Rapid Communication

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

Ming Zhang, Bo Li, Lu-Nan Yan, Fei Yin, Tian-Fu Wen, Yong Zeng, Ji-Chun Zhao, Yu-Kui Ma

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.

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

Peer reviewers: Francesco Feo, Professor, Dipartimento di Scienze Biomediche, Sezione di Patologia Sperimentale e Oncologia, Università di Sassari, Via P, Manzella 4, 07100 Sassari, Italy; Wei Tang, MD, EngD, Assistant Professor, H-B-P Surgery Division, Artificial Organ and Transplantation Division, Department of surgery, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan

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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[8]. Liver transplantation (LT) has become accepted as an effective therapeutic modality for these patients[2], 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[9]. 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[8-7], 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[9], 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(TB) (mg/dL) + 11.20 × log(INR) + 9.57 × log(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, their creatinine was 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, 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 ≥ 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.

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

| Variables | mean ± SD | Min value | Max value |
|-----------|-----------|-----------|-----------|
| Hb (g/dL) | 12.23 ± 2.62 | 4.3 | 18.7 |
| PLT (× 10^11) | 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 ± 3.74 | 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 | 1.25 ± 0.24 | 1 | 2.36 |
| AFP (µg/L) | 426.65 ± 393.91 | 1.97 | 3000 |
| Na⁺ (mEq/L) | 137.12 ± 5.33 | 114.2 | 150.3 |
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:

\[ PI = 0.663 \times \log(\text{APK} \, \mu g/L) + 0.122 \times \log(\text{AFP} \, \mu g/L) - 8.755 \times \log(\text{Na}^+ \, \text{mEq/L}) - 0.631 \times \text{the number of tumor nodules} \] (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\textsuperscript{[10,11]}:

\[ S(t) = S_0(t)^\hat{\beta} = \exp(\hat{\beta} \cdot \text{PI}) \]

where \( S(t) \) is the survival function, and \( S_0(t) \) is the 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 \( \chi \) 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 \( \chi \).

**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\textsuperscript{[11,12]}. When a c-statistic above 0.50 has statistical significance compared with 0.50, it means the model is valid\textsuperscript{[13,14]}. Meanwhile, for the prognostic model, with a c-statistic above 0.7 it is generally considered as a useful model\textsuperscript{[9]}, and a c-statistic below 0.7 suggests poorly predictive ability\textsuperscript{[10]}. So the new model was valuable in assessing the post transplant outcome.

**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\textsuperscript{[5,8,9]}, but abundant further investigations indicate it’s not adequate for HCC candidates\textsuperscript{[8,17]}. 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\textsuperscript{[9]}. Therefore, modifications were made in the MELD/HCC allocation system in April 2003\textsuperscript{[10]}. 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-

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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 |
| Perihpatic lymphadenectomy | Present | 1 | 10 | 6.7 |
|                   | Absent | 0 | 140 | 93.3 |

Table 4  Univariate Cox analysis of parameters

| Variable    | Regression coefficient | Regression coefficient SE | Wald | P-value | Exp' |
|-------------|------------------------|---------------------------|------|---------|------|
| Hb (log)    | -0.510                 | 0.510                     | 0.997| 0.318   | 0.601|
| PLT (log)   | 0.060                  | 0.230                     | 0.068| 0.795   | 1.062|
| Urea (log)  | 0.024                  | 0.457                     | 0.003| 0.958   | 1.025|
| Crea (log)  | -0.427                 | 1.671                     | 0.065| 0.798   | 0.652|
| ALB (log)   | -2.056                 | 0.695                     | 8.758| 0.003   | 0.126|
| TB (log)    | 0.277                  | 1.165                     | 2.683| 0.092   | 1.320|
| AKP (log)   | 0.581                  | 0.214                     | 7.328| 0.001   | 1.787|
| GGT (log)   | 0.254                  | 0.148                     | 2.930| 0.087   | 1.289|
| AST (log)   | 0.535                  | 0.202                     | 6.987| 0.008   | 1.707|
| ALT (log)   | -0.172                 | 0.178                     | 0.926| 0.336   | 0.842|
| INR (log)   | -0.065                 | 0.086                     | 1.006| 0.357   | 0.937|
| AFP (log)   | 0.104                  | 0.071                     | 2.742| 0.098   | 1.129|
| Na+ (log)   | -7.161                 | 3.144                     | 5.190| 0.023   | 0.991|
| History of hepatectomy Tumor diameter | 6.245 | 0.089 |
| 1           | -1.057                 | 0.505                     | 4.385| 0.036   | 0.347|
| 2           | 0.278                  | 0.359                     | 0.603| 0.457   | 1.321|
| Tumor nodule| 5.410                  | 0.067                     | 5.048| 0.025   | 1.056|
| 1           | -0.391                 | 0.364                     | 1.153| 0.283   | 0.767|
| 2           | 0.419                  | 0.419                     | 1.000| 0.317   | 1.520|
| Vascular invasion | 0.368 | 0.150 |
| Intrahepatic tumor dissemination | 0.190 | 0.345 | 0.305 | 0.581 | 1.210|
| Perihpatic lymphadenectomy | 0.583 | 0.526 | 1.226 | 0.268 | 1.979|

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

| Variable    | Regression coefficient | Regression coefficient SE | Wald | P-value | Exp' |
|-------------|------------------------|---------------------------|------|---------|------|
| AKP (log)   | 0.663                  | 0.222                     | 8.917| 0.003   | 1.941|
| AFP (log)   | 0.122                  | 0.074                     | 4.042| 0.048   | 1.130|
| Na+ (log)   | -8.755                 | 3.252                     | 7.247| 0.007   | 0.000|
| Tumor nodule| 8.189                  | 0.017                     | 0.532| 0.991   | 1.001|
| 1           | -0.631                 | 0.373                     | 4.265| 0.041   | 0.701|
transplant survival\textsuperscript{[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\textsuperscript{[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\textsuperscript{+} 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\textsuperscript{[24]}. Also, AFP level is an important predictor of HCC prognosis\textsuperscript{[25]}. The pretransplant AFP level was proved to associate with tumor recurrence and prognosis\textsuperscript{[26]}, and the adjuvant treatments often fail to prevent tumor progression in patients with high AFP level\textsuperscript{[27]}. Ochiai \textit{et al}\textsuperscript{[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 \textit{et al}\textsuperscript{[29]} and Del Gaudio \textit{et al}\textsuperscript{[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\textsuperscript{[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\textsuperscript{[35]}. Further, studies from Heuman \textit{et al}\textsuperscript{[35]} and Biggins \textit{et al}\textsuperscript{[36]} 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\textsuperscript{[37,38]}. Compared to the serum sodium, ascites are 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\textsuperscript{[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[30].

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[19,30,37,38]. 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 idea is deserved to explore.

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.

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