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RAPID COMMUNICATION

Development of a survival evaluation model for liver transplant recipients with hepatocellular carcinoma secondary to hepatitis B

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Abstract

AIM: To develop a model using easily obtainable, objective, verifiable preoperative parameters, to help evaluate post transplant survival probability for hepatocellular carcinoma (HCC) patients with hepatitis B.

METHODS: We retrospectively examined a cohort of 150 consecutive primary cadaveric liver transplants with HCC in our center over 6 years. Thirteen preoperative biochemical parameters and six tumor-related factors were analyzed to identify their correlation with post transplant survival using the Cox proportional-hazards regression model. The predictive power of a new model and the model for end stage liver disease was compared by the receiver operating characteristic curve.

RESULTS: In univariate analysis, the factors significantly associated with post transplant survival were serum concentrations of albumin, total bilirubin, alkaline phosphatase, alpha-fetoprotein, γ-glutamyltransferase, aspartate aminotransferase, sodium, tumor diameter and the number of tumor nodules. Multivariate analysis showed alpha-fetoprotein, serum sodium, alkaline phosphatase and the number of tumor nodules were significantly associated with the post transplant outcome. Based on the four variables, we established a new model with a c-statistic of 0.72 which was significantly greater than 0.50 (P = 0.001), and the c-statistic of MELD was 0.59 (P = 0.146).

CONCLUSION: The new model based on four objective tumor-related parameters has the capacity to evaluate the risk of post transplant mortality for HCC patients with hepatitis B.

Key words: Liver neoplasms; Hepatitis B; Liver transplantation; Survival evaluation; Model for End Stage Liver Disease

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INTRODUCTION

As a high hepatitis risk region, hepatocellular carcinoma (HCC) patients in China account for approximately 55% of HCC over the world, and more than 90% HCC in China are related to hepatitis B and accompanied by cirrhosis[1]. Liver transplantation (LT) has become accepted as an effective therapeutic modality for these patients[2,3], but the discrepancy between the livers available and patients in need of transplantation is outstanding. In 2002, the new MELD-based allocation policy was implemented by the United Network of Organ Sharing (UNOS) as the criteria for liver allocation[4]. Although the model for end stage liver disease (MELD) has been validated to predict disease severity and ranking in LT candidates on the waiting list[5-7], its capacity to predict post-LT outcome remains controversial. Heretofore, the relationship between severity of illness at LT and outcome after LT is still a major area of debate[8], especially for HCC candidates.

MELD was developed based on benign liver diseases and many aspects of malignant tumor were not taken into

account[9], therefore, the proposal to use the MELD system for post transplant evaluation lacks predictive power. Some studies supported that HCC-related parameters should be added into MELD to improve its assessing capacity for the HCC patients[10]. The aim of our study, therefore, is to find some risk factors associated with post transplant outcome of HCC recipients and attempt to develop a new model using some easily obtainable, objective, verifiable preoperative parameters, to help assess post-LT survival probability.

MATERIALS AND METHODS

Subjects

We followed 161 consecutive HCC patients aged 18 years or older who underwent primary cadaveric LT at West China Liver Transplantation Center between February 1999 and June 2006. All of the diagnoses of HCC were confirmed by pathology. Among these 161 recipients, eight were eliminated because of failure in follow-up; three, for death within 10 d after transplantation due to some perioperative factors. The remaining 150 transplants were under analysis. All included recipients' demographic characteristics, pre-LT laboratory data and HCC-related parameters were abstracted from our liver transplant database (Tables 1, 2 and 3), and all data were from the latest examination before LT. Just as the radiological Milan criteria, the tumor features in our study were also obtained by CT or MRI, and all last images were within 3 d before transplantation. The same surgical team performed all LTs using standard techniques, and all recipients were followed up by June 30, 2007.

MELD calculation

The MELD scores were calculated according to the following model[5]: MELD = 3.78 × $\log_e$TB (mg/dL) + 11.20 × $\log_e$INR + 9.57 × $\log_e$Crea (mg/dL) + 6.4. In this formula, values for creatinine, INR and TB less than 1.0 were reset to equal 1, and values for creatinine were capped at 4. In patients with creatinine value less than 4 who were on dialysis at the time of transplantation, the creatinine should be increased to equal 4.

