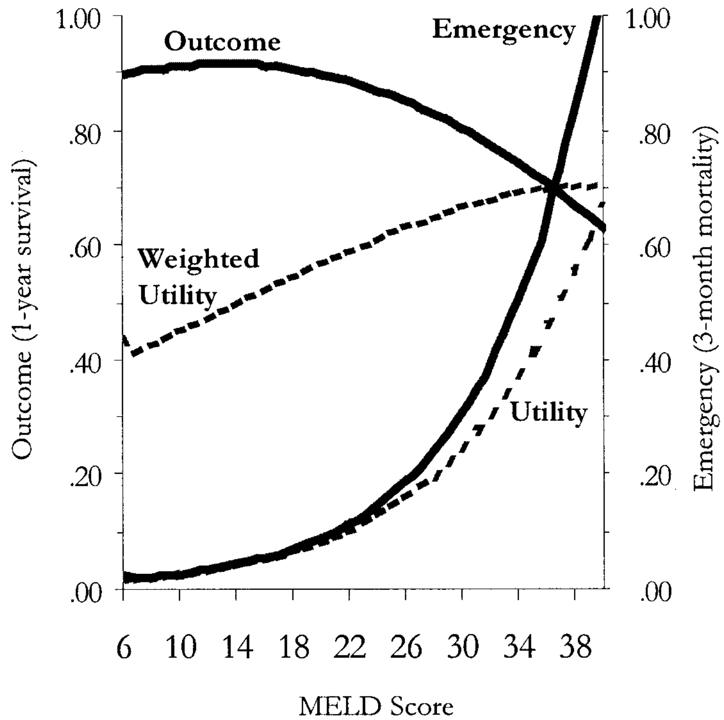

Figure 1. Outcome, emergency, and utility curves for primary LT. The outcome-curve was generated using data by Saab et al.[28] The emergency-curve was generated from data published by Kamath et al.[29] In case of equally weighted outcome and emergency, the maximal value of utility occurs when the MELD score is 40. Weighted utility is associated with a maximal value at a MELD score of 38.

The utility function (U) can be modeled as the product of outcome times emergency:

$$\mathbf{U = O \times E}$$

where U = utility; O = outcome; and E = emergency.

In the equation above, outcome and emergency contribute equally to utility. Emphasis or weight can be added to outcome and emergency by the use of exponents.

$$\mathbf{U_w = O^a \times E^b}$$

where U_w = weighted utility, and a + b = 1.

The two positive constants a and b characterize the relative contribution of each preference to the overall utility. In economics, this relationship is known as the Cobb-Douglas function.[25,26] If utility was weighted toward outcome in such a way that outcome contributed 4 times more to overall utility than emergency, then the values of a and b would be 0.8 and 0.2, respectively.

To address our aims, the following data were needed: 1) 1-year survival (outcome) after primary transplantation[27,28] and re-LT[8,19] in terms of MELD score, and 2) 3-month mortality (emergency) *without* liver transplantation for end-stage liver disease[29] and for allograft failure in terms of MELD score. For the present analysis, 3-month mortality was defined as: 1 – 3-month survival (without LT). No data for allograft failure are available in terms of MELD score. Berenguer et al.[4] has described rates of decompensation and associated mortality as being greater in allograft cirrhosis than in non-LT cirrhotics.[2] Based on these limited data, we assumed that the 3-month mortality for a given MELD would be worse in patients with allograft cirrhosis as compared to patients awaiting primary LT. Therefore, we shifted the emergency-curve by 10 MELD points to the left so that a patient with allograft cirrhosis and a MELD score of 15 points, for instance, would have a survival comparable to a primary transplant recipient with a MELD score of 25 points.

Results

Optimal MELD for Primary Liver Transplantation

For primary LT with equally weighted outcome and emergency (U = O × E), maximal utility occurs at a MELD score of 40 (Fig. 1). Weighting outcome 4 times more importantly than emergency ($U_w = O^{.8} \times E^{.2}$) alters the shape of the utility-curve but does not change the MELD score associated with maximal utility (Fig. 1). Maximal values of weighted utility for HCV and non-HCV diagnoses undergoing primary LT are similar, occurring at MELD scores of 38 and 39, respectively (data not shown).

