Does adding variceal status to the Child–Turcotte–Pugh score improve its performance in predicting mortality in cirrhosis?

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Abstract

The Child–Turcotte–Pugh (CTP) score is widely used worldwide to predict outcomes across a broad spectrum of liver diseases, mainly cirrhosis. Portal hypertension and variceal bleed are significant causes of morbidity and mortality in cirrhotic patients, although the variceal status is not incorporated into the classical CTP score. We sought to determine whether the inclusion of variceal status, specifically the Child–Turcotte–Pugh–Kumar (CTPK) score, would improve the utility of the classical CTP score to predict the clinical outcomes of cirrhotic patients in a single but high-volume center in China.

We retrospectively analyzed the records of 253 patients from January 1, 2014 to December 31, 2014 and performed follow-up for at least 12 months. The CTPK score and the CTP score were obtained as soon as possible after the patient's admission. Telephone follow-up was performed to assess survival situations.

At 3 and 12 months, the cumulative number of deaths was 9.1% (n = 23) and 13.8% (n = 35), respectively. In the multivariate Cox proportional hazards models, the CTPK score was independently associated with death within 3 and 12 months after adjusting for potential confounders. The predictive ability related to the 2 scores was evaluated by the area under the receiver operating characteristic curve (AUC-ROC) respectively. At 3 months of enrollment, the AUCs of CTPK and CTP were 0.814 and 0.838, respectively. At 12 months of enrollment, the AUCs of CTPK and CTP were 0.825 and 0.840, respectively. No significant difference between time points was observed. Both the CTPK score and the CTP score displayed prognostic value in cirrhotic patients, as the Kaplan–Meier analysis showed that the CTPK score could clearly discriminate patients in the intermediate term ($P < 0.001$).

The CTPK score provides reliable prediction of mortality in Chinese cirrhotic patients for both short-term and medium-term prognoses, although it is not superior to the CTP score. Therefore, the CTP score remains an excellent tool for outcome prediction in patients with cirrhosis, and greater attention to variceal status may be in veins, even for patients with a history of variceal bleed or medium/large varices.

Abbreviations: AIH = autoimmune hepatitis, AST = aspartate aminotransferase, AUC = area under the receiver operating characteristic curve, BUN = blood urea nitrogen, CI = confidence interval, CTP = Child–Turcotte–Pugh, CTPK = Child–Turcotte–Pugh–Kumar, HR = hazard ratio, INR = international normalized ratio, IQR = interquartile range, LT = liver transplant, PBC = primary biliary cholangitis, ROC = receiver operating characteristic, TIPS = transjugular intrahepatic portosystemic shunt, WBC = white blood cell.

Keywords: liver cirrhosis, predictive scores, prognosis

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1. Introduction

The Child–Turcotte–Pugh (CTP) score was developed in 1964 to evaluate the severity of liver dysfunction and predict survival in cirrhotic patients.[1] Due to its briefness and fairly good predictive value, it is widely used worldwide to evaluate liver function, predict outcomes, and optimize organ allocation for cirrhotic patients.[2–5] Gastroesophageal varices are one of the most common and severe complications of cirrhosis, and the presence of gastroesophageal varices is often correlated with severity. Indeed, the prevalence of esophageal varices reaches as high as 80% to 90%.

Hemorrhage occurs at a yearly rate of 5% to 15% and is associated with a mortality of at least 20% at 6 weeks despite significant improvements in its early diagnosis and treatment.[6–8] Gastric varices are present in 5% to 33% of patients with portal hypertension, with a lower incidence of hemorrhage but higher mortality.[9,10] Consistent with our own data, variceal hemorrhage remains the main cause of hospitalization,[11] although this complication is not included in the classical CTP score. To our

knowledge, there have been few reports on predictive scores that include variceal status for outcome prediction in cirrhosis patients.[12] Whether the incorporation of variceal status improves the predictive ability of the CTP score, particularly for those with a history of variceal bleed or medium/large varices, remains unknown.

