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*Original Article*

# A simple prediction score for in-hospital mortality after hepatectomy in hepatitis B-related hepatocellular carcinoma

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**Abstract:** Despite of advances in surgical techniques and peroperative managements, hepatectomy remains one of the most common and effective treatment for HCC. The aim of the study was to develop a simple, applicable prediction score for stratifying patients with hepatitis B virus (HBV) related hepatocellular carcinoma (HCC) undergoing hepatectomy accurately by risk of in-hospital mortality. Records from 2224 consecutive HBV-related HCC patients underwent hepatectomy in West China Hospital between 2008 and 2013 were identified. A random sample of 80% of the cohort was used to create the risk score and the remaining 20% was used for validation. Factors that contributed toward in-hospital death after hepatectomy were identified. An integer-based risk score for estimating the risk of in-hospital mortality in patients undergoing hepatectomy was created by using logistic regression and bootstrap methods. The overall in-hospital mortality was 3.06%. The risk factors for the final model included age, the Charlson Comorbidity index, type of hepatectomy, extrahepatic procedure, the platelet count and the American Society of Anesthesiologists category. Integer values were assigned to these factors based on the beta coefficient and then calculated to an additive score. Three clinically relevant groups were defined to stratify the risk of in-hospital mortality after hepatectomy. The estimate incidences of in-hospital mortality were 20.96%, 4.73% and 0.49% for high, moderate and low risk group respectively. The model discriminated well in both development set and validation set with c-statistics of 0.875 and 0.815 respectively. In conclusion, a simple integer-based risk score can be used to accurately predict in-hospital mortality of patients with HBV-related HCC undergoing hepatectomy. It might be helpful in risk stratification, patients consulting and decision making.

**Keywords:** Risk score, hepatectomy, hepatocellular carcinoma, hepatitis b, in-hospital mortality

## Introduction

More than half a million people worldwide are newly diagnosed with hepatocellular carcinoma (HCC) annually, half of them occurred in China because of high rates of hepatitis B Virus (HBV) infections [1-4]. With the advances in surgical techniques and postoperative managements, the criteria for resectability of HCC have expanded and hepatectomy remains one of the most common and effective treatment for HCC [5-7]. The postoperative mortality has decreased from >10% historically to <4% recently with a high morbidity ranging from 20% to 50% in addition [8-12].

Several investigators have attempted to established reliable risk models to predict mortality following surgical procedures for hepatic neoplasm [13-16]. Balzan et al advocated the "50-50 criteria" to predict mortality after hepatectomy in a simple, early and accurate method [16]. It was defined as prothrombin time <50% and serum bilirubin level >50 μmol/L on postoperative day 5. Hyder and colleagues created a model by using a composite risk score on postoperative day 3 international normalized ratio, bilirubin, creatinine, and complication grade to predicted 90-day mortality after hepatectomy [15]. Simons et al had investigated and validated two simple scores to predict in-hospital mortality after surgical procedures by preoperative characteristics [13, 14]. Although with great importance, some of these studies used the data postoperative and some included hepatectomy for various liver diseases

**Table 1.** Romano adaptation of the charlson comorbidity index

| Co morbidity | Points |
|---|---|
| AIDS | 6 |
| Cerebrovascular disease | 1 |
| Chronic pulmonary disease | 1 |
| Congestive heart failure | 1 |
| Connective tissue/rheumatic disease | 1 |
| Dementia | 1 |
| Diabetes | |
| Without end organ damage | 1 |
| With end organ damage | 2 |
| Hemiplegia | 1 |
| Myocardial infarction | 1 |
| Peripheral vascular disease | 1 |
| Renal disease | 2 |
| Ulcer disease | 1 |
| Liver disease | |
| Mild to moderate | 1 |
| Severe | 3 |

that cannot be applicable to HBV-related HCC patients. The aim of the study was to develop a applicable, simple prediction score for stratifying HBV-related HCC patients undergoing hepatectomy accurately by risk of in-hospital mortality, guiding patients consulting and decision making.

