Original Article

Usefulness of the estimation of physiologic ability and surgical stress (E-PASS) system for prediction of complication and prognosis in hepatocellular carcinoma patients after hepatectomy

Yili Dai[1#], Guoqiao Chen[1,2#], Yongle Chen[1#], Zhaoqi Shi[1], Junhai Pan[1], Xiaoxiao Fan[1], Hui Lin[1]

[1]Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China; [2]Department of Emergency Medicine, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Contributions: (I) Conception and design: X Fan; (II) Administrative support: H Lin; (III) Provision of study materials or patients: Z Shi, J Pan; (IV) Collection and assembly of data: Y Chen, Z Shi, J Pan; (V) Data analysis and interpretation: G Chen, Y Chen, Y Dai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xiaoxiao Fan, MD; Hui Lin, PhD. Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, 3 East Qingchun Rd., Hangzhou 310016, China. Email: fanxx_gs@zju.edu.cn; 369369@zju.edu.cn.

Background: Estimation of physiologic ability and surgical stress (E-PASS) system was verified in predicting postoperative complications or mortality in many surgical operations. This research aimed to investigate whether the E-PASS system could predict postoperative complications and was related with long-term prognosis in primary hepatocellular carcinoma (HCC) patients.

Methods: A total of 236 HCC patients who underwent liver resection were collected in this study. We performed univariate analyses to determine the potential risk factors for complications after hepatectomy. The potential independent risk factors were then included in the logistic regression for multivariable analysis. The optimal cutoff value of Comprehensive Risk Score (CRS) was identified by a receiver operating characteristic (ROC) curve. Based on this value, the patients were divided into two groups to investigate the relation between CRS with postoperative complications. The relation between CRS and overall survival (OS) or recurrence-free survival (RFS) was analyzed further in these two groups.

Results: Postoperative complications occurred in 79 patients. Multivariable analysis suggested that CRS was independent factor for predicting postoperative complications (P<0.001). The optimal CRS cutoff value in our study was 0.126. Patients with high Preoperative Risk Score (PRS) had a higher rate of postoperative complications occurrence, both major and mild complications (P<0.001). Our study showed that HCC patients with higher CRS had poorer survival prognosis [hazard ratio (HR): 3.735, 95% confidence interval (CI): 1.200–11.631, P=0.023]. The 3-year OS rate of high CRS group (CRS ≥0.126) and low CRS group (CRS <0.126) were 66.2% vs. 84.8% (P<0.001), respectively.

Conclusions: For HCC patients after liver resection, E-PASS was an effective predictive system for evaluating the risks of postoperative complications and may can predict prognosis in long term.

Keywords: Estimation of physiologic ability and surgical stress (E-PASS); postoperative complication; hepatocellular carcinoma (HCC); prognosis

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Introduction

Globally, liver cancer ranks the sixth cancer incidence and is the fourth leading cause of cancer related-death (1). As the most common pathological type of liver malignant tumor, hepatocellular carcinoma (HCC) accounts for 70–80% of all cases (2). The prognosis of HCC patients depends on the tumor staging, benefits of interventions and individual's physical characteristics (3,4). Surgeries, including hepatic resection and liver transplantation, are considered to be the backbone of curative treatment, especially in patients with early-stage HCC (5). Undoubtedly, most patients have to choose surgical resection because of the organ rejection and the shortage of available donors. However, around 90% of HCC patients developed in a background of liver cirrhosis, and the mortality of cirrhotic patients after surgical resection is estimated between 3 and 14% (6,7).

The purpose of surgical treatment is to improve the prognosis of HCC patients, so the risk of postoperative complications or death after hepatectomy deserves the attention of surgeons. Though remarkable development in surgical technique and perioperative management have significantly reduced postoperative mortality or morbidity in HCC patients undergoing hepatectomy, the incidence of postoperative complications after hepatectomy are still higher than other oncologic operations (8,9). Post-hepatectomy liver failure is a serious complication after hepatectomy and the leading cause of postoperative death in patients with incidence rates ranging from 0.7% to 34% (10). Other common but serious complications include hemorrhage, biliary fistula, pneumonia, ascites, abdominal abscess, organ dysfunction and so on. Therefore, it is extremely matters to evaluate and identify the high-risk patients after hepatectomy rapidly and intuitively.

In 1999, Haga *et al.* (11) proposed E-PASS system in predicting postoperative morbidity and mortality after gastrointestinal surgery. The E-PASS system took preoperative factors [Preoperative Risk Score (PRS)] and surgical factors [Surgical Stress Score (SSS)] into account, whose efficiency has been validated in many surgical operations, such as in gastrointestinal and pancreatic surgery (12-15). The duration of surgery and portal occlusion are also thought to be associated with the occurrence of complications after hepatectomy (16,17). Given that the E-PASS system comprehensively assesses individual's physiological state and surgical stress, it may predict postoperative morbidity after hepatectomy. Banz *et al.* (18) reported that for patients undergoing liver resection due to various etiologies, the E-PASS system seems to be an effective predictor of postoperative mortality, but not suitable for postoperative complications. In another research (19), only PRS may be associated with systemic complications after hepatectomy.

