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Spleen stiffness and volume help to predict posthepatectomy liver failure in patients with hepatocellular carcinoma

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Abstract

Posthepatectomy liver failure (PHLF) is the main cause of perioperative death, and liver cirrhosis is one of the most important risk factors for PHLF. Spleen stiffness (SS) is a novel ultrasonic indicator for liver cirrhosis and portal hypertension, however, it is not clear that whether it has a significant influence on PHLF. Future remnant liver volume (FRLV) is a significant factor for liver regeneration after hepatectomy, spleen volume (SV) could also predict the degree of liver cirrhosis, and recent literatures reported that SV to FRLV ratio (SV/FRLV) could predict small for size syndrome (SFSS) in liver transplantation, however, the relationship between SV/FRLV and PHLF in patients receiving hepatectomy is not known. Systemic inflammatory response (SIR) plays a significant role in the pathogenesis and progression of liver cirrhosis, however, it is not very clear about the exact relationship between SIR and PHLF.

We prospectively collected the medical data of consecutive patients diagnosed with hepatocellular carcinoma (HCC) who underwent hepatectomy from August 2015 to February 2016. Preoperative measurements of SS, liver stiffness (LS), SV, FRLV, and SIR were performed on all patients. A univariate analysis was performed to find the risk factors of PHLF and a multivariate analysis was used to identify independent risk factors. The predictive efficiency of the risk factors was evaluated by receiver operating characteristic (ROC) curve.

Twenty three (23) (14.6%) patients developed PHLF. Univariate analysis found several variables significantly related to PHLF, they were as follows: tumor diameter ($P=.01$), cirrhosis ($P=.001$), neutrophil to lymphocyte ratio (NLR) ($P=.018$), LS ($P=.001$), SS ($P=.001$), SV/FRLV ($P<.001$), operation duration ($P=.003$), transfusion ($P=.009$), hepatic inflow occlusion (HIO) ($P=.001$). Finally, SV/FRLV ($P<.001$, hazard ratio (HR)$=26.356$, 95% confidence interval (CI) 1.627–425.21), SS ($P=.009$, HR$=1.077$, 95%CI 1.017–1.141), and HIO time ($P=.002$, HR$=1.043$, 95%CI 1.014–1.072) were determined as the independent risk factors of PHLF by multivariate analysis.

SS and SV/FRLV help to predict the development of PHLF in patients with hepatocellular carcinoma.

Abbreviations: AUC = area under the curve, CI = confidence interval, FRLV = future remnant liver volume, HCC = hepatocellular carcinoma, HIO = hepatic inflow occlusion, HR = hazard ratio, LS = liver stiffness, NLR = neutrophil to lymphocyte ratio. PHLF = posthepatectomy liver failure, RFA = radiofrequency ablation, SFSS = small for size syndrome, SIR = systemic inflammatory response, SS = spleen stiffness, SV = spleen volume, SV/FRLV = spleen volume to future remnant liver volume ratio, TACE = transhepatic arterial chemotherapy and embolization.

Keywords: hepatectomy, hepatocellular carcinoma, liver stiffness, posthepatectomy liver failure, spleen stiffness, spleen volume to future remnant liver volume ratio, systemic inflammatory response

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies, and the third leading cause of cancer-related death worldwide.[1,2] Hepatectomy remains one of the standard treatments for HCC.[3] Even though the incidence of post-hepatectomy liver failure (PHLF) has significantly decreased with help of integrated preoperative evaluation and patient selection over the decades, it troubles the surgeons. PHLF is still the primary morbidity and mortality following hepatectomy with the reported incidence of 7% (ranging from 1% to 30%).[4,5] An unremitting effort to predict PHLF is needed.

Various parameters have been developed to predict PHLF. Among them, liver cirrhosis was a prominent risk factor for PHLF.[6] The noninvasive measurements of liver stiffness (LS) and spleen stiffness (SS) with transient elastography were proved to be the safe and useful test for assessing liver cirrhosis.[7,8] Takuma et al[9] even found that SS was a better parameter to assess portal hypertension than LS. LS was further reported to be

an effective tool to predict development of PHLF.[10] However, it remains unknown whether SS could also predict the development of PHLF or not.