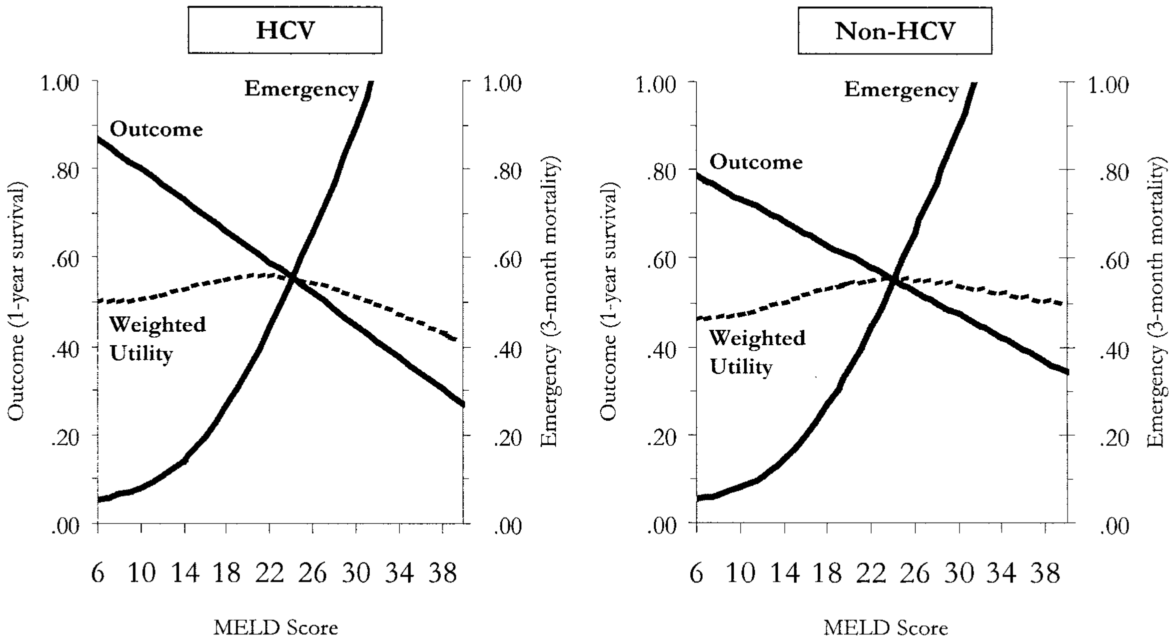

Figure 2. Outcome, emergency, and weighted utility curves for re-LT among patients with HCV (left panel) and without HCV (right panel). The outcome-curves were generated from European data.[19] Compared with primary transplantation, the emergency-curve of re-LT is shifted to the left by 10 MELD points to account for the poorer outcome associated with allograft cirrhosis. The maximal value of weighted utility is achieved at a MELD score of 21 for HCV (left) and at a MELD score of 24 for non-HCV (right).

Caution should be used in interpreting this finding. It does not necessarily imply that primary LT should only be performed in patients with the highest MELD scores in the upper 30s. Instead, it illustrates that the utility-curve is influenced primarily by emergency rather than outcome, as increasing the weight of outcome fails to appreciably change the maximal utility value. This finding supports the current system of allocating organs to the sickest patients, that is, those with the highest MELD scores.

Optimal MELD for Re-LT for HCV Allograft Failure

Using the same type of analysis as above, but with new outcome data for re-LT, maximal utility for HCV and non-HCV diagnoses occur at MELD scores of 21 and 24, respectively (Fig. 2). Both weighted utility curves rise smoothly to a peak between MELD scores of 18 and 28, suggesting that high utility in re-LT is achieved until the MELD score reaches 28. As mentioned above, emergency data (3-month mortality *without* transplant) for re-LT are available neither from published nor unpublished series. To account for higher mortality awaiting re-LT, we shifted the emergency-curve to the left such that 3-month mortality is similar for re-LT but at a MELD score of 10 points less. Despite shifting the emergency-curve to the left, however, the maximal weighted utility remained unchanged (data not shown). This finding suggests that, unlike primary transplantation where emergency drives the utility-curve, in re-LT the utility-curve is driven primarily by outcome.

We used our own outcome data for re-LT[19] because they were felt to be more accurate than the registry data by Watt et al.[8] If the registry data for HCV diagnoses are utilized instead of our own data, a rather flat utility-curve emerges (data not shown). This may indicate that the MELD score is not a very important factor in re-LT for HCV and that other influential factors exist. This contention is supported by a recent report of Mount Sinai Hospital's experience with re-LT for HCV recurrence.[20] Using the registry data for non-HCV diagnoses, the maximal utility lies between MELD scores 21 and 30 (data not shown). This closely overlaps the MELD range of 18 and 28 from our own hand-collected data, suggesting that the optimal MELD score for re-LT for non-HCV diagnoses may be located between 21 and 28.