Therefore, the purpose of this research was to verify whether the E-PASS system can predict occurrence of postoperative complication in HCC patients. Meanwhile, we explored the relationship between the E-PASS system and the long-term prognosis of such patients. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-352/rc).

Methods

Patients

We retrospectively analyzed patients who underwent hepatectomy for liver tumors in Sir Run Run Shaw Hospital, Zhejiang University from January 2018 to December 2019. The inclusion criteria were as follows: (I) the patient was diagnosed as primary HCC in postoperative pathological examination; (II) complete examination results, hospitalization records and follow-up records required for the study were available; (III) the age was more than 18 years old. The exclusion criteria were as follows: (I) the postoperative pathological diagnosis was other intrahepatic tumors or metastatic hepatic cancer; (II) undergone liver resection for any disease previously; (III) diagnosed as HCC preoperatively and suffered adjuvant therapy such as transarterial chemoembolization; (IV) data was incomplete or lost follow-up. The ways of follow-up were based on telephone connections and outpatient examinations. The last time of follow-up was September 2021 and the median fellow-up time was 27 months (range, 1 to 44 months). A total of 236 cases were eventually analyzed in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University, Hangzhou, China (No. 20210729-282). Individual consent for this retrospective analysis was waived.

Data collection

Baseline characteristics of patients, including age, gender, body mass index (BMI), chronic diseases. Preoperative laboratory data includes hemoglobin, lymphocyte, neutrophil, platelet, albumin, total bilirubin, alpha-fetoprotein (AFP), C-reactive protein (CRP) and hepatitis B virus surface antigen were completely collected. The estimated bleeding volume and operation time were obtained according to the operation notes. The cancer stage was determined according to the eighth edition of the American Joint Committee on Cancer (AJCC) and Barcelona Clinic Liver Cancer (BCLC) staging system (20,21). Postoperative complications were defined as complications that occurred before discharge or within 1 month after discharge and related to the surgery. Meanwhile, according to the Clavien-Dindo classification (22), complications of Clavien-Dindo grade II were defined as mild complications, while Clavien-Dindo grades III–IV were classified into major complications.

E-PASS system, prognostic nutritional index (PNI) and albumin-bilirubin index (ALBI)

The equations of the E-PASS system were developed from a previous study (11).

$$PRS = -0.0686 + 0.00345X_1 + 0.323X_2 + 0.205X_3 + 0.153X_4 + 0.148X_5 + 0.0666X_6 \quad [1]$$

X1: age; X2: the absence [0] or presence [1] of severe heart disease; X3: the absence [0] or presence [1] of severe pulmonary disease; X4: the absence [0] or presence [1] of diabetes mellitus; X5: the performance status (PS) index (range, 0 to 4); X6: the American Society of Anesthesiologists (ASA) physiologic status classification (range, 1 to 5).

Severe heart disease is defined as heart failure meeting the NYHA Class III or IV or severe arrhythmia requiring mechanical support (23). Severe pulmonary disease is defined as any condition of vital capacity (VC) <60% and/or forced expiratory volume in 1 second (FEV_1) <50%. Diabetes mellitus is defined according to the World Health Organization criteria (24). The PS index is defined according to the Japan Society for Cancer Therapy, which is similar to the Eastern Cooperative Oncology Group (ECOG) criteria (25): grade 0, without symptoms or restriction in social activities; grade 1, mild symptoms that restrict physically strenuous activity; grade 2, capable of all self-care but unable to carry out any activities; grade 3, in need of physical assistance for daily living; grade 4, requirement of constant physical assistance without any self-care ability. The ASA physiologic status classification: class 1, a healthy patient; class 2, a patient with mild systemic disease; class 3, a patient with severe systemic disease without life threat; class 4, a patient with severe systemic disease that is a threat to life; class 5, a patient who is expected to die in 24 hours with or without surgery (26).

$$SSS = -0.342 + 0.0139X_1 + 0.0392X_2 + 0.352X_3 \quad [2]$$

X_1 = estimated blood loss/body weight (mL/kg). X_2 = operation time (h). X_3 = extent of skin incision: laparotomy plus thoracotomy [2], laparotomy [1], laparoscopy [0].

$$\textit{Comprehensive Risk Score } (CRS) = -0.328 + 0.936 \times PRS + 0.976 \times SSS \quad [3]$$

The calculation formula of PNI:

$$PNI = \textit{serum albumin}(g/L) + 0.005 \times \textit{lymphocyte count}(\textit{per } mm^3) \quad [4]$$

The calculation formula of ALBI (27,28):

$$ALBI = 0.66 \times \log_{10}\left[\textit{total bilirubin}(\mu mol/L)\right] - 0.085 \times \textit{albumin}(g/L) \quad [5]$$