Initially proposed by Kumar et al,[12] the Child–Turcotte–-Pugh–Kumar (CTPK) score is obtained by adding the points for variceal status to the CTP score and was shown to predict short-term and medium-term mortality in cirrhotic patients.[12] The authors, however, did not take all possible factors affecting the prognosis into account to adjust the influence of potential confounders when evaluating the accuracy of this score in their cohort, likely resulting in bias in their research. Therefore, we assessed the ability of the CTPK score compared to the CTP score to evaluate short-term and medium-term prognosis in a cohort of Chinese patients with cirrhosis.

2. Materials and methods

2.1. Patient population

This study was a retrospective analysis of 253 hospitalized patients with cirrhosis who were in the Department of Gastroenterology and Hepatology of West China Hospital affiliated with Sichuan University from January 1, 2014 to December 31, 2014. Their medical profiles, including patient demographics and underlying diseases, were analyzed. The primary exclusion criteria included patients with acute liver damage, hepatocellular carcinoma, and serious diseases in other systems. A total of 351 consecutive patients with cirrhosis were analyzed in the primary cohort. After we verified the medical information in our database, we excluded patients with previous transjugular intrahepatic portosystemic shunt (TIPS) placement before admission (n=4), those who had undergone liver transplant (LT) (n=4), and patients with incomplete medical profiles (n=23). The natural history and outcome of the remaining 320 patients were assessed for at least 12 months by telephone. Of the 320 patients, 5 patients died of other diseases, and 62 patients were lost to follow-up. Ultimately, 253 patients with cirrhosis were enrolled in our final cohort for retrospective analysis (Fig. 1). The demographics and clinical

Figure 1. Flow chart of cirrhotic patients admitted to our hospital between January 1, 2014 and December 31, 2014 and selection of the study cohort. TIPS=transjugular intrahepatic portosystemic shunt.

features of the 62 patients were not significantly different from the final cohort of 253 candidates (data not shown).

2.2. Clinical data

Baseline clinical characteristics of all patients were obtained at admission. Measurements of baseline laboratory parameters were performed immediately in urgent cases or the morning after admission. The results of endoscopy or computed tomography (CT) were acquired as soon as possible. Survival was evaluated at 3 and 12 months via direct phone call and/or assessment of medical records in our database. The main end point was 3- and 12-month mortality.

2.3. Calculation of CTP and CTPK

The CTP score was calculated using the standard equation.[1] We determined the CTPK score by adding the points for variceal status into the classical CTP score as follows: history of variceal hemorrhage present, 3 points; no history of variceal hemorrhage but medium/large varices present, confirmed by endoscopy, 2 points; and no history of variceal hemorrhage with small or absent varices, confirmed by endoscopy, 1 point. In most centers, esophageal varices are classified into 3 sizes: small, medium, or large. Small varices are generally defined as minimally elevated veins above the esophageal mucosal surface, straight or slightly tortuous, <3 mm, and without red-color signs. Medium varices are defined as straight small-calibered or slightly tortuous varices, 3 to 6 mm, with red color signs or ridgy tortuous without red-color signs. Large varices are defined as markedly enlarged, nodular, or tumor-shaped varices, >6 mm, with or without red-color signs. Gastric varices were classified as follows: <5, 5–10, and >10 mm. Therefore, the CTPK score had maximum and minimum values of 18 and 6, respectively.[12]

All data were corroborated with the hospital records. The study was approved by Ethic committee of West China hospital. All subjects provided written informed consent before enrollment.