Discussion

Using the product of outcome (1-year survival *with* transplantation) times emergency (3-month mortality *without* transplant), we have developed a simple means to determine the MELD score associated with greatest utility for both primary LT and re-LT. We have chosen to weight outcome as being more relevant than emergency because in LT, preference is usually granted to patients with a better long-term prognosis than patients facing imminent death without transplantation. We feel that such weighting better reflects the reality of clinical decision-making in LT and re-LT. On first sight, the assumptions built into our model may appear too restrictive, and weighting outcome 4 times more importantly than emergency may appear too utilitarian. In reality the opposite holds true, as the influence of emergency tends to void the influence of outcome altogether and overwhelm the results of the utility analysis in its favor. With rising MELD scores, a relatively smooth fall in outcome occurs concomitantly with a steep rise in emergency (Fig. 1). To achieve a better balance between the contributions of both factors, therefore, outcome has to be assigned more weight than emergency. In the sensitivity analysis, other relative weights, such as outcome / emergency = 1 / 1, 2 / 1, 3 / 1, . . . , 9 / 1, bias the utility too much in favor of emergency or outcome (if the weighting exceeds 4 / 1). Although the main objective of our analysis was to determine the MELD score associated with maximal utility for re-LT after HCV recurrence, it was also important to validate our analytical model in primary LT. Our model for primary LT reliably predicted the current allocation system of "sickest first," as it assigned maximal utility to the highest MELD scores.

Our model was partly limited by the lack of complete datasets for both outcome and emergency in terms of MELD scores. For primary LT, the available outcome data were similar in 2 published studies[27,28] analyzing survival in terms of pretransplant MELD scores. Emergency data for primary LT[29] are already well established and form the basis for the MELD scoring system currently being used in organ allocation. The outcome data for re-LT in terms of MELD did not appear to be markedly different between these 2 sources.[8,19] For re-LT emergency, no published data were available. Our assumptions were, therefore, based on the known natural history of cirrhosis after LT. There is no published evidence that the MELD curve should be shifted to the left for re-LT as we have assumed here. Nonetheless, this maneuver proved relatively unimportant for determining the final MELD score, as the ideal MELD score for re-LT changed little by varying the actual shift between 0 and 10 MELD points. This relative insensitivity of utility to the exact shape of the emergency-curve occurs because, different from primary LT in which emergency "drives" the utility-curve, in re-LT outcome "drives" utility.

We have shown that, unlike primary LT, in order to achieve maximal utility for re-LT, patients need to be transplanted at lower MELD scores. Our model suggests that maximal utility is achieved at MELD scores below 28. This is supported by studies of prognostic criteria in re-LT that have found MELD scores over 25 to be associated with a poor outcome.[8,22] The absolute MELD score associated with maximal utility in re-LT, however, may be of lesser relevance than the marked differences in MELD scores between primary LT and re-LT. This has important implications in the way patients are selected for re-LT, since the current allocation system favors patients with higher MELD scores. To best allocate scarce organs among patients in need of re-LT, changes to the current system will have to take place. To maximize utility, we will need to offer re-LT at lower MELD scores than in primary LT. Patients awaiting re-LT may need to be given additional priority points as is done currently with hepatocellular carcinoma. Additionally, if we are to offer re-LT to patients with HCV-related graft failure, we need to address what is considered an acceptable survival outcome after re-LT. Whereas more restrictive policy on re-LT will limit access, a more selective approach will undoubtedly result in improved outcomes and better use of a scarce resource.

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References

1. Ganes E. The natural history and outcome of liver transplantation in hepatitis C virus-infected recipients. Liver Transpl 2003; 9:S28–S34.
2. Fattovich G, Giustina G, Degos F, Diodati G, Tremolada F, Nevens F, et al. Effectiveness of interferon alfa on incidence of hepatocellular carcinoma and decompensation in cirrhosis type C. J Hepatol 1997;27:201–205.
3. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 1999;340:1228–1233.
4. Berenguer M, Preito M, Rayon JM, Mora J, Pastor M, Ortiz V, et al. Natural history of clinically compensated HCV-related graft cirrhosis following liver transplantation. Hepatology 2000; 32:852–858.
5. Gopal DV, Rabkin JM, Berk BS, Corless CL, Chou S, Olyaei A, et al. Treatment of progressive hepatitis C recurrence after liver transplantation with combination interferon plus ribavirin. Liver Transpl 2001;7:181–190.