Statistical analysis

Continuous variables were presented as median (range) or mean ± standard deviation (SD) and analyzed by the Mann-Whitney U test or the Student's *t*-test. Categorical variables were presented as numbers (percentage) and analyzed by the Pearson's chi-square test or the Fisher's exact test. Factors with statistically difference between the complication group and non-complication group were further included in the logistic regression analysis. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were constructed to select an optimal critical value according to the incidence of postoperative complications. Cox proportional hazards model was applied to analyze the impact of univariate or multivariate on overall survival (OS) and recurrence-free survival (RFS). Survival curve was analyzed by Kaplan-Meier method and log-rank test was used for further comparison. The inverse variance method was performed for dichotomous variables and the effect measure was odds ratio (OR) with 95% confidence interval (CI). Statistical difference was considered to be significant at P<0.05. The software tools of statistical analyses were conducted by SPSS 22.0 (Armonk, NY, USA: IBM Corp.).

Results

Characteristics of patients in two groups

A total of 236 patients diagnosed pathologically as primary HCC and underwent radical surgery were included in this study. According to the presence or absence of postoperative complications, these patients were divided into two groups. The baseline characteristics and preoperative laboratory data of each group are shown in *Table 1*. Seventy-nine (33.5%) patients suffered from postoperative complications after surgery while 157 (66.5%) did not. Most of baseline data and baseline characteristics including age, gender, BMI, concurrent diseases showed no significant differences between two groups. However, total bilirubin and ALBI were significantly different between two groups (19.0±8.3 *vs.* 15.3±6.9, P<0.001; −2.58±0.37 *vs.* −2.69±0.42, P=0.046, respectively). In E-PASS system, patients suffered postoperative complication had higher SSS and CRS [0.047 (−0.267 to 1.118) *vs.* −0.180 (−0.297 to 0.450), P<0.001; 0.169 (−0.351 to 1.159) *vs.* −0.128 (−0.421 to 0.686), P<0.001, respectively]. PRS showed no significant difference between complication group and non-complication group. Notably, maximum diameter of tumors was different in two groups, which was larger in patients with higher postoperative complications rate [4.5 (1.0–15.5) *vs.* 3.4 (0.7–15.0), P=0.012].

Multivariable analysis and ROC curve of the CRS

As shown in *Table 2*, multivariable analysis showed that CRS (OR: 26.556, 95% CI: 7.823–90.147, P<0.001) was independent risk factors for postoperative complications in HCC patients. Furthermore, the ROC curve based on presence of postoperative complications were plotted in order to determine an optimal critical value of the CRS. As shown in *Figure 1*, the AUC was 0.732. The highest Youden index was 0.383 with the corresponding cutoff value of the CRS as 0.126.

Comparison between the high and low CRS groups

According to the critical value of CRS calculated previously (0.126), HCC patients were further divided into the low CRS group and the high CRS group. Eight-three (35.2%) patients were included in high CRS group while 153 (64.8%) were in low CRS group.

Table 3 shows demographic characteristics between these two groups. Several parameters of E-PASS were statistically different between two groups, including age (P<0.001), diabetes mellitus (P<0.001), PS (P<0.001), ASA (P<0.001), blood loss (P<0.001), operation time (P<0.001) and extent of skin incision (P<0.001). High CRS group had higher PRS [0.454 (0.216–1.224) *vs.* 0.289 (0.144–0.670), P<0.001] and SSS [0.204 (−0.267 to 1.118) *vs.* −0.182 (−0.297 to 0.292), P<0.001]. In addition, patients in high CRS group also had lower hemoglobin (P<0.001), albumin (P=0.009) and larger maximum tumor diameter (P<0.001).

As shown in *Table 4*, 46 (55.4%) patients in high CRS group suffered from different degrees of postoperative complications, which was significantly higher than that in low CRS group [33 (21.6%), P<0.001]. As to mild complications (Clavien-Dindo Grade II), the incidence was 55.4% in the high CRS group and 15.0% in the low CRS group (P<0.001), including postoperative blood transfusion [26 (31.3%) *vs.* 12 (7.8%), P<0.001], high fever after surgery (>38.5 ℃) [13 (15.7%) *vs.* 6 (3.9%), P<0.001], deep venous thrombosis or pulmonary embolus [11 (13.3%) *vs.* 2 (1.3%), P<0.001] and superficial infections [4 (4.8%) *vs.* 0, P=0.015]. However, there is no statistical difference in the incidence of atrial fibrillation (P=0.524). In major complications (Clavien-Dindo grade III to grade V), the incidence was higher in high CRS group than another group [28 (33.7%) *vs.* 13 (8.5%), P<0.001)], including pneumonia [6 (7.2%) *vs.* 2 (1.3%), P<0.024], intra-abdominal infection [7 (8.4%) *vs.* 0, P=0.001], puncture in thoracic or abdominal effusion [20 (24.1%) *vs.* 9 (5.9%), P<0.001], postoperative hemorrhage [6 (7.2%) *vs.* 1 (0.7%), P=0.008], Single or multiple organs dysfunction [5 (6.0%) *vs.* 1 (0.7%), P=0.021] and dead case [6 (7.2%) *vs.* 0, P=0.002]. Biliary fistula or shock showed no difference statistically (P=0.123, P=0.348 respectively).