Statistical analysis

Cox proportional-hazards regression was the main statistical tool for survival modeling. Recipients' survival was estimated by the Kaplan-Meier method, and comparison of survival differences performed by the log-rank test. To decrease the influence of extreme laboratory values, all quantitative variables were transformed to their natural logarithms ($\log_e$ value)[5]. We first performed univariate Cox regression analysis of all parameters shown in Tables 2 and 3, and those found to be significant at the 0.10 level were selected for the multivariate analysis. The final multivariate model was obtained by a backward elimination stepwise selection method with the criteria for factor removal being $P \geqslant 0.05$. Based on the selected variables, prognostic index (PI) and survival function could be constructed.

To assess the validity in predicting the risk of post transplant death, we performed ROC curves for the two models and measured their concordance statistic (c-statistic), the mathematical measure to determine the validity of a model[11,12]. Comparison of the c-statistic was done using the method of Hanley[13]. All analyses were performed using SPSS13.0 statistical software.

Table 1 Demographic characteristics of recipients

Gender	*n* (%)
Male	129 (86.0)
Female	21 (14.0)
Median age (range)	51 (28-68)
Hepatitis B	150 (100)
Child's score	
A (5-6)	89 (59.3)
B (7-9)	46 (30.7)
C (10-15)	15 (10.0)
MELD score	
⩽ 18	132 (88.0)
> 18	18 (12.0)

Table 2 Pretransplant biochemical features of recipients

Variables	mean ± SD	Min value	Max value
Hb (g/dL)	12.23 ± 2.62	4.3	18.7
PLT (× 10^9)	131.4 ± 86.0	17	569
Urea (mmol/L)	4.90 ± 2.01	2.4	16.2
Crea (mg/dL)	1.06 ± 0.10	1	1.44
ALB (g/dL)	3.79 ± 0.68	2.01	5.28
TB (mg/dL)	26.8 ± 37.4	10	260.2
AKP (u/L)	160.51 ± 130.97	18	779
GGT (u/L)	215.34 ± 255.40	24	1630
AST (u/L)	89.83 ± 76.23	19	421
ALT (u/L)	101.49 ± 99.19	12	486
INR for PT	1.25 ± 0.24	1	2.16
AFP (μg/L)	426.65 ± 393.91	1.97	3000
Na^+ (mEq/L)	137.12 ± 5.33	114.2	150.3

RESULTS

Univariate analysis

Table 4 shows the results of the univariate analyses: serum concentration of ALB, TB, AKP, GGT, AST, AFP, Na^+, tumor diameter and the number of tumor nodules were significantly associated with survival after transplantation. The positive regression coefficient implies that the risk of death would increase with increasing values of a risk factor.

Multivariate analysis

Of the candidate variables derived from univariate analyses, serum concentration of AKP, AFP, Na^+ and the number of tumor nodules were significant predictors of survival after transplantation (Table 5). The negative regression coefficients of "Na^+" and "single tumor nodule" imply that the risk of death would decrease with their increasing values.

Calculating the prognostic index and predicted survival probabilities

The prognostic index for individual patients can be

Table 3 HCC-related features of recipients

Variable		Code	Frequency	Proportion (%)
History of hepatectomy for HCC	Present	1	15	10
	Absent	0	135	90
Tumor diameter	1: < 5 cm	1	65	43.3
	2: 5 cm-	2	58	38.7
	Reference: > 10 cm	3	27	18
Tumor nodule	Nodule 1: one	1	93	62
	Nodule 2: two	2	31	20.7
	Reference: > two	3	26	17.3
Vascular invasion	Present	1	20	13.3
	Absent	0	130	86.7
Intrahepatic tumor dissemination	Present	1	33	22
	Absent	0	117	78
Perihepatic lymphadenectasis	Present	1	10	6.7
	Absent	0	140	93.3

calculated by combining their four prognostic values with the regression coefficients reported in Table 5. The formula for PI as well as the MELD is given as follow:

PI = 0.663 × $\log_e$ (AKP u/L) + 0.122 × $\log_e$ (AFP μg/L) - 8.755 × $\log_e$ (Na^+ mEq/L) - 0.631 × the number of tumor nodules (single nodule coded 1, multinodular tumor coded 0).