2.4. Statistical analysis

We performed statistical analyses on a retrospective basis. Descriptive statistics are displayed as the mean ± SD and median [interquartile range (IQR)], and categorical variables are reported as counts and percentages. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on Cox proportional hazards regression models. Univariate Cox proportional hazards regression analysis was used to evaluate the influence of demographic data, laboratory values, complications, premedication, and discharge medication on patient outcomes. Variables displaying a statistical significance on the univariate analysis were incorporated into a multivariate Cox proportional hazards regression analysis. To assess the predictive value of the 2 scores in predicting the risk of mortality at 3 and 12 months, receiver operating curve (ROC) analysis was performed, and the area under the ROC curves (AUC) for each score was obtained. The cumulative survival at 12 months by tertile ranges was performed using Kaplan–Meier analysis. Pearson correlation test was structured to evaluate the correlation between the 2 scores. $P < 0.05$ was considered statistically significant. All statistical analyses were computed with SPSS for Windows version 22.0 release and MedCalc for Windows version 11.4.2 (MedCalc Software, Mariakerke, Belgium).
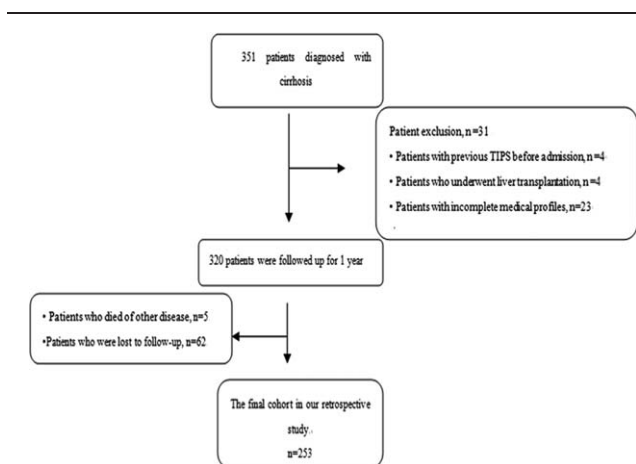
Table 1

Clinical characteristics and demographics of cirrhosis.

Variables	
Age, y [median (IQR)]	51 (43–61)
Sex (male/female)	186:67
Laboratory values	
Total bilirubin, μmol/L [median (IQR)]	24.2 (15.8–36.7)
Creatinine, μmol/L [median (IQR)]	73.4 (61.9–86)
Blood urea nitrogen, mmol/L [median (IQR)]	5.7 (4.4–8.7)
White blood cell, ×10^9/L [median (IQR)]	4.3 (2.8–7.4)
Platelet, ×10^9/L [median (IQR)]	71 (49–108.5)
Hemoglobin, g/L [median (IQR)]	90 (69–110)
Albumin, g/L (mean ± SD)	32.4 ± 5.4
Cholesterol, mmol/L [median (IQR)]	3.0 (2.5–3.8)
Prothrombin time, s [median (IQR)]	14.7 (13.3–16.4)
International normalized ratio [median (IQR)]	1.3 (1.2–1.5)
Sodium, mmol/L [median (IQR)]	139.2 (135.9–141.5)
Complication at admission	
Encephalopathy [n (%)]	12 (4.7%)
Ascites	
Absent/modicum/medium-massive	74/94/85
Variceal status	
a/b/c	27/32/194
Medical history	
History of variceal bleeding [n (%)]	155 (61.3%)
History of encephalopathy [n (%)]	16 (6.3%)
Active bleeding [n (%)]	81 (32.0%)
Prehospitalization therapy	
Etiological therapy [n (%)]	104 (41.1%)
Splenectomy/splenic embolization [n (%)]	33 (13.0%)
Devascularization [n (%)]	12 (4.7%)
Endoscopic therapy [n (%)]	48 (19.0%)
Discharge therapy	
Etiological therapy [n (%)]	182 (72.0%)
Heteropathy [n (%)]	251 (99.2%)

IQR = interquartile range, SD = standard deviation.

Variceal status: (a) no history of variceal bleed with small or absent varices; (b) no history of variceal bleed but medium/large varices present; (c) history of variceal bleed present.

3. Results

3.1. Clinical characteristics of the patients

The mean age of the patients was 51 years, with 186 males and 67 females. A majority of patients were Han Chinese (97.2%). The etiology of cirrhosis was hepatitis B virus (HBV) in 121 (47.8%), alcohol-related in 46 (18.2%), immunological in 23 (9.1%), hepatitis C virus (HCV) in 10 (4.0%), and other in 53 (20.9%) patients. Ascites and hepatic encephalopathy occurred in 179 (70.8%) and 12 (4.7%) of the 253 patients, respectively. The distributions of the patients' baseline data are presented in Table 1.