Future remnant liver volume (FRLV) was thought to be a dominant factor for development of PHLF.[11] Previous researches mainly focused on FRLV itself or FRLV to total liver volume ratio, and several cut-off values were advocated to predict PHLF.[12] Spleen volume (SV) was reported to precisely reflect cirrhosis and portal hypertension.[13,14] Some researchers focused on both SV and FRLV, Gruttadauria et al[15] found SV to graft volume ratio in patients with small for size syndrome (SFSS) undergoing living donor liver transplantation was lower than those without SFSS. However, the effect of SV to FRLV ratio (SV/FRLV) on predicting PHLF in patients with HCC remains unknown.

The present study was designed to evaluate the predictive value of SS and SV/FRLV on development of PHLF in patients who underwent hepatectomy for treatment for HCC.

2. Patients and methods

2.1. Patients

This prospective cohort study included consecutive adult patients with HCC who admitted to the Department of Liver Surgery & Transplantation Center of West China Hospital, Sichuan University from August 2015 to August 2016. The study was approved by the Ethics Committee of West China Hospital, Sichuan University.

2.2. Diagnosis, inclusion and exclusion criteria

Patients were diagnosed with HCC when two types of imaging examinations revealed the typical features of HCC or positive findings on one imaging examination together with an alpha fetoprotein level of more than 400 ng/mL. The diagnosis was confirmed by a postoperative pathologic report. The demographic characteristics, laboratory data, and radiological data of each patient were collected for further evaluation.

In the present study, our inclusion criteria were as follows: first, more than 18 years old; second, appropriate liver reserve function (Child-Pugh grade A) and renal function (serum creatinine level less than 124 mmol/L); third, receiving hepatectomy as the initial treatment.

Exclusion criteria included the followings: first, extrahepatic malignancies or massive intrahepatic metastasis; second, recurrent HCC; third, portal vein or/and hepatic vein tumor thrombus; fourth, previous splenectomy or splenectomy and hepatectomy at the same time as planned; fifth, radiofrequency ablation (RFA) or transhepatic arterial chemotherapy and embolization (TACE) were recommended after the preoperative conference.

2.3. Preoperative assessment and preparation

Ordinary preoperative assessment including ECG, blood routine test, liver, and renal function test were arranged in the first day after administration.

All patients underwent prospective elastography point quantification examination in the morning after a ≥8-hour fast before surgery. The measurement was performed by one experienced physician with an iU22 ultrasonic system (Philips iU22, Philips Medical Systems, Royal Philips Electronics, Netherlands). The background liver was defined as liver parenchyma that was more than 2 cm from the lesion periphery. LS measurement was

performed vessel-free area of the background liver in liver segments IV, V, and VI during a 5-second breath hold at inspiration with either subcostal or intercostal scanning.[16] The penetration depth for all measurements ranged from 2 to 7 cm. SS measurement was performed by the similar way. For each patient, five measurements in different locations were performed. The mean stiffness value of the five measurements in each patient was calculated for further analysis. The results of LS and SS were expressed in kilopascals (kPa).

A preoperative enhanced abdominal CT scan was performed to evaluate the resectability of the tumor. And all the images of CT scan were uploaded to IQQA LIVER software (EDDA Technology, Princeton, NJ). Surgeons could establish the 3D model of liver with the help of IQQA LIVER software based on the CT images. Then virtual operation was performed and volumetric measurement including total liver volume, FRLV and SV was done after that. A preoperative conference was held to determine the final therapeutic schedule.