To assess the probability of survival at a certain time after LT, we constructed the survival function of the new model[9,14]: $S(t) = [S_0(t)]^P$ P = expPI. $S(t)$ was the survival function, and $S_0(t)$ was the individual baseline survival function which could be calculated using the linear interpolation method in baseline survival rate series. Finally, the survival probability $S(t = \chi)$ of time point χ could be computed by putting both the PI value and the $S_0(t = \chi)$ into the above formula. The larger the $S(t)$ is, the higher probability of death of the patient would be after time point χ.

Validation of the new model and comparison with MELD

The recipients' post transplant survival was compared based on this new model. Because their PI values did not follow the normal distribution (*Shapiro-Wilk* test, $W = 0.949$, $P = 0.001$), recipients were stratified into two risk groups according to the median of PI values, namely a high PI value (high risk) group and a low PI value (low risk) group. The low risk group had a better prognosis than the high risk group, and the survival difference between them was statistically significant (*log-rank* test, $\chi^2 = 10.71$, $P = 0.001$ Figure 1A).

According to ROC analysis (Figure 1B), the c-statistic of the new model was 0.72 (95% CI = 0.609-0.824) which was significantly greater than 0.50 ($P = 0.001$), and the c-statistic of MELD was only 0.59 (95% CI = 0.470-0.711) which did not have significantly predictive value ($P = 0.146$). The c-statistic may range from 0 to 1, with 1 indicating perfect discrimination and 0.5 (the area under the chance line) indicating what is expected by chance only[15]. When a c-statistic above 0.50 has statistical significance compared with 0.50, it means the model is valid[9]. Meanwhile, for the prognostic model, with a c-statistic above 0.7 is generally considered as a useful model[5], and a c-statistic below 0.7 suggests poorly predictive ability[16]. So the new model was valuable in assessing the post transplant outcome.

Table 4 Univariate Cox analysis of parameters

Variable	Regression coefficient	Regression coefficient SE	Wald	*P*-value	Exp$^\beta$
Hb ($\log_e$)	-0.510	0.510	0.997	0.318	0.601
PLT ($\log_e$)	0.060	0.230	0.068	0.795	1.062
Urea ($\log_e$)	0.024	0.457	0.003	0.958	1.025
Crea ($\log_e$)	-0.427	1.671	0.065	0.798	0.652
ALB ($\log_e$)	-2.056	0.695	8.758	0.003	0.128
TB ($\log_e$)	0.277	0.165	2.838	0.092	1.320
AKP ($\log_e$)	0.581	0.214	7.328	0.007	1.787
GGT ($\log_e$)	0.254	0.148	2.930	0.087	1.289
AST ($\log_e$)	0.535	0.202	6.987	0.008	1.707
ALT ($\log_e$)	-0.172	0.178	0.926	0.336	0.842
INR ($\log_e$)	-0.065	0.818	0.006	0.937	0.937
AFP ($\log_e$)	0.104	0.071	2.742	0.098	1.109
Na^+ ($\log_e$)	-7.161	3.144	5.190	0.023	0.001
History of hepatectomy	-0.160	0.474	0.115	0.735	0.852
Tumor diameter			6.245	0.089	
1	-1.057	0.505	4.385	0.036	0.347
2	0.278	0.359	0.603	0.437	1.321
Tumor nodule			5.410	0.067	
1	-0.391	0.364	1.153	0.283	0.677
2	0.419	0.419	1.000	0.317	1.520
Vascular invasion	0.368	0.300	1.503	0.22	1.445
Intrahepatic tumor dissemination	0.190	0.345	0.305	0.581	1.210
Perihepatic lymphadenectasis	0.583	0.526	1.226	0.268	1.791

Table 5 Multivariate Cox assessment of risk factors associated with post-LT mortality

Variable	Regression coefficient	Regression coefficient SE	Wald	*P*-value	Exp$^\beta$
AKP ($\log_e$)	0.663	0.222	8.917	0.003	1.941
AFP ($\log_e$)	0.122	0.074	4.042	0.048	1.130
Na^+ ($\log_e$)	-8.755	3.252	7.247	0.007	0.000
Tumor nodule			8.189	0.017	0.532
1	-0.631	0.373	4.265	0.041	