3.2. Factors associated with mortality at 3 and 12 months

At 3 and 12 months, the cumulative percentage of deaths was 9.1% (n = 23) and 13.8% (n = 35), respectively. Factors associated with mortality at 3 and 12 months were explored with multivariate Cox proportional hazards analyses. Because the CTPK score contains 5 components and the variceal status, these factors were not entered into the Cox proportional hazards analyses. Significant univariate associations with 3-month mortality included blood urea nitrogen (BUN), international normalized ratio (INR), white blood cell (WBC), sodium, CTPK score, history of encephalopathy, etiological therapy, and heteropathy after discharge. Significant univariate associations with 1-year mortality included creatinine, BUN, INR, WBC, aspartate aminotransferase (AST), sodium, CTPK score, history of encephalopathy, and etiological therapy after discharge (Table 2). However, in the multivariate analysis, only the CTPK score and etiological therapy after discharge were associated with both 3- and 12-month outcomes. Therefore, there was an independent association between CTPK score and survival for both short-term and intermediate-term prognosis (HRs adjusted for all covariates were 1.379 and 1.642, respectively).

Table 2

Univariate and multivariate analyses of the relationships between clinical characteristics, cirrhosis conditions, and death.

	β	Stand error	Hazard ratio	P	β	Stand error	Hazard ratio	P
3-month risk of death								
At admission								
Blood urea nitrogen, mmol/L	0.099	0.025	1.104	<0.001	0.050	0.039	1.052	0.194
International normalized ratio	2.133	0.462	8.436	<0.001	0.287	0.771	1.345	0.700
White blood cell, ×10^9/L	0.08	0.031	1.083	0.010	−0.032	0.055	0.969	0.564
Sodium, mmol/L	−0.079	0.034	0.924	0.020	−0.040	0.039	0.961	0.311
CTPK	0.429	0.082	1.536	<0.001	0.321	0.124	1.379	0.009
History of encephalopathy	−1.245	0.550	0.288	0.024	−0.608	0.627	0.544	0.332
Discharge therapy								
Etiological therapy	1.306	0.421	3.690	0.002	1.062	0.451	2.892	0.018
Heteropathy	2.14	1.025	8.501	0.037	1.050	1.046	2.857	0.316
12-month risk of death								
At admission								
Creatinine, μmol/L	0.014	0.004	1.014	<0.001	0.003	0.007	1.003	0.688
Blood urea nitrogen, mmol/L	0.090	0.023	1.095	<0.001	0.029	0.036	1.029	0.427
International normalized ratio	1.902	0.400	6.698	<0.001	−0.968	0.904	0.380	0.284
White blood cell, ×10^9/L	0.077	0.026	1.080	0.003	−0.026	0.046	0.974	0.573
Aspartate transaminase, IU/L	<0.001	<0.001	1.00	0.011	<0.001	<0.001	1	0.855
Sodium, mmol/L	−0.086	0.027	0.917	0.001	−0.035	0.032	0.965	0.267
CTPK	0.445	0.067	1.560	<0.001	0.496	0.132	1.642	<0.001
History of encephalopathy	−1.303	0.449	0.272	0.004	−0.645	0.492	0.525	0.189
Discharge therapy								
Etiological therapy	0.763	0.342	2.144	0.026	0.775	0.368	2.171	0.035

CTPK = Child–Turcotte–Pugh–Kumar.