2.4. Definition of PHLF

In the present study, PHLF was defined as the impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia (serum bilirubin more than 28 μmol/L according to the normal limits of our hospital) on or after postoperative day 5.[4]

2.5. Statistical analysis

We used SPSS software version 21.0 (SPSS Company, Chicago, IL) to perform statistical analysis. Continuous variables were compared by the independent sample t-test. Categorical data were compared by the chi-square test or Fisher exact test. Logistic regression analysis was used to evaluate the risk factors of PHLF. The clinical values of SS, SS/FRLV, and hepatic inflow occlusion (HIO) were assessed by receiver operating characteristic (ROC) analysis. The area under the curve (AUC), sensitivity, and specificity were calculated. Calculated P values were two-sided, and a P value less than .05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

From August 2015 to February 2016, 223 patients were enrolled based on the inclusion criteria. A total of 65 patients were excluded from the study: 3 had previous splenectomy, 3 had hepatectomy and splenectomy at the same time, 16 received RFA, and 43 received TACE after preoperative conference.

The mean age of the 158 patients was 52.3 ± 11.8 (range from 27 to 83) years, 129 (81.6%) were male and 29 (18.4%) were female. The baseline characteristics of the study population are described in Table 1.

3.2. Comparison of clinical parameters in patients with and without cirrhosis

Based on the postoperative pathologic reports, liver cirrhosis was found in 78 (49.4%) patients. Comparison of several potential clinical parameters in patients with and without cirrhosis was shown in Table 2. SV (P < .01), LS (P < .01), and SS (P < .01) were found to be related to liver cirrhosis. And there existed a positive correlation

Table 1

The baseline characteristics of the study population.

Variables	Value
Gender (n)	
Male/Female	129/29
Age (Y)	52.33 ± 11.82
TB (μmol/L)	15.17 ± 5.68
ALT (IU/L)	41.13 ± 22.29
AST (IU/L)	42.04 ± 25.89
ALB (g/L)	42.48 ± 4.06
INR	1.03 ± 0.10
Creatinine (μmol/L)	68.63 ± 13.51
PLT (10^9/L)	140.13 ± 58.49
WBC (10^9/L)	5.86 ± 2.01
Diameter (cm)	5.98 ± 3.63
Cirrhosis (n)	
Yes/No	78/80
ICG-R15 (%)	4.73 ± 3.31
NLR	2.71 ± 1.56
PLR	101.62 ± 56.99
APRI	0.91 ± 0.65
FIB-4	2.96 ± 1.93
FRLV (mL)	826.73 ± 214.38
SV (mL)	287.32 ± 219.32
SV/FRLV	0.36 ± 0.28
LS (kPa)	8.22 ± 3.85
SS (kPa)	16.81 ± 9.62
OD (min)	213.89 ± 64.76
HIO (min)	28.97 ± 20.55
Transfusion (n)	
Yes/No	7/151
PHLF (n)	
Yes/No	23/135

ALB = albumin, ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate transaminase, FIB-4 = fibrosis index based on four factors, FRLV = future remnant liver volume, HIO = hepatic inflow occlusion, ICG-R15 = indocyanine green retention rate at 15 min, INR = international normalized ratio, LS = liver stiffness, NLR = neutrophil to lymphocyte ratio, OD = operation duration, PHLF = posthepatectomy liver failure, PLR = platelet to lymphocyte ratio, PLT = platelet, SS = spleen stiffness, SV/FRLV = spleen volume to future remnant liver volume ratio, SV = spleen volume, TB = total bilirubin, WBC = white blood cell.

between LS and SS ($P < .01$, Pearson correlation coefficient = 0.650, Fig. 1). A positive correlation was found between SS and SV ($P < .01$, Pearson correlation coefficient = 0.453, Fig. 2).

3.3. Univariate and multivariate analysis of risk factor for PHLF

Based on the criteria, PHLF developed in 23 (14.6%) patients with HCC. To identify the risk factors for PHLF in patients with

Table 2

Comparison of clinical parameters in patients with and without cirrhosis.

Variables	With cirrhosis (n = 78)	Without cirrhosis (n = 80)	P Value
TB (umol/L)	15.30 ± 6.16	15.04 ± 5.21	.78
ALB (g/L)	42.60 ± 4.21	42.37 ± 3.92	.72
PLT (10_9/L)	132.31 ± 61.24	147.75 ± 54.99	.09
SV (mL)	382.49 ± 72.02	194.53 ± 76.24	<.01
LS (kPa)	9.78 ± 4.03	6.70 ± 2.96	<.01
SS (kPa)	21.42 ± 10.46	12.31 ± 5.96	<.01

ALB = albumin, LS = liver stiffness, PLT = platelet, SV = spleen volume, TB = total bilirubin.