## Materials and method

### *Patient selection*

From January 2007 to July 2013, 2224 consecutive HBV-related HCC patients underwent elective hepatectomy in West China Hospital of Sichuan University were included in our study. The diagnosis of HCC was proved by histology and with HBV infection or a history of HBV infection. The selection criteria for liver resection were described as follows: (1) the estimated remnant liver volume more than 50% of the total liver volume, (2) only patients with the Child-Turcotte-Pugh score A were considered for surgery to prevent from poor outcomes. Patients under 18 years old or those who underwent emergency surgery were excluded from analysis. The cohort was randomly divided into 2 groups for score development (selected 80% of the cohort) and validation (the remaining 20%) respectively.

### *Ethics statement*

Informed consent was obtained from each patient before surgery. The protocol was approved by the Ethics Committee of West China Hospital, Sichuan University and carried out in accordance with ethical principles of the Declaration of Helsinki.

### *Predictor parameters*

The in-hospital mortality was studied. It was defined as death from any cause occurred during the same hospitalization. Preoperative parameters were analyzed to determine the variables associated with in-hospital mortality. The parameters included the following: age, sex, the Charlson Comorbidity Index (CCI), procedure type (major liver resection or minor liver resection), extrahepatic procedure, aspartate aminotransferase (AST), alanine aminotransferase (ALT), BMI, hemoglobin (HGB), platelet (PLT) count, the American Society of Anesthesiologists (ASA) grade and portal hypertension status. The CCI [17, 18] was used to quantify comorbidities for individual (**Table 1**). It was assigned by sum of the points based on the comorbidities presented of each case. The score of "liver disease" was evaluated by the categories of "mild-to-moderate" or "severe" for 1 point and 3 points respectively. The mild-to-moderate category includes patients with "cirrhosis", "liver damage, unspecified", and "chronic hepatitis" from various causes, including unknown etiologies. Since all the patients had HBV infections, 1 point was detracted from each case of the cohort. The comorbidity "cancer" was excluded for the same reason. The severe category includes "hepatic encephalopathy", "portal hypertension", "hepatorenal syndrome", "hepatic infarction" and "esophageal varices". Portal hypertension was defined as esophageal varice confirmed by endoscopy or splenomegaly with a PLT count less than 100,000/mm$^3$ [19]. Major liver resection is defined by resection of ≥3 Couinaud segments [20], or as minor liver resection. Extrahepatic procedures included bowel surgery, biliary surgery, splenectomy, vascular procedures, diaphragmatic repair and adhesion separation due to reoperation, except for cholecystectomy. HBV-DNA positive was defined as more than 2000 U/ml.

**Table 2.** Patient demographics of the development set and validation set

| Factors | Development set (n = 1801) | Validation set (n = 423) | P |
|---|---|---|---|
| Charlson score ≥3 (%) | 34.9% | 32.4% | 0.334 |
| Male (%) | 83.4% | 83.5% | 0.979 |
| Age >55 years (%) | 38.4% | 38.5% | 0.949 |
| Major resection (%) | 37.5% | 38.8% | 0.622 |
| Extrahepatic procedures (%) | 20.2% | 18.4% | 0.411 |
| AST U/L (%) | | | 0.405 |
| 40-80 | 34.6% | 32.6% | |
| >80 | 15.2% | 17.7% | |
| ALT U/L (%) | | | 0.741 |
| 50-100 | 24.4% | 23.4% | |
| >100 | 9.6% | 8.7% | |
| BMI >28 Kg/m$^2$ (%) | 4.8% | 4.7% | 0.967 |
| Hemoglobin <120 g/L (%) | 13.0% | 15.6% | 0.157 |
| WBC <4*10^9/L (%) | 19.5% | 21.5% | 0.348 |
| Platelet count <60*10^9/L (%) | 7.0% | 6.1% | 0.533 |
| HBV DNA (+) (%) | 32.3% | 29.6% | 0.272 |
| ASA grade of III to IV (%) | 15.5% | 16.1% | 0.483 |
| Portal hypertension (%) | 29.0% | 25.5% | 0.15 |
| In-hospital death | 3.1% | 2.8% | 0.77 |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; WBC, white blood cell; ASA, the American Society of Anesthesiologists. HBV-DNA positive was defined as more than 2000 U/ml.