The hazard ratios reflect the risk of the death for the exposure variable. Variables that were significant (P < 0.05) in the univariate analysis were included in the multivariate analysis.
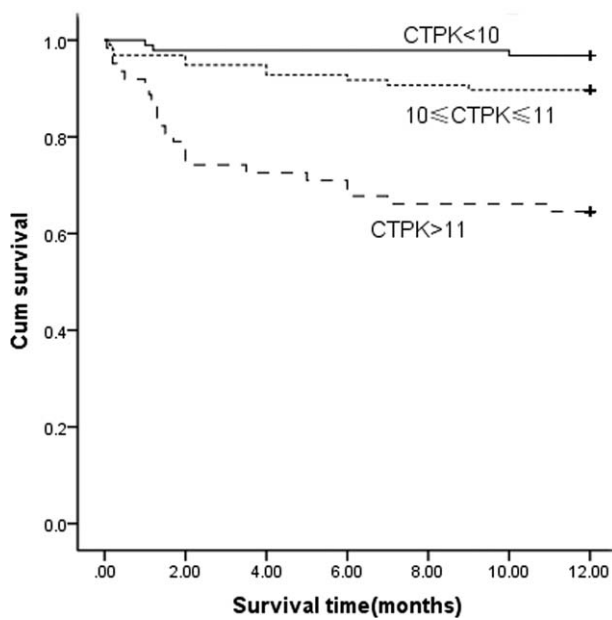
Figure 2. Kaplan–Meier fractional survival curves using the quartiles identified by the distribution of CTPK for 12 months and compared by log-rank test.

3.3. Comparison of different groups by CTPK scores

To assess the potential heterogeneity of the effect of CTPK score on 12-month mortality, we performed subgroup analyses by tertile ranges as follows: $CTPK < 10$, $10 \leq CTPK \leq 11$, and $CTPK > 11$, According to these tertiles, the survival curve by log-rank test is shown in Fig. 2 ($P < 0.001$). These results suggest that the CTPK score can discriminate between patients who will survive and those who will die within 12 months.

3.4. Predictive capacity of the CTPK compared to CTP

After 3 months of enrollment, the AUCs of CTPK and CTP were 0.814 and 0.838, respectively. After 12 months of enrollment, the AUCs of CTPK and CTP were 0.825 and 0.840, respectively. Both the CTPK score and the CTP score displayed prognostic value in cirrhotic patients, and the predictive ability of the CTP

score was superior to the CTPK score; however, there was no significant difference based on the Z test (Fig. 3).

3.5. Correlation between the CTPK and CTP

Positive correlations were observed between the CTP and CTPK ($r = 0.943$, $P < 0.001$).

4. Discussion

The determination of prognosis is an important part of the evaluation in cases of cirrhosis, helping physicians provide information to patients and guide clinical approaches. The CTP score has been widely used worldwide and has demonstrated superiority for predicting outcomes of cirrhotic patients or stratifying the risk of death for patients awaiting LT.[3,4] The model for end-stage liver disease (MELD) score and MELD-based scores have been proposed by scholars over the years and also have been proven effective for predicting outcomes or prioritizing the assignment of LT.[13–17] However, adequate research is lacking regarding the status of varices as a factor when the short-term and intermediate-term prognosis of cirrhotic patients is evaluated. Thus, we investigated whether adding variceal status to the CTP score would be beneficial for the prognosis of cirrhotic patients in the present study.