DISCUSSION

The MELD has been validated to predict the pretransplant mortality risk in patients with many types of end-stage liver disease and to determine the medical urgency for transplantation[5,7,8], but abundant further investigations indicate it's not adequate for HCC candidates[4,17]. We hold that the main reason could be attributed to the fact that the development of MELD was based on benign liver diseases and did not incorporate aspects of malignant tumors[9]. Therefore, modifications were made in the MELD/HCC allocation system in April 2003[18]. Meanwhile, although the value of MELD for assessing disease severity and predicting pretransplant survival has been convincingly established, its ability to evaluate post transplant outcome is still under controversy. To date, many studies have proved the poor capacity of MELD in predicting post

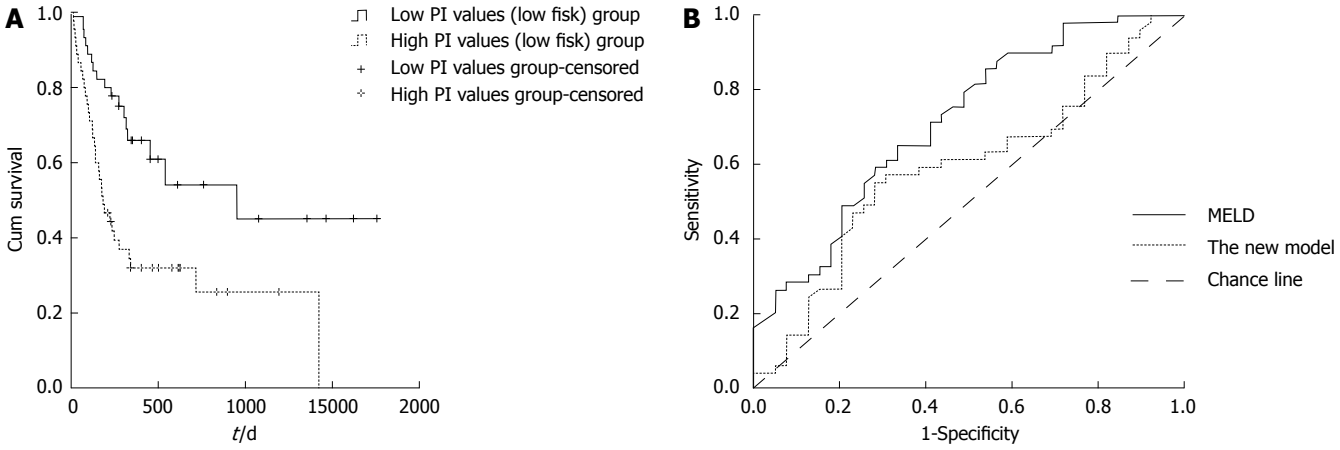

Figure 1 **A**: Comparison of posttransplant survival (Kaplan-Meier) for two groups of recipients according to the median of their PI values; **B**: Receiver operating characteristic curve (ROC) for MELD and the new model.

transplant survival[19-22]. We also confirmed the MELD scores were poorly correlated with the post transplant prognosis of HCC recipients, its c-statistic was only 0.59.

A model like the MELD which can stratify disease severity may optimize the timing of LT, and a prognostic model which can predict the post transplant survival probability may screen the appropriate candidates who can benefit mostly from the transplantation. The importance of understanding predictors of post-LT outcome before surgery was first recognized in 1987 by Malatack[23], who identified several pretransplant parameters associated with post transplant prognosis in pediatric recipients. Similarly, we also identified four variables correlated with post transplant outcome of HCC/LT recipients in our study: the serum concentration of AKP, AFP, Na^+ and the number of tumor nodules, which were easily available, objective and reproducible biochemical tests and tumor-related factors before operation. Further analyses confirmed this newly derived model based on these four variables resulting in a c-statistic of 0.72, which indicates its validity in post transplant outcome evaluation. We consider that the inclusion of these tumor-related parameters may contribute to the validity of our model because of the close correlativity between cancer biological features and patients' prognosis.