*Statistical analyses*

Patients discharged or died in hospital after hepatectomy were compared. Categorical variables were analyzed by using the Pearson Chi-square test. Variables with statistical significance were took into a multivariable logistic regression and created a model of in-hospital mortality. Then bootstrapping methods were subsequently used to generate 200 samples. The medians for beta coefficients were then used to develop a integer-based prediction score for predicting in-hospital morality. Referents of each variable were assigned with a value of zero. The score of each patient was calculated by summing risk points of the variables. Then they were stratified into risk groups according to the resultant estimated mortality. For the development of the risk score, the risk score was calculated for each patient in the development set and the discrimination was identify by using the area under the receiver operator characteristic (ROC) curve. Then the 20% random sample was used for the validation of the risk score. The ROC curve analysis was performed to evaluate the discrimination after applied the risk score model in the validation set. Level of P<0.05 was considered significant and all calculated *P* values were 2-sided. The predictive ability was considered poor if an AUROC curve was <0.7. All the statistical analysis was performed by using SPSS Version 19 statistical analysis software (SPSS Inc., Chicago, Illinois, USA).

## Result

*Demographics*

A total of 2224 consecutive HBV-related HCC patients who underwent hepatectomy were included in our study. The cohort was randomly divided into 2 groups for score development (selected 80% of the cohort) and validation (the remaining 20%) respectively. The development set included 1801 patients and the validation included 423 patients. The overall in-hospital mortality was 3.06%. Most of the patients were male (83.0%). 38.2% of the patients were older than 55 years old and 34.4% had a CCI ≥3. 37.7% of the patients underwent major liver resection while extrahepatic surgeries were performed on 19.9% at the same time. 15.6% of the patients with higher ASA grade (III-IV). Portal hypertension was diagnosed in 28.2% of the patients while only 6.8% of the patients with a PLT count <60,000/mm$^3$. Serum HBV DNA was positive in almost one third of the patients (31.6%). 4.7% of the patients were defined as obese with BMI more than 28 Kg/m$^2$. Demographics of each set were displayed in **Table 2**. There was no significant difference between the 2 groups in demographics by Pearson Chi-square test.

*Development and validation of the prediction score*

Univariate analysis (**Table 3**) in the development set showed 8 factors were statistically significant predictors affecting in-hospital mortality. They were CCI (*P*<0.001), age (*P*<0.001), procedure type (*P* = 0.003), extrahepatic procedures

**Table 3.** Risk factors for in-hospital mortality after hepatectomy for patients in the development set according to the univariate analysis

| Factors | Discharged (n = 1696) | In-hospital death (n = 55) | *P* |
|---|---|---|---|
| Charlson score ≥3 (%) | 581 | 47 | <0.001 |
| Male (%) | 1450 | 52 | 0.063 |
| Age >55 years (%) | 654 | 37 | <0.001 |
| Major resection (%) | 643 | 32 | 0.003 |
| Extrahepatic procedures (%) | 344 | 20 | 0.004 |
| AST U/L (%) | | | |
| 40-80 | 607 | 17 | 0.584 |
| >80 | 264 | 10 | 0.723 |
| ALT U/L (%) | | | |
| 50-100 | 426 | 14 | 0.805 |
| >100 | 166 | 7 | 0.436 |
| BMI >28 Kg/m$^2$ (%) | 81 | 5 | 0.147 |
| Hemoglobin <120 g/L (%) | 221 | 13 | 0.024 |
| WBC <4*10^9/L (%) | 339 | 12 | 0.71 |
| Platelet count <60*10^9/L (%) | 116 | 10 | 0.002 |
| HBV DNA (+) (%) | 566 | 16 | 0.543 |
| ASA grade of III to IV (%) | 256 | 24 | <0.001 |
| Portal hypertension (%) | 495 | 28 | <0.001 |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; WBC, white blood cell; ASA, the American Society of Anesthesiologists. HBV-DNA positive was defined as more than 2000 U/ml.