HCC, 20 potential variables were analyzed, as shown in Table 3. Univariate analysis suggested that SV/FRLV, LS, SS, duration of surgery, diameter of tumor, HIO time, and transfusion were significantly related to development of PHLF. Multivariate analysis demonstrated that SV/FRLV ($P < .001$, hazard ratio (HR) = 26.356, 95% confidence interval (CI) 1.627–425.21), SS ($P = .009$, HR = 1.077, 95%CI 1.017–1.141), and HIO time ($P = .002$, HR = 1.043, 95%CI 1.014–1.072) were the independent risk factors for PHLF in patients with HCC.

3.4. Predictive effectiveness of SV/FRLV, SS, and HIO in development of PHLF

We performed ROC analysis to evaluate the efficacy of SV/FRLV, SS, and HIO for predicting PHLF, as shown in Figure 3. The AUC of SV/FRLV for predicting PHLF was 0.856 ($P < .001$, 95%CI 0.763–0.949), and the optimal cut-off value was set at 0.49 for predicting PHLF with a maximum joint sensitivity and specificity (specificity = 0.783, specificity = 0.919). The AUC of SS for predicting PHLF was 0.867 ($P < .001$, 95%CI 0.794–0.940) and the optimal cut-off value was set at 20.7 kPa (specificity = 0.783, specificity = 0.862). The AUC of HIO to predict PHLF was 0.694 ($P = .003$, 95%CI 0.555–0.832) and the optimal cut-off value was set at 40 minutes (specificity = 0.696, specificity = 0.741).

4. Discussion

PHLF remains one of the most serious complications after liver resection. Patient related, liver related, and surgery related factors are thought to be the main risk factors of PHLF.[17] Most studies focus on liver or spleen alone but few studies focused on both liver and spleen.[18,19] Actually, they are related and influenced by each other. In the present study, we investigated the stiffness and volume of liver and spleen at the same time, and we demonstrated that SV/FRLV and SS predicted development of PHLF in patients with HCC.

Liver cirrhosis has a great effect on liver regeneration following hepatectomy. It is extremely significant to evaluate the degree of liver cirrhosis since it is the dominant risk factor for both PHLF and long-term prognosis of HCC patients.[20] LS was recently proved to be a simple, fast, safe, and noninvasive procedure to evaluate liver fibrosis and cirrhosis. Cescon et al[21] reported that LS was associated with liver cirrhosis and portal hypertension, furthermore, LS value more than 15.7 kPa was an independent risk factor for PHLF in cases of HCC. Similarly, Nishio et al[10] analyzed the clinical data of 177 HCC cases and found that LS could predict the development of PHLF. Consistent with the previous studies, the present study showed LS was significantly related to liver cirrhosis ($P < .001$) and development of PHLF ($P < .001$). SS was another noninvasive alternative method to assess liver fibrosis and cirrhosis. Leung et al[22] reported that SS was able to distinguish different extent of liver fibrosis and cirrhosis in chronic hepatitis B carriers. Moreover, latest literature[23] suggested both LS and SS correlate with hepatic vein pressure gradient, SS was superior to LS in predicting portal hypertension. However, little attention was paid to SS on the impact of PHLF. In the present study, for the first time, we found that SS was an independent risk factor for the development of PHLF. Wu et al[24] reported that the median SS in patients who developed PHLF was 48.0 and 21.6 kPa in those who did not, but unfortunately no significant difference ($P = .36$) was found. In
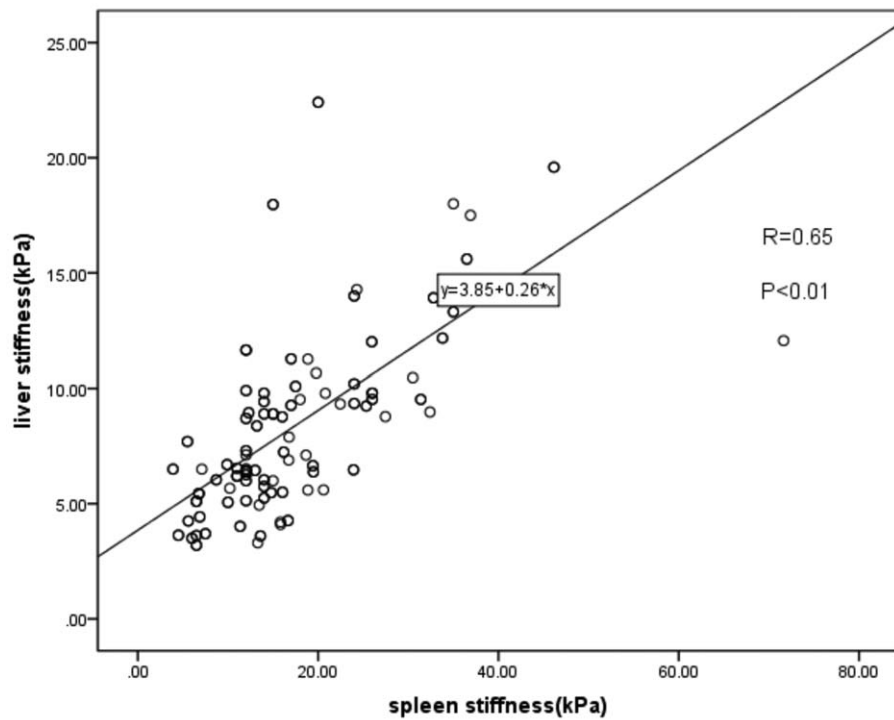
Figure 1. Relationship between liver stiffness and spleen stiffness.