The serum concentration of AFP, combining with specific imaging techniques, has been one of the diagnostic criteria for HCC on account of its satisfactory sensitivity and specificity[24]. Also, AFP level is an important predictor of HCC prognosis[25]. The pretransplant AFP level was proved to associate with tumor recurrence and prognosis[26], and the adjuvant treatments often fail to prevent tumor progression in patients with high AFP level[27]. Ochiai *et al*[28] investigated 95 HCC patients undergoing hepatectomy and found that the serum AFP concentration above 400 μg/L was one of the preoperative risk factors associated with postoperative prognosis. Furthermore, studies from Carlis *et al*[29] and Del Gaudio *et al*[30], who retrospectively analyzed 121 and 87 HCC patients who received LT, verified serum AFP level was not only significantly related to the development of tumor recurrence, but also a significant independent risk factor of patient overall-survival after transplantation. Our finding was consistent with these studies which all identified AFP level did associate with the postoperative outcome.

Liver is a main organ to synthesize and secrete AKP in adults. Pathological changes of the hepatocytes, therefore, will cause certain changes of AKP, so it is a parameter to indicate the hepatic function. Meanwhile, since the elevated serum concentration of AKP can be observed in several liver malignant tumors such as intrahepatic cholangiocellular carcinoma and HCC, it has also been accepted as a kind of tumor marker even though its specificity is not so satisfactory yet. Screening by mathematical statistics in our study revealed that combination of AFP and AKP could have predictive value for HCC recipients in post-LT survival evaluation. If the serum concentration of AFP and AKP stay at a high level continuously or increase again after transplantation, it is usually parallel to the presence of residual tumor cells or the probability of cancer recurrence. That is consistent with what we observed clinically.

MELD does not encompass complications of portal hypertension, but many studies suggest some complications, especially the refractory ascites and serum sodium are predictors of mortality for patients with liver diseases[31-34]. In 2004, a preliminary report from Argentina first documented that addition of serum sodium to the MELD as either a dichotomous or a continuous variable could improve its predictive power[35]. Further, studies from Heuman *et al*[31] and Biggins *et al*[32] confirmed serum sodium could enhance MELD and help risk-stratify patients more accurately. The correlation between ascites and hyponatremia had been already documented by several reports[6,31]. Compared to the serum sodium, ascites is not consistently quantified, and standardization of ascites measurement among centers cannot be easily accomplished because it's a subjective and ambiguous variable. According to abundant evidence-based proofs, a conference in 2004 recognized this fact and recommended collection of serum sodium for all liver registrants to ascertain the value of adding this parameter into MELD[36]. The UNOS/OPTN Board also approved inclusion of serum sodium, either as

a dichotomous or as a continuous variable, to the list of laboratory tests collected in liver transplant recipients[36].

In our study, serum sodium showed significant association with post transplant prognosis. Its prognostic value may be reflected by the way that serum sodium can characterize patients with the hemodynamic or internal environmental derangement and the poor general conditions. Its negative regression coefficient indicates that the effect of serum sodium in whole model is protective, which means the higher the serum sodium concentration is, the lower risk of mortality the patient would be.

The number of tumor nodules is a specific character for tumor patients and a well-recognized predictor of prognosis in patients with HCC. Various clinical and pathologic factors related to the cancer recurrence and recipients' outcome have been validated in many studies, including the tumor size, the presence of satellite nodules, multilobarly distributed tumors, intrahepatic or extrahepatic dissemination, vascular invasion (microscopic and macroscopic), histological degree of differentiation[10,30,37,38]. Our results identified the number of tumor nodule as an independently predictive variable associated with post transplant survival, which was consistent with the findings from Bismuth[37]. Not surprisingly, either the tumor development from multicenter or the presence of intrahepatic metastasis will apparently parallel the poor prognosis in HCC recipients. That's why the selection guidelines for HCC candidates which have been generally acknowledged and widely used, such as the Milan criteria and the UCSF criteria, not only pay attention to the tumor size, but have severe restrictions to the number of tumor nodules.

The results of our study showed the new model, which employs four objective and widely reproducible variables, were more useful in assessing the prognosis of HCC recipients than MELD. Our study supported that incorporation of related biochemical parameters and tumor-specific variables would be a feasible way to develop a model for post transplant outcome assessment in HCC recipients. This kind of prognostic model, we believe, should play an important role in the selection of the best appropriate HCC candidates into liver allocation schemes. Whether the new model is widely useful or not, still needs to be validated by further investigation. We hope there would be continued improvement of the model, and we are looking forward to the confirmation of our findings in larger-volume patients' series.