(*P* = 0.004), HGB (*P* = 0.024), PLT count (*P* = 0.002), ASA grade (*P*<0.001) and portal hypertension status (*P*<0.001). Then the variables above were included in a multivariable logistic regression model and the results showed that age, CCI, procedure type, extrahepatic procedure, the PLT count and the ASA grade were significantly different (**Table 4**). After adjusting of other factors, Chalson score ≥3 had the greatest association on rising the odds of in-hospital mortality with a odds ratio (OR) of 11.055; 95% confidence interval (CI), 5.182-23.585, *P*<0.001, followed by major liver resection (OR, 4.182; 95% CI 2.310-7.573, P<0.001), high ASA grade (III-IV) (OR, 2.536; 95% CI 1.365-4.711, P = 0.003), PLT count <60*10^9/L (OR, 2.449; 95% CI 1.125-5.331, P = 0.024), extrahepatic procedure (OR, 2.380; 95% CI 1.301-4.353, P = 0.005) and age >55 (OR, 1.991; 95% CI 1.059-3.743, P = 0.033).

Medians of the beta coefficients were transformed to integers for estimating the risk of in-hospital mortality conveniently (**Table 4**). The lowest beta coefficients (age) was 0.689 and was set to 1 while the referent groups were set to 0. The point scores were ranged from 0 to 4 for each predictor and were calculated (ranged from 0 to 10) for estimating the risk of mortality. The total risk scores were grouped into three clinically relevant risk groups (0-3 for low risk, 4-6 for moderate and 7-10 for high). The estimate incidences of in-hospital mortality were 20.96%, 4.73% and 0.49% for high, moderate and low risk group respectively. ROC curve (**Figure 1**) analysis with an area under the curve of 0.875 revealed that the model discriminated well in the development set. Similar discrimination was observed in the validation set with an area under ROC curve of 0.815 (**Figure 2**).

## Discussion

With the developments in surgical techniques and postoperative managements, the criteria for resectability of HCC have expanded and hepatectomy remains one of the most common and effective treatment for HCC. Despite of advances above, hepatectomy was associated with high postoperative mortality still. In the cases of HBV-related HCC, the tumor always arises in a liver with cirrhosis which might worse the outcome [3, 19, 21]. In this study, we have developed a simple, integer-based risk score to accurately predict in-hospital mortality after hepatectomy for HBV-related HCC patients.

The current study represented an important step in predicting and quantifying risk of in-hospital mortality. The biochemical parameters which reflecting liver function such as albumin, bilirubin, prothrombin time were not considered, because all the patient underwent hepatectomy with a CTP class A. Six preoperative parameters were revealed by logistic regression analysis as predictors of in-hospital mortality. They were age, major liver resection, CCI, extrahepatic procedure, ASA grade and PLT count. The overall in-hospital mortality was 3.35% which is in line with recent publication

**Table 4.** Results of multivariable logistic regression in the development set and assignment of predictor scores based on beta coefficients

| Factors | OR (95% CI) | *P* | β | Risk score |
|---|---|---|---|---|
| Age group | | | | |
| ≤55 years | 1 | | | 0 |
| >55 years | 1.991 (1.059-3.743) | 0.033 | 0.689 | 1 |
| Procedure type | | | | |
| Minor resection | 1 | | | 0 |
| Major resection | 4.182 (2.310-7.573) | <0.001 | 1.431 | 2 |
| Charlson Score | | | | |
| <3 | 1 | | | 0 |
| ≥3 | 11.055 (5.182-23.585) | <0.001 | 2.403 | 4 |
| Extrahepatic procedure | | | | |
| No | 1 | | | 0 |
| Yes | 2.380 (1.301-4.353) | 0.005 | 0.867 | 1 |
| ASA stage | | | | |
| I-II | 1 | | | 0 |
| III-IV | 2.536 (1.365-4.711) | 0.003 | 0.93 | 1 |
| Patelet count | | | | |
| ≥60*10^9/L | 1 | | | 0 |
| <60*10^9/L | 2.449 (1.125-5.331) | 0.024 | 0.896 | 1 |

ASA, the American Society of Anesthesiologists. The total risk scores were grouped into three clinically relevant risk groups: 0-3 for low risk, 4-6 for moderate and 7-10 for high.

<4% [6-8]. We integrated the six risk predictors in a simple prediction score for clinical usability. The estimate mortality according to different risk groups ranged from 0.49% to 20.96%. In the current study, all the factors combined to the risk model can be obtained before surgery. It is useful in patients consulting and decision-making according to a simple fully understand of the risk. Surgeons can also use this simple risk score to classify patients at different risks in order to guiding patients' assessment, patients' selection and providing personalized perioperative managements as well.