their study, authors believed that severity of cirrhosis might influence the clinical utilities of SS in PHLF prediction since more than 90% patients belonged to the Child-Pugh A class and the issue of esophageal variceal bleeding was rare. However, we would prefer to ascribe that to the small number of patients included (n = 54) and over strict PHLF criteria (50–50 criteria) used in their study. Furthermore, results of the present study confirmed part of previous studies, we found SS could distinguish
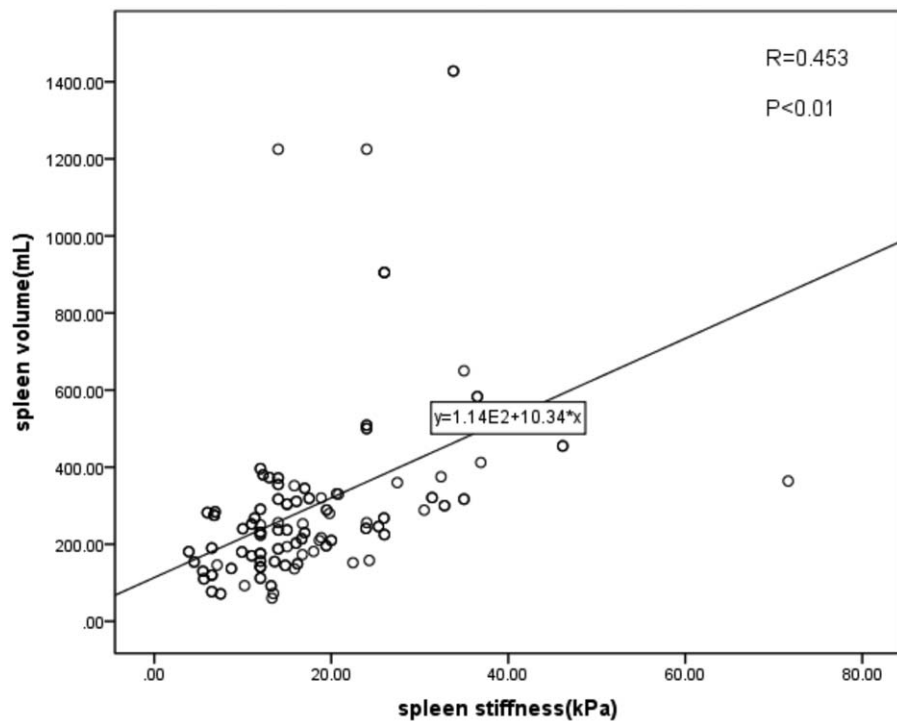

Figure 2. Relationship between spleen stiffness and spleen volume.