COMMENTS

Background

Liver transplantation has been accepted as an effective therapeutic modality for HCC patients, but the relationship between severity of illness at LT and outcome after LT is still a major area of debate. Although the MELD has been proved to accurately predict pretransplant mortality, it's still controversial whether the MELD can evaluate post transplant outcome for HCC recipients.

Research frontiers

Although the value of MELD for assessing disease severity and predicting pretransplant survival has been convincingly established, abundant further investigations proved its poor capacity in predicting post transplant survival. Many studies have supported the HCC-related parameters should be added into MELD to improve its assessing capacity for the HCC patients.

Innovations and breakthroughs

In this study, we developed a new model to evaluate the risk of post transplant mortality in recipient of liver transplantation for HCC with hepatitis B. Our results also confirmed that this new model based on the four objective tumor-related parameters is more useful than MELD in assessing the prognosis of HCC recipients.

Applications

A prognostic model which can evaluate the risk of post transplant mortality may screen the appropriate candidates who can benefit mostly from the transplantation. So the new model, we believe, could play some role in selection of the best appropriate HCC candidates into liver allocation schemes.

Peer review

This paper is of some interest, its results support that incorporation of related biochemical parameters and tumor-specific variables would be a feasible way to develop prognostic model for post transplant outcome assessment in HCC recipients. This idea is deserved to explore.

REFERENCES

1 **Tang ZY**, Ye SL, Liu YK, Qin LX, Sun HC, Ye QH, Wang L, Zhou J, Qiu SJ, Li Y, Ji XN, Liu H, Xia JL, Wu ZQ, Fan J, Ma ZC, Zhou XD, Lin ZY, Liu KD. A decade's studies on metastasis of hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130**: 187-196

2 **Jonas S**, Bechstein WO, Steinmuller T, Herrmann M, Radke C, Berg T, Settmacher U, Neuhaus P. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001; **33**: 1080-1086

3 **Yao FY**, Bass NM, Nikolai B, Davern TJ, Kerlan R, Wu V, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. *Liver Transpl* 2002; **8**: 873-883

4 **Freeman RB Jr**, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl* 2002; **8**: 851-858

5 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470

6 **Wiesner RH**, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, Krom RA, Kim WR. MELD and PELD: application of survival models to liver allocation. *Liver Transpl* 2001; **7**: 567-580

7 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96

8 **Brown RS Jr**, Kumar KS, Russo MW, Kinkhabwala M, Rudow DL, Harren P, Lobritto S, Emond JC. Model for end-stage liver disease and Child-Turcotte-Pugh score as predictors of pretransplantation disease severity, posttransplantation outcome, and resource utilization in United Network for Organ Sharing status 2A patients. *Liver Transpl* 2002; **8**: 278-284

9 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871

10 **Cheng SJ**, Freeman RB Jr, Wong JB. Predicting the probability of progression-free survival in patients with small hepatocellular carcinoma. *Liver Transpl* 2002; **8**: 323-328

11 **Lusted LB**. Decision-making studies in patient management. *N Engl J Med* 1971; **284**: 416-424