Several studies have developed simple scores to predict the risk of postoperative mortality in liver resection. Simons et al [13, 14] had investigated two simple score to predict mortality after hepatic surgical procedures by using preoperative characteristics. In their first study [14], about 78% of the patients had metastasis neoplasm and 1/3 received radiofrequency ablation (RFA). In the second study [13], overall in-hospital mortality was 6.52% which seemed higher than recently and the causes associated to HCC was undefined. Both the predictors of two scores lack certain clinical information. For those HBV-related HCC patients, tumors usually occurred in livers with cirrhosis which might worse outcome of the liver procedure, especially in China. Their research cannot be applicable well to patients with HBV-related HCC undergo hepatectomy because of the abnormalities of the liver status. Researches done by Hyder et al. [15] or Balzan et al. [16] were useful in predicting postoperative mortality. However they included postoperative factors and could not be used for preoperative patient selection. As far as we know, we developed the first prediction score of in-hospital mortality for HBV-related HCC patients before hepatectomy.

The current study had several limitations. The scores were not be validated in other hospital that it should be interpreted with caution. All the cases in this study were from a single large teaching hospital with rich experiences. Moreover, our study was only restricted to patients with HBV-related HCC, this may not be appropriate for patients with other liver diseases undergoing hepatectomy. Third, only preoperative factors were included in our study for patients assessment, other factors such as blood loss and fibrosis severity were not included. Last but not the least, the end point of our research is in-hospital mortality which would not be appropriate to assess mortality in postoperative period. The current simple prediction score required validated broadly in the future.

Despite of the limitations above, we developed and validated an integer-based simple risk score to predict in-hospital mortality for HBV-related HCC patients after liver resection. This score may be useful for in-hospital mortality stratification, allows identifying patients at high

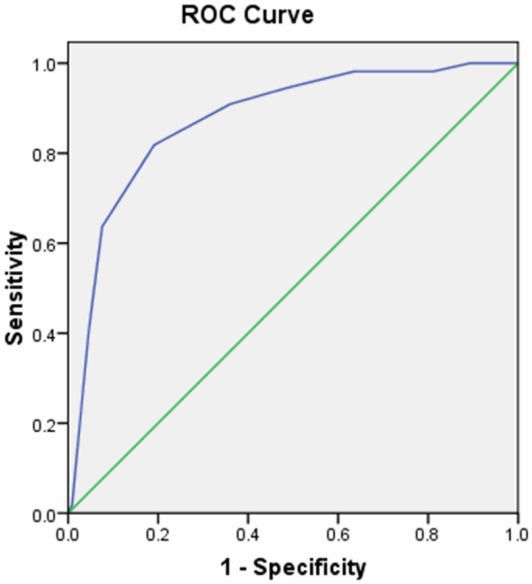


**Figure 1.** Receiver operator characteristic curve analysis of risk factors to predict in-hospital mortality in development set (area under the curve = 0.875, P<0.001).

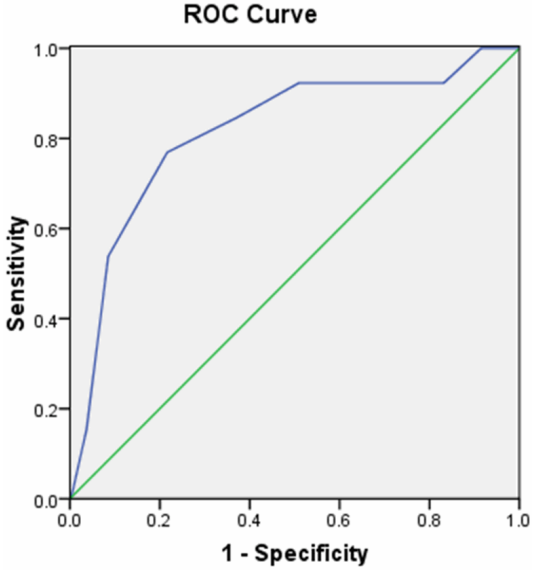


**Figure 2.** Receiver operator characteristic curve analysis of risk factors to predict in-hospital mortality in validation set (area under the curve = 0.815, P<0.001).

risk and contribute to patients consulting and decision making.

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## Disclosure of conflict of interest

None.

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