Table 3

Univariate and multivariate analysis of risk factor for PHLF in 158 patients with HCC.

Factors	Univariate P-value	Multivariate HR	95%CI	P-value
Gender (F/M)	.419			
Age (≥65 VS < 65)	.509			
TB	.234			
ALT	.328			
ALB	.288			
INR	.947			
Diameter	.010			.241
Cirrhosis	.001			.738
ICG-R15	.336			
NLR	.018			.152
PLR	.151			
PNI	.157			
APRI	.491			
FIB-4	.319			
SV/FRLV	<.001	26.356	1.627–425.21	<.001
LS	.001			.679
SS	.001	1.077	1.017–1.141	.009
OD	.003			.349
HIO	.018	1.043	1.014–1.072	.002
Transfusion (Yes VS No)	.009			.335

ALB = albumin, ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, FIB-4 = fibrosis index based on four factors, FRLV = future remnant liver volume, HIO = hepatic inflow occlusion, INR = international normalized ratio, LS = liver stiffness, NLR = neutrophil to lymphocyte ratio, OD = operation duration, PHLF = posthepatectomy liver failure, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, SS = spleen stiffness, SV/FRLV = spleen volume to future remnant liver volume ratio, SV = spleen volume, TB = total bilirubin.
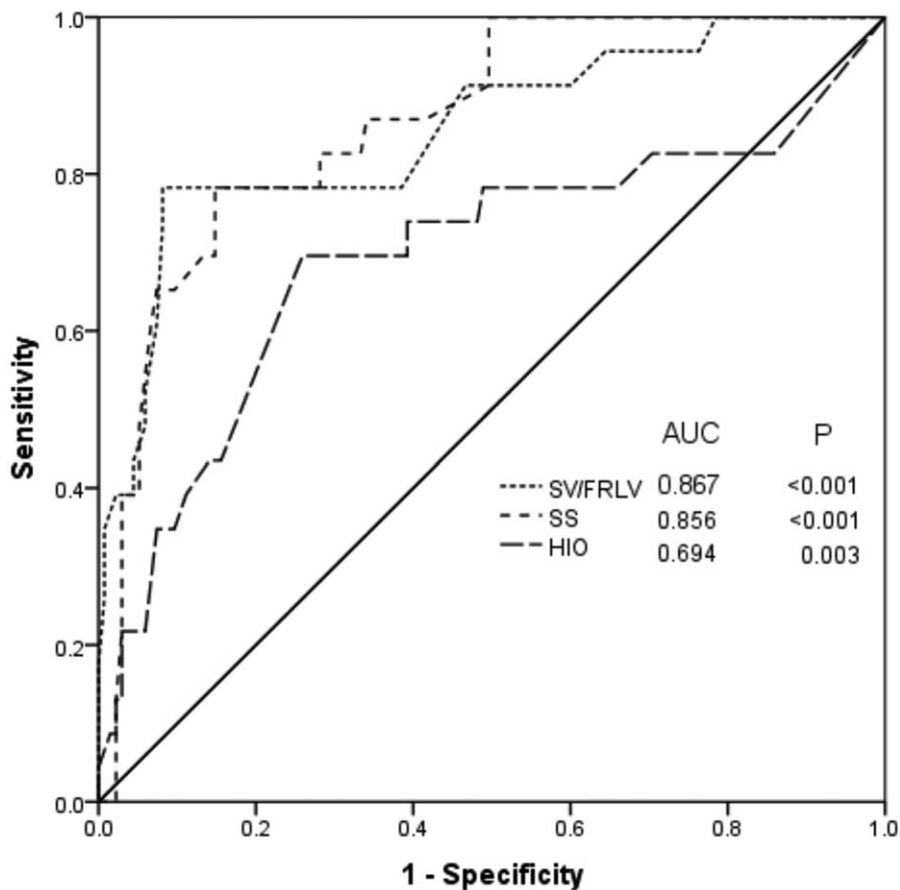