6. Narayanan Menon KV, Poterucha JJ, El-Amin OM, Burgart LJ, Kremers WK, Rosen CB, et al. Treatment of posttransplantation recurrence of hepatitis C with interferon and ribavirin: lessons on tolerability and efficacy. Liver Transpl 2002;8:623–629.
7. Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. Transplantation 1998;66:1612–1616.
8. Watt KDS, Lyden ER, McCashland TM. Poor survival after liver transplantation: is hepatitis C to blame? Liver Transpl 2003;9: 1019–1024.
9. Yoo HY, Maheshwari A, Thuluvath PJ. Retransplantation of liver: primary graft nonfunction and hepatitis C virus are associated with worse outcome. Liver Transpl 2003;9:897–904.
10. Biggins SW, Beldecos A, Rabkin JM, Rosen HR. Retransplantation for hepatic allograft failure: prognostic modeling and ethical considerations. Liver Transpl 2002;8:313–222.
11. Doyle HR, Morelli F, McMichael J, Doria C, Aldrighetti L, Starzl TE, et al. Hepatic Retransplantation—an analysis of risk factors associated with outcome. Transplantation 1996;61: 1499–1505.
12. Wong T, Devlin J, Rolando N, Heaton N, Williams R. Clinical characteristics affecting the outcome of liver retransplantation. Transplantation 1997;64:878–882.
13. Markmann JF, Markowitz JS, Yersiz H, Morrisey M, Farmer DG, Farmer DA, et al. Long-term survival after retransplantation of the liver. Ann Surg 1997;226:408–418.
14. Markmann JF, Gornbein J, Markowitz JS, Levy MF, Klintmalm GB, Yersiz H, et al. A simple model to estimate survival after retransplantation of the liver. Transplantation 1999;67:422–430.
15. Rosen HR, Madden JP, Martin P. A model to predict survival following liver retransplantation. Hepatology 1999;29: 365–370.
16. Kim WR, Wiesner RH, Poterucha JJ, Therneau TM, Malinchoc M, Benson JT, et al. Hepatic retransplantation in cholestatic liver disease: impact of the interval to retransplantation on survival and resource utilization. Hepatology 1999;30:395–400.
17. Facciuto M, Heidt D, Guarrera J, Bodian CA, Miller CM, Emre S, et al. Retransplantation for late liver graft failure: predictors of mortality. Liver Transpl 2000;6:174–179.
18. Azoulay D, Linhares MM, Huguet E, Delvart V, Castaing D, Adam R, et al. Decision for retransplantation of the liver: an experience- and cost-based analysis. Ann Surg 2002;236:713–721.
19. Rosen HR, Prieto M, Casanovas-Taltavull T, Cuervas-Mons V, Guckelberger O, Muiesan P, et al. Validation and refinement of a survival models for liver retransplantation. Hepatology 2003; 38:460–469.
20. Roayaie S, Schiano TD, Thung SN, Emre SH, Fishbein TM, Miller CM, et al. Results of retransplantation for recurrent hepatitis C. Hepatology 2003;38:1428–1436.
21. Ghobrial RM, Saab S, Lassman C, Lu DS, Raman S, Limanond P, et al. Donor and recipient outcomes in right lobe adult living donor liver transplantation. Liver Transpl 2002;8:901–909.
22. Yao FY, Saab S, Bass NM, Hirose R, Ly D, Terrault N, et al. Prediction of survival after liver retransplantation for late graft failure based on preoperative prognostic scores. Hepatology 2004;39:230–238.
23. Burton JR Jr, Rosen HR. Liver retransplantation for HCV recurrence: a national survey of practice patterns in liver transplant programs. Gastroenterology 2004;126(Suppl):211A.
24. Organ Procurement and Transplantation Network. Health Resources and Services Administration, HHS. Final rule. Fed Regist 1999;64:56650–56661.
25. Varian HR. Microeconomic analysis, 3rd ed. New York: WW Norton & Company, 1992:94–115.
26. Chiang AC. Fundamental methods of mathematical economics, 3rd ed. New York: McGraw-Hill Publishing Company, 1984: 400–410.
27. Onaca NN, Levy MF, Sanchez EQ, Chinnokotla S, Fasola CG, Thomas MJ, et al. A correlation between the pretransplantation MELD score and mortality in the first two years after liver transplantation. Liver Transpl 2003;9:117–123.
28. Saab S, Wang V, Ibrahim AB, Durazo F, Han S, Farmer DG, et al. MELD score predicts 1-year patient survival post-orthotopic liver transplantation. Liver Transpl 2003;9:473–476.
29. Kamath PS, Wiesner RH, Malinchoc M, Dremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.