12 **Hanley JA**, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**: 29-36

13 **Hanley JA**, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from

the same cases. *Radiology* 1983; **148**: 839-843
14 **Liu RX**, Xiao CP, Gong Q, Li X. Description of Multivariate Survival Period and Prediction of Multivariate Survival Rate with Cox Regression. *Zhongguo Gonggong Weisheng* 2001; **17**: 561-562
15 **Desai NM**, Mange KC, Crawford MD, Abt PL, Frank AM, Markmann JW, Velidedeoglu E, Chapman WC, Markmann JF. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function. *Transplantation* 2004; **77**: 99-106
16 **McDiarmid SV**, Anand R, Lindblad AS. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation* 2002; **74**: 173-181
17 **Kremers WK**, van IJperen M, Kim WR, Freeman RB, Harper AM, Kamath PS, Wiesner RH. MELD score as a predictor of pretransplant and posttransplant survival in OPTN/UNOS status 1 patients. *Hepatology* 2004; **39**: 764-769
18 **Wiesner RH**, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology* 2004; **127**: S261-S267
19 **Freeman RB**, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R. Results of the first year of the new liver allocation plan. *Liver Transpl* 2004; **10**: 7-15
20 **Onaca NN**, Levy MF, Sanchez EQ, Chinnakotla S, Fasola CG, Thomas MJ, Weinstein JS, Murray NG, Goldstein RM, Klintmalm GB. A correlation between the pretransplantation MELD score and mortality in the first two years after liver transplantation. *Liver Transpl* 2003; **9**: 117-123
21 **Jacob M**, Copley LP, Lewsey JD, Gimson A, Toogood GJ, Rela M, van der Meulen JH. Pretransplant MELD score and post liver transplantation survival in the UK and Ireland. *Liver Transpl* 2004; **10**: 903-907
22 **Northup PG**, Berg CL. Preoperative delta-MELD score does not independently predict mortality after liver transplantation. *Am J Transplant* 2004; **4**: 1643-1649
23 **Malatack JJ**, Schaid DJ, Urbach AH, Gartner JC Jr, Zitelli BJ, Rockette H, Fischer J, Starzl TE, Iwatsuki S, Shaw BW. Choosing a pediatric recipient for orthotopic liver transplantation. *J Pediatr* 1987; **111**: 479-489
24 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430
25 **Iida H**, Honda M, Kawai HF, Yamashita T, Shirota Y, Wang BC, Miao H, Kaneko S. Ephrin-A1 expression contributes to the malignant characteristics of {alpha}-fetoprotein producing hepatocellular carcinoma. *Gut* 2005; **54**: 843-851
26 **Xu J**, Shen ZY, Chen XG, Zhang Q, Bian HJ, Zhu P, Xu HY, Song F, Yang XM, Mi L, Zhao QC, Tian R, Feng Q, Zhang SH, Li Y, Jiang JL, Li L, Yu XL, Zhang Z, Chen ZN. A randomized controlled trial of Licartin for preventing hepatoma recurrence after liver transplantation. *Hepatology* 2007; **45**: 269-276
27 **Sala M**, Varela M, Bruix J. Selection of candidates with HCC for transplantation in the MELD era. *Liver Transpl* 2004; **10**: S4-S9
28 **Ochiai T**, Sonoyama T, Ichikawa D, Fujiwara H, Okamoto K, Sakakura C, Ueda Y, Otsuji E, Itoi H, Hagiwara A, Yamagishi H. Poor prognostic factors of hepatectomy in patients with resectable small hepatocellular carcinoma and cirrhosis. *J Cancer Res Clin Oncol* 2004; **130**: 197-202
29 **De Carlis L**, Giacomoni A, Pirotta V, Lauterio A, Slim AO, Sammartino C, Cardillo M, Forti D. Surgical treatment of hepatocellular cancer in the era of hepatic transplantation. *J Am Coll Surg* 2003; **196**: 887-897
30 **Del Gaudio M**, Grazi GL, Principe A, Ravaioli M, Ercolani G, Cescon M, Varotti G, Gardini A, Cavallari A. Influence of prognostic factors on the outcome of liver transplantation for hepatocellular carcinoma on cirrhosis: a univariate and multivariate analysis. *Hepatogastroenterology* 2004; **51**: 510-514
31 **Heuman DM**, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004; **40**: 802-810
32 **Biggins SW**, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology* 2005; **41**: 32-39
33 **Said A**, Williams J, Holden J, Remington P, Gangnon R, Musat A, Lucey MR. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol* 2004; **40**: 897-903
34 **Altman C**, Grange JD, Amiot X, Pelletier G, Lacaine F, Bodin F, Etienne JP. Survival after a first episode of spontaneous bacterial peritonitis. Prognosis of potential candidates for orthotopic liver transplantation. *J Gastroenterol Hepatol* 1995; **10**: 47-50
35 **Ruf AE**, Yantorno SE, Descalzi VI, Andriani OC, Podesta LG, Vilamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone-A single center experience. *Am J Transplant* 2004; **4** Suppl 8: 438
36 **Freeman RB Jr**. MELD and liver allocation: continuous quality improvement. *Hepatology* 2004; **40**: 787-789
37 **Bismuth H**, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 1999; **19**: 311-322
38 **Iwatsuki S**, Dvorchik I, Marsh JW, Madariaga JR, Carr B, Fung JJ, Starzl TE. Liver transplantation for hepatocellular carcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg* 2000; **191**: 389-394

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