Analyses of possible factors in relation to RFS and OS

As presented in *Table 5*, in univariate analysis of RFS, only maximum tumor diameter was the predictor (HR: 1.090, 95% CI: 1.013–1.172, P=0.021). In univariate analysis of OS, nine factors including CRS were considered significant. Before multivariate analyses, we excluded two variables (albumin and SSS). In the end, CRS (P=0.023) and maximum tumor diameter (P<0.001) were

Table 1 Characteristics between complication group and non-complication group

Characteristics	Complication (+) (n=79)	Complication (–) (n=157)	P
Age (years)	61.0±11.4	59.1±10.8	0.210
Gender (male/female)	67/12	132/25	0.884
Weight (kg)	64.3±11.7	64.6±9.7	0.826
BMI (kg/m^2)	23.1±3.3	23.2±2.9	0.868
Hypertension (with)	33 (41.8)	50 (31.8)	0.132
Diabetes mellitus (with)	18 (22.8)	21 (13.4)	0.066
Hemoglobin (g/L)	140.9±17.2	139.2±16.6	0.453
Lymphocyte count (×10^9/L)	1.5±0.7	1.6±0.7	0.702
Neutrophils count (×10^9/L)	3.1±1.2	3.4±1.4	0.061
Platelet (×10^9/L)	142.1±65.8	149.7±56.7	0.385
Albumin (g/L)	40.0±4.5	40.6±5.0	0.374
Total bilirubin (μmol/L)	19.0±8.3	15.3±6.9	<0.001
PT (s)	13.8±0.9	13.8±1.0	0.939
INR	1.06±0.07	1.06±0.07	0.939
ALBI	–2.58±0.37	–2.69±0.42	0.046
PNI	47.6±6.1	48.0±6.5	0.637
CRP (mg/L)	1.8 (0.2–86.2)	1.3 (0.1–59.5)	0.102
AFP (ng/mL)	18.3 (1.5–251,299.0)	26.4 (1.0–114,971.0)	0.833
HBV surface antigen (with)	62 (78.5)	13 (8.3)	0.981
Cirrhosis (with)	52 (65.8)	109 (69.4)	0.575
Child-Pugh grade A	74 (93.7)	152 (96.8)	0.258
Maximum tumor diameter (cm)	4.5 (1.0–15.5)	3.4 (0.7–15.0)	0.012
PRS	0.423 (0.114–1.162)	0.389 (0.168–1.224)	0.054
Performance status (0 or 1)	68 (86.1)	142 (90.4)	0.312
ASA physiologic status (1 or 2)	72 (91.1)	148 (94.3)	0.367
SSS	0.047 (–0.267 to 1.118)	–0.180 (–0.297 to 0.450)	<0.001
Estimated blood loss (mL)	500 (50–4,000)	200 (30–2,000)	<0.001
Operation time (min)	255 (100–650)	175 (60–400)	<0.001
Laparoscopy	48 (60.8)	128 (81.5)	0.001
CRS	0.169 (–0.351 to 1.159)	–0.128 (–0.421 to 0.686)	<0.001
BCLC (0/A/B/C)	12/49/11/7	38/94/17/8	0.302
TNM (I/II/III)	57/10/12	129/13/15	0.206

Data are expressed as number, number (%), median (range) or mean ± standard deviation. BMI, body mass index; PT, prothrombin time; INR, international normalized ratio; ALBI, albumin-bilirubin index; PNI, prognostic nutritional index; CRP, C-reactive protein; AFP, alpha-fetoprotein; HBV, hepatitis B virus; PRS, Preoperative Risk Score; SSS, Surgical Stress Score; CRS, Comprehensive Risk Score; ASA, American Society of Anesthesiologists; BCLC, Barcelona Clinic Liver Cancer stage; TNM, tumor node metastasis.

Table 2 Multivariable analysis of postoperative complications in patients undergoing surgery

Characteristics	Multivariate		
	OR	95% CI	P
Total bilirubin (μmol/L)	1.083	1.037–1.130	<0.001
Maximum tumor diameter (cm)	1.040	0.930–1.163	0.493
CRS	26.556	7.823–90.147	<0.001

CI, confidence interval; CRS, Comprehensive Risk Score; OR, odds ratio.