Our findings suggest that both the CTP score and the CTPK score precisely predict the prognosis of patients with cirrhosis for short and intermediate periods, and the comparisons of predictive ability showed no significant differences. Kumar et al[12] originally proposed the CTPK score as a predictive method in patients with cirrhosis. According to their findings, the CTPK score performed significantly better than the CTP score in predicting early mortality, particularly at 1 and 2 weeks in cirrhotic patients, whereas the AUCs of CTPK scores in predicting 3- and 12-month mortality were less than 0.8. Our findings are not consistent with these previous results, and the discrepancy between studies may be interpreted based on the following considerations. First, we did not perform an analysis of the CTPK score for predicting early mortality because only 7 patients died within 2 weeks. Second, the discrepancy may be related to the severity of cirrhosis cases included. Data on consecutive cirrhotics who died in the unit within 2 years were analyzed in the study by Kumar et al, whereas a total of 253
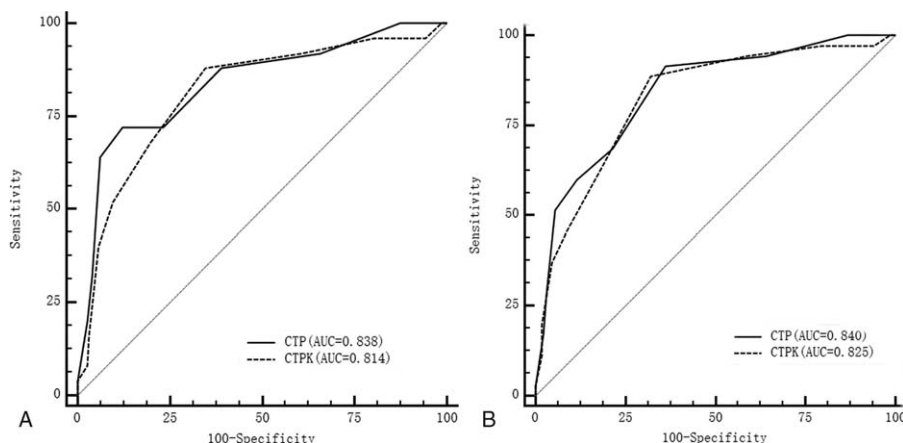

Figure 3. The area under the receiver operating characteristic curve (AUC) of CTP and CTPK. (A) At 3 months of enrollment; (B) at 1 year of enrollment. The comparisons between CTP and CTPK at 3- and 12-month showed no significant differences ($P > 0.05$).

patients with cirrhosis who were treated in our 4950-bed teaching hospital affiliated with Sichuan University were enrolled in the present study. Third, potential confounders, including medical history, laboratory characteristics, premedication, and discharge medication (e.g., abstinence, antiviral therapy, and heteropathy), and complications were entered into the Cox proportional hazards model, supporting our findings. As the fact that, HBV is the major cause of liver cirrhosis in China, here, a subgroup analysis was analyzed among those with hepatitis B infection, and the result stayed the same (data not shown). We also found that etiological therapy after discharge was an independent factor associated with 3- and 12-month mortality, which was consistent with previous studies.[18–20]

Our data showed that the cumulative percentage of deaths was 9.1% and 13.8% at 3 and 12 months, respectively, which was lower than that reported previously.[21] Furthermore, 9.1% of liver cirrhosis in our cohort was induced by autoimmune liver diseases, including primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and PBC-AIH overlap syndrome, indicating that autoimmune liver diseases should be evaluated before a diagnosis of "cryptogenic cirrhosis." Early diagnosis and treatment for these cirrhotics could improve survival without LT.[22,23]

Although promising results were obtained in our study, certain limitations should be noted. First, because our investigation was a single-center observational study, confounding factors were relatively difficult to avoid. Second, with the limitation of sample size and the relatively short follow-up period, additional well-designed prospective studies with larger sample sizes are required, particularly for predicting early mortality in cirrhosis cases. In fact, this study did not demonstrate a causal relationship between admission CTPK scores or CTP scores and prognosis. Our data demonstrate that the incorporation of variceal status into the CTP score did not perform better than the classical CTP score, although the variceal status is an important factor for cirrhotic patients. We deemed possible reasons why CTPK score showed no superiority as scoring system compared to the classical CTP score. First, the CTP score was an excellent tool for evaluating liver cirrhosis, although our comparison achieved a noninferiority result which did not mean CTPK score was less effective, from a statistical point of view. On the other hand, because the variceal status differed, a large portion of patients in our cohort underwent primary or secondary prevention for bleeding during the follow-up period, which may have reduced variceal hemorrhage and related mortality and then the utility of the CTPK score.[8,10]

In conclusion, our findings demonstrate that the CTP score is an excellent score for outcome prediction in Chinese patients with cirrhosis, and with features of invasive way and expensiveness, greater attention to variceal status may be redundant, even for those with a history of variceal bleed or medium/large varices. Thus, the relationship between the CTPK score and long-term prognosis is unclear, and further prospective validation of this score is warranted to provide more robust evidence.

Acknowledgment

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