Figure 3. Clinical values of SV/FRLV, SS, and HIO for predicting development of PHLF are assessed using receiver operating characteristic analysis. HIO = hepatic inflow occlusion, SS = spleen stiffness, SV/FRLV = spleen volume to future remnant liver volume ratio.

patients with cirrhosis from others as well as LS (Table 2). And SS was linearly related to LS (Fig. 1). Theoretically, Portal vein pressure would increase along with the progression of liver fibrosis/cirrhosis in a number of patients.[25] Then the spleno-megaly emerged, which would result in an increased stiffness when measured with elastography.

FRLV is still the dominant factor for development of PHLF.[26] Generally, FRLV to total liver volume ratio should be more than 40% in patients with cirrhosis aim to prevent PHLF in the published literatures.[12] However, it is extremely difficult to evaluate the exact degree of cirrhosis in each patient, 40% criterion seems too rough in the precise hepatectomy era. SV was reported to evaluate the degree of cirrhosis and even portal hypertension.[27,28] Theoretically, SV/FRLV, which means SV to FRLV ratio, is an ideal index to reflect liver cirrhosis and FRLV. Gruttadauria et al[15] reported that a greater SV/FRLV was a reliable predictor of liver regeneration in patients who underwent right hepatectomy for living donation. Interestingly, they also found that a greater SV/FRLV was associated with a higher incidence of SFSS. In their study, they supposed portal flow and portal pressure were crucial in the development of SFSS, regardless of FRLV. Another study got the similar conclusion in patients with liver tumors.[29] In the present study, for the first time, we found that a greater SV/FRLV was an independent predictor for development of PHLF in patients with HCC. The relationship between SV/FRLV and greater liver regeneration or PHLF is complex. This could be potentially explained with fluid dynamics change of portal vein. Hepatectomy exposes the remaining liver sinusoids to an overproportional portal vein flow. Patients with a higher SV/FRLV may have a relatively bigger spleen and smaller FRLV. A bigger spleen might lead to a higher perfusion to portal vein from splenic vein. A certain degree of high perfusion to sinusoids would lead to a greater liver regeneration and faster liver function restoration,[30] on the other hand, an overperfusion to sinusoids might lead to hepatic sinusoidal endothelium injury, which might result in suppression of liver regeneration and PHLF.[31]

Surgery related factors including intraoperative transfusion, intraoperative bleeding more than 1000 mL and prolonged HIO were reported to be independent risk factors for PHLF.[32] Results of the present study confirmed the previous studies, we found patients who developed PHLF had a longer HIO and more intraoperative transfusion than those who did not (Table 2) and prolonged HIO could predict PHLF independently (Fig. 3). Generally, HIO was closely related to intraoperative bleeding, a massive transfusion and fluid exchange might lead to bacterial translocation, coagulation disorders, and PHLF finally devel-oped.[33] Interestingly, we investigated three indices of SIR including NLR, platelet to lymphocyte ratio and prognostic nutritional index, however, the predictive value was not verified in the multivariable analysis even though it was higher in patients who developed PHLF (Table 3). NLR > 2.8 was an independent risk factor for PHLF in a previous study,[34] which indicated that severe SIR might increase the surgical risk of patients received hepatectomy. However, this relationship was not confirmed in the present study. We assumed that the effect of SIR on liver was slow but persistent, so SIR could help to predict the long-term prognosis of patents with HCC. However, the predictive value for short-term prognosis of SIR was limited.

There are some limitations in the present study. First, this study was conducted at a single center, with a small number of cases. Therefore, our results may not exactly reflect the condition of the

entire country. Second, our study primarily focused on HCC caused by HBV infection; therefore, the cut-off value may not be generalizable to patients with other liver diseases such as nonalcoholic fatty liver disease, alcoholic liver disease, and autoimmune hepatitis. Future work will estimate the practical value of SS and SV in hepatectomy with more patients and institutes, which will also enable a more sufficient study of the underlying mechanisms.

Author contributions

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Writing – review & editing: Chuan Li, Xiao-Yun Zhang.

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