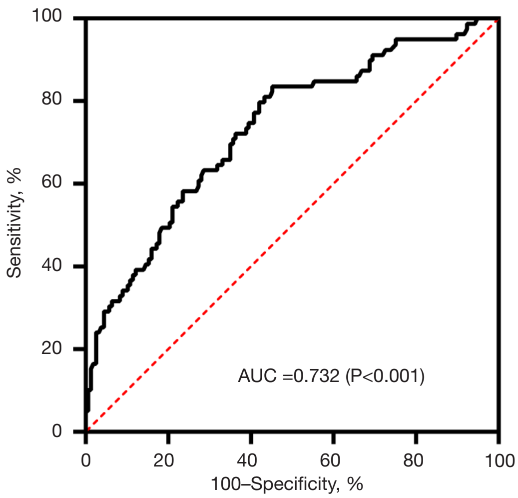

Figure 1 The ROC curve of CRS based on presence of postoperative complications. AUC, area under the curve; CRS, Comprehensive Risk Score; ROC, receiver operating characteristic.

significant independent predictors of OS. ALL cases were separated into two groups according to the cutoff value of CRS (0.126).

In RFS, there was no significant difference between two groups (P=0.897, *Figure 2A*). In OS, the 3-year OS of CRS high group (CRS ≥0.126) was 66.2% and CRS low group (CRS <0.126) was 84.8% (P=0.001, *Figure 2B*). In patients with TNM I, RFS showed no difference between CRS high group and low group (P=0.893, *Figure 2C*). Similarly, patients in staging TNM I with high CRS may had a worse long-term prognosis (P=0.001, *Figure 2D*). These results showed that the higher CRS was associated with worse OS.

Discussion

In this study, we assessed the predictive power of the E-PASS models in postoperative complications of HCC patients firstly. For these patients, our results revealed that the CRS of E-PASS system was associated with the occurrence of postoperative complications independently, indicating that a higher CRS was associated with a higher risk. HCC accounts for the vast majority of the liver malignancies. Surgical resection and liver transplantation have been the basic curative therapy in early-stage cases, with a 5-year survival up to 70–80% (5,29,30). Therefore, it is necessary to evaluate the risks and benefits of surgery for HCC patients.

E-PASS system which proposed by Haga *et al.* took preoperative factors (PRS) and surgical factors (SSS) into account, which has been proven to predict incidence of morbidity and mortality after digestive surgeries (11,12,31). In this system, PRS acts as a comprehensive assessment of the preoperative physiological state of patients. In our study, most of the cases were in low score of PS index or ASA physiologic status and seldom had severe heart or pulmonary disease. Therefore, physiologic risk of cases in our study were low, and PRS showed no difference between our two groups. Nanashima *et al.* (19) analyzed elderly HCC patients underwent operations, and PRS significantly differed between subgroups which divided by age. It was showed in previous study that operative risk is higher in elderly patients as deterioration of liver functions with age (32). In addition, elderly patients were usually accompanied by other diseases and higher risk of anesthesia (33). The weight of PRS in CRS cannot be ignored. Similar to other previous literature (13,14,34,35), the SSS which reflects the surgical stress had significant predictive ability between two groups in our study. Both operation time and blood loss were higher in groups suffered postoperative complication. Intraoperative blood loss has been reported as a postoperative predictor of liver failure and postoperative morbidity (36,37). Various host responses induced by surgical intervention were activated to maintain individual homeostasis. The balanced host defense mechanism may be destroyed if the surgical stress exceeds patient's reserve capacity. Considering that CRS mainly

Table 3 Characteristics between low CRS group and high CRS group

Characteristic	CRS <0.126 (n=153)	CRS ≥0.126 (n=83)	P
Age (years)	57.3±10.8	64.2±10.1	<0.001
Gender (male/female)	129/24	70/13	0.096
Weight (kg)	65.1±10.4	63.4±10.5	0.259
BMI (kg/m^2)	23.2±3.0	23±3.1	0.590
Hypertension (with)	47 (30.7)	36 (43.4)	0.052
Diabetes mellitus (with)	18 (11.8)	21 (25.3)	0.008
Hemoglobin (g/L)	142.6±15.5	134.6±17.8	<0.001
Lymphocyte count (×10^9/L)	1.5±0.7	1.4±0.6	0.103
Neutrophils count (×10^9/L)	3.3±1.3	3.3±1.5	0.891
Platelet (×10^9/L)	148.3±55.7	145.0±67.2	0.701
Albumin (g/L)	41.0±4.8	39.3±4.7	0.009
Total bilirubin (μmol/L)	16.7±7.4	16.2±7.9	0.634
PT (s)	13.8±1.0	13.8±0.9	0.604
ALBI	–2.7±0.4	–2.6±0.4	0.014
PNI	48.7±6.4	46.3±6.0	0.004
CRP (mg/L)	1.2 (0.1–46.6)	2.2 (0.1–86.2)	<0.001
AFP (ng/mL)	27.5 (1.0–114,971.0)	16.2 (1.2–251,299.0)	0.581
HBV surface antigen (with)	127 (83.0)	59 (71.1)	0.032
Cirrhosis (with)	107 (69.9)	54 (65.1)	0.443
Child-Pugh grade A	148 (96.7)	78 (94.0)	0.328
Maximum tumor diameter (cm)	3.2 (0.7–15.0)	5.4 (1.0–15.5)	<0.001
PRS	0.289 (0.144–0.670)	0.454 (0.216–1.224)	<0.001
Performance status (0 or 1)	151 (98.7)	59 (71.1)	<0.001
ASA physiologic status (1 or 2)	150 (98.0)	70 (84.3)	<0.001
SSS	–0.182 (–0.297 to 0.292)	0.204 (–0.267 to 1.118)	<0.001
Estimated blood loss (mL)	200 (30–1,500)	500 (50–4,000)	<0.001
Operation time (min)	180 (60–400)	250 (100–650)	<0.001
Laparoscopy	145 (94.8)	31 (37.3)	<0.001
CRS	–0.154 (–0.421 to 0.124)	0.301 (0.129 to 1.159)	<0.001
BCLC (0/A/B/C)	38/89/18/8	12/54/10/7	0.258
TNM (I/II/III)	124/17/12	62/6/15	0.049

Data are expressed as number, number (%), median (range) or mean ± standard deviation. BMI, body mass index; PT, prothrombin time; ALBI, albumin-bilirubin index; PNI, prognostic nutritional index; CRP, C-reactive protein; AFP, alpha-fetoprotein; HBV, hepatitis B virus; PRS, Preoperative Risk Score; SSS, Surgical Stress Score; CRS, Comprehensive Risk Score; ASA, American Society of Anesthesiologists; BCLC, Barcelona Clinic Liver Cancer stage; TNM, tumor node metastasis.

Table 4 Postoperative complication between high-CRS group and low-CRS group

Characteristic	CRS ≥0.126 (n=83), n (%)	CRS <0.126 (n=153), n (%)	P
Overall complications	46 (55.4)	33 (21.6)	<0.001
Mild complications (grade II)	46 (55.4)	23 (15.0)	<0.001
Postoperative blood transfusion	26 (31.3)	12 (7.8)	<0.001
Postoperative fever >38.5 ℃	13 (15.7)	6 (3.9)	<0.001
DVT or pulmonary embolus	11 (13.3)	2 (1.3)	<0.001
Atrial fibrillation	5 (6.0)	6 (3.9)	0.524
Superficial infections	4 (4.8)	0 (0)	0.015
Major complications (grade III to grade V)	28 (33.7)	13 (8.5)	<0.001
Pneumonia	6 (7.2)	2 (1.3)	0.024
Intra-abdominal infection	7 (8.4)	0 (0)	0.001
Biliary fistula	2 (2.4)	0 (0)	0.123
Puncture in thoracic or abdominal effusion	20 (24.1)	9 (5.9)	<0.001
Postoperative hemorrhage	6 (7.2)	1 (0.7)	0.008
Single organ dysfunction	5 (6.0)	1 (0.7)	0.021
Multiple organs dysfunction	5 (6.0)	1 (0.7)	0.021
Shock	3 (3.6)	2 (1.3)	0.348
Dead case	6 (7.2)	0 (0)	0.002

CRS, Comprehensive Risk Score; DVT, deep venous thrombosis.

reflect the patient's preoperative reserve capacities and surgical pressure comprehensively, it may be more accurate in predicting the occurrence of postoperative complications theoretically, which requires a larger sample of research to confirm. Preoperatively, by estimating the patient's SSS through previous similar operations and evaluating the PRS, the surgeon can get an approximate CRS, which could predict postoperative morbidity rates of surgical procedures. If an estimated CRS exceeds 1.0, the surgeon should consider revising the surgical plan to reduce the CRS and improve postoperative outcome (31). Haga *et al.* (11) indicated that the SSS potentially has a better correlation with postoperative complications than the PRS in younger patients, which means that SSS may bears more weight than the PRS in E-PASS system. Undoubtedly, surgeons should try their best to reduce the operation time and blood loss by optimizing operation process to minimize surgical stress.

Both tumor diameter and ALBI score were significant different between two groups. Larger tumors may be related to larger wounds and more bleeding, which could get a higher SSS and CRS. Comparing with Child-Pugh score, ALBI score was validated to stratify the risk of HCC patients undergoing liver resection more accurately (28,38). This score, comprised of serum bilirubin and albumin, acts as a liver function measuring model. E-PASS system does not include evaluation of liver function directly, thus restricting the applications of this system in liver operation. There is, however, up to 90% patients occurring HCC were in a background of cirrhosis (6,39). It was reported that liver resection in HCC patients of Child-Pugh B grade or accompanied by portal vein hypertension may resulted in a 5-year survival less than 50% and a perioperative mortality of 4% (40). Liver function evaluation preoperatively matters for patients undergoing liver resection. Except for ALBI score and Child-Pugh score, indocyanine green clearance has been used conventionally to assess liver function prior to resection (29). Using imaging technology as assessment tools for liver function have been reported, but the results are still not convincing (41). E-PASS system has been verified as an effective model for predicting postoperative morbidity and mortality. If E-PASS system could be combined with other indicators of liver function, its

Table 5 Univariate and multivariate analysis of prognostic factors of recurrence-free survival and overall survival in HCC patients

Variables	RFS		OS			
	Univariate, HR (95% CI)	P	Univariate		Multivariate	
			HR (95% CI)	P	HR (95% CI)	P
Age <65 years	1.061 (0.669–1.683)	0.801	1.089 (0.571–2.077)	0.796	–	–
Gender (female)	0.744 (0.383–1.444)	0.382	1.183 (0.546–2.564)	0.671	–	–
BMI (<25 kg/m²)	0.788 (0.490–1.266)	0.324	1.104 (0.541–2.251)	0.787	–	–
HBsAg (positive)	1.462 (0.820–2.605)	0.198	2.187 (0.858–5.575)	0.101	–	–
Cirrhosis (positive)	1.309 (0.800–2.142)	0.283	1.817 (0.867–3.808)	0.114	–	–
Albumin (<35 g/L)	1.635 (0.917–2.917)	0.096	2.619 (1.312–5.229)	0.006	–	–
Total bilirubin (<17.1 μmol/L)	1.011 (0.645–1.585)	0.961	1.429 (0.740–2.760)	0.288	–	–
AFP (<400 μg/L)	0.805 (0.465–1.394)	0.440	0.567 (0.284–1.132)	0.108	–	–
ALBI	1.376 (0.794–2.383)	0.255	2.517 (1.213–5.226)	0.013	0.917 (0.186–4.515)	0.915
PNI	0.976 (0.942–1.012)	0.185	0.935 (0.890–0.982)	0.008	0.955 (0.858–1.063)	0.401
PRS	0.989 (0.276–3.537)	0.986	1.493 (0.266–8.394)	0.649	–	–
SSS	1.329 (0.510–3.467)	0.561	10.066 (3.571–28.372)	<0.001	–	–
CRS	1.189 (0.548–2.579)	0.661	5.725 (2.288–14.320)	<0.001	3.735 (1.200–11.631)	0.023
Maximum tumor diameter (cm)	1.090 (1.013–1.172)	0.021	1.263 (1.170–1.363)	<0.001	1.179 (1.078–1.289)	<0.001
Tumor number (≥2)	1.283 (0.678–2.427)	0.443	1.273 (0.535–3.027)	0.585	–	–
Tumor thrombosis (positive)	1.096 (0.346–3.475)	0.876	2.724 (0.970–7.650)	0.057	–	–
Micro thrombosis	1.231 (0.634–2.390)	0.539	2.283 (1.089–4.785)	0.029	1.999 (0.771–5.183)	0.154
Postoperative TACE (positive)	0.649 (0.417–1.010)	0.055	1.487 (0.758–2.915)	0.248	–	–
TNM (I)	0.669 (0.406–1.102)	0.114	0.501 (0.262–0.956)	0.036	1.341 (0.419–4.294)	0.621
BCLC (0 & A)	0.796 (0.460–1.379)	0.416	0.458 (0.237–0.885)	0.020	0.764 (0.263–2.217)	0.620

HCC, hepatocellular carcinoma; BMI, body mass index; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; ALBI, albumin bilirubin index; PNI, prognostic nutritional index; PRS, Preoperative Risk Score; SSS, Surgical Stress Score; CRS, Comprehensive Risk Score; BCLC, Barcelona Clinic Liver Cancer stage; TNM, tumor node metastasis; TACE, transarterial chemoembolization.

application value in the field of liver surgery will increase.

Furthermore, we plotted a ROC curve to decide an optimal cutoff value of the CRS for predicting postoperative complication. According to the curve, we selected 0.126 as the cutoff value with the sensitivity =0.835, the specificity= 0.548 and AUC =0.732. The cut-off value of CRS differs in different literatures due to differences in research topics and methods. Previous study has shown that CRS >0.5 was associated with a higher incidence of poor postoperative events (12). There are several possible reasons to account for low CRS levels in our research. First of all, as we described before, PRS were low because of our cases were in a relatively balanced physiological state. Secondly, the use of laparoscopy continues to increase and 73.9% patients underwent laparoscopic surgery. According to the algorithm of the E-PASS system, laparoscopic surgery is assigned 0 points while laparotomy is 1. Difference of extent of skin incision ultimately accounted for a gap of 0.344 points in the CRS.

Referring to our CRS cutoff valve, the cases were divided into high-CRS group and low-CRS group. The analytical results indicated that patients with low CRS were less likely to develop postoperative complications after surgery statistically, including mild and major complications. But our results found no significant difference in postoperative

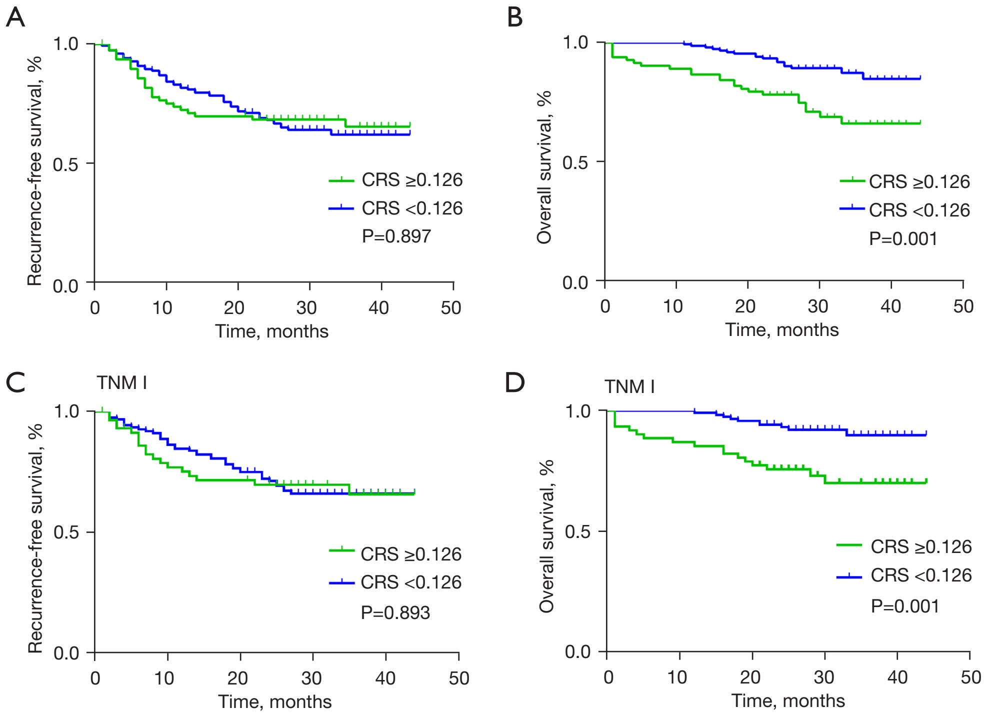

Figure 2 The RFS or OS curve between high-CRS group and low-CRS group. (A) RFS; (B) OS; (C) RFS in TNM I patients; (D) OS in TNM I patients. CRS, Comprehensive Risk Score; RFS, recurrence-free survival; OS, overall survival; TNM, tumor node metastasis.

atrial fibrillation and shock. Usually, mild complications are not fatal, but major complications are probably associated with poor perioperative prognosis in patients. All deaths were observed to have multiple serious complications, such as pneumonia, organ dysfunction or shock.

We also supposed CRS is related to RFS or OS of HCC patients (*Table 5*). In univariate analyze of survive, we found that high PNI may be a protective factor for long-term survival. Low PNI as reported previously was an independent poor prognostic factor in HCC patients received hepatectomy (42). PNI model contains two parameters: peripheral lymphocyte count and serum albumin, which reflects individual's nutritional and immunological status. Low PNI indicates poor nutritional status or immune malfunction, which may be related with higher tumor burden and promotes cancer progression (43). The result also showed that CRS and maximum tumor diameter were independent prognostic factors of OS in our study. Tumor staging system usually regard tumor diameter as an important parameter. Patients in early stage (TNM = I or BCLC = 0 or A) showed better prognosis in univariate analysis. The relationship between CRS and long-term prognosis is uncertain. In fact, except for patients who died due to severe postoperative complications, the majority of deaths in our study were accompanied by tumor recurrence or metastasis. Most previous studies focused on mortality and morbidity in perioperative period (12,13,15,18,31). Although our research found that high CRS was correlated with poor long-term prognosis. Considering that parameters contained in E-PASS model seem not to be related to recurrence and metastasis of tumor directly (11), more researches will be needed to give a comprehensive explanation. However, our results may be a reference for surgeons in treatment decision when facing patients with poor physiological conditions or estimated long operation time.

There were some limitations in our study. Firstly, the number of patients was limited, so the cutoff value of CRS in HCC patients remains correction. Secondly, the fellow-up time was not long enough. Thirdly, our study did not take postoperative antiviral-therapy or immunotherapy, etc. into consideration.

Conclusions

E-PASS is an effective predictive system for evaluating the risk of postoperative complications of liver resection in HCC patients. This system has many advantages, such as easily accessible data and simple evaluation steps, as well as incorporation of preoperative measurements with intraoperative measurements. Preoperative prediction of CRS can give surgeons guidance. Patients with higher CRS should be given effective preoperative management to reduce postoperative complications and improve prognosis. E-PASS system may be a predictor of the long-term prognosis of HCC patients undergoing resection. In addition, this system requires further evaluation and correction to fit different kinds of surgeries.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-352/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University, Hangzhou, China (No. 20210729-282). Individual consent for this retrospective analysis was waived.

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