BMC Gastroenterology

RESEARCH

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Low preoperative serum creatinine levels are associated with poor prognosis in patients with hepatocellular carcinoma after liver resection: a multicenter study

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Abstract

Background Previous studies have typically focused on the effect of high preoperative serum creatinine (SCr) levels on the prognosis of hepatocellular carcinoma (HCC) patients but have often ignored the role of low SCr levels. This study aimed to assess the impact of low SCr levels on HCC patient prognosis.

Methods 3857 patients who underwent primary liver resection from seven centers were divided into low, normal and high SCr groups according to their baseline SCr levels. Factors independently associated with textbook outcome (TO) and overall survival (OS) were analyzed. Propensity score matching (PSM) was used to balance the baseline characteristics between the low- and normal-SCr groups, as well as between the high- and normal-SCr groups.

Results TO was observed in 2403 (62.3%) patients. The TO rate in the normal SCr group was 63.4%, which was significantly higher than that in the low (48.5%, $P<0.001$) and high (53.3%, $P=0.017$) SCr groups in the whole cohort. Multivariate analysis confirmed that both low and high SCr levels independently contributed to non-TO achievement. The 5-year OS was 67.6% for the normal SCr group, which was significantly better than that of the low SCr group (51.1%, $P<0.001$) but similar to that of the high SCr group (66.4%, $P=0.697$) in the whole cohort. Similar results were observed after PSM. Multivariate analysis suggested that a low SCr level (HR = 1.328, 95% CI = 1.076–1.639, $P=0.008$) was independently associated with OS, whereas a high SCr level (HR = 1.173, 95% CI = 0.870–1.583, $P=0.294$) was not.

Conclusions Low SCr levels could affect both TO achievement and OS in HCC patients after liver resection. A low SCr level offers useful information for preoperative risk stratification, optimizes perioperative care and improves the prognosis of HCC patients. We should not ignore the effect of low preoperative SCr levels on HCC patient prognosis.

Keywords Serum creatinine level, Hepatocellular carcinoma, Textbook outcomes, Liver resection

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common life-threatening malignancies and causes more than 800,000 deaths per year worldwide. [1] The incidence of HCC is decreasing in some traditionally highly endemic areas because of great efforts to prevent chronic hepatitis virus infection. [1] Unfortunately, with the epidemic of obesity-related nonalcoholic fatty liver disease, alcohol abuse and so on, the incidence of this disease is increasing in some low endemic areas. [2, 3] Liver resection is widely accepted as a curative treatment for HCC patients. However, the 50%–70% recurrence rate 5 years after liver resection greatly limits the satisfactory management of this disease. [4–6].

Many factors can influence the prognosis of patients with HCC after liver resection. The serum creatinine (SCr) concentration is one of the tools that most commonly used to evaluate patients' renal function. Moreover, creatinine is a breakdown product of creatine phosphate in muscle, which can also reflect skeletal muscle mass in the steady state. [7] Thongprayoon et al. even reported that a low SCr level, most likely due to sarcopenia, was independently associated with increased in-hospital mortality in hospitalized patients. [8] Additionally, the SCr level can also reflect a patient's nutritional status. [9] Previous investigations regarding the impact of SCr on the outcomes of HCC patients have focused mainly on the safety and prognosis of HCC patients with chronic renal failure. [10, 11] There is little information about the influence of low preoperative SCr concentrations on the prognosis of HCC patients after liver resection. However, in clinical practice, low SCr concentrations are not rare among patients who undergo nonemergent operations. [12].

Moreover, previous studies have often focused on individual health care outcome variables, such as postoperative complications and perioperative mortality, among others. [13, 14] However, as a high risk complex surgical procedure, a single outcome variable cannot cover the multidimensional aspects of liver resection. Recently, the concept of the textbook outcome (TO), which consists of several important individual outcome variables related to the surgical process, has been widely accepted by investigators for assessing the quality of the surgical procedure and hospital performance. [15] However, whether preoperative SCr contributes to the TO achievement of patients with HCC after liver resection is unclear. Accordingly, we carried out this study to clarify these issues.

Patients and methods

The data of HCC patients who underwent primary liver resection from 2013 to 2023 at West China Hospital of Sichuan University, Ziyang Central Hospital, Sichuan Province People's Hospital, the First People's Hospital of Neijiang, the Second People's Hospital of Yibin, the Second People's Hospital of Chengdu, and the Affiliated Hospital of Chengdu University were retrospectively reviewed. Patients who underwent reresection for recurrent HCC, received preoperative antitumor treatment, had other types of tumors or spontaneous rupture of the tumor, or whose data were missing were excluded.

Definitions

TO was defined as no 30-day severe complication (≥ Clavien–Dindo grade 3), no readmission within 30 days after discharge, no 90-day mortality, R0 resection, no blood transfusion and no prolonged hospital stay (≥ 75th percentile). [16–18] The albumin–bilirubin (ALBI) grade was calculated using the following formula: ALBI = (log10 bilirubin (μmol/L) × 0.66) + (albumin (g/L) × −0.085). [19] ALBI values were divided into 3 grades as follows: Grade 1 (< − 2.60), Grade 2 (between − 2.60 and − 1.39), and Grade 3 (> − 1.39). [19, 20] The prognostic nutritional index (PNI) was calculated with the following formula: serum albumin (g/L) + 5 × lymphocyte count (10^9/L). [21] A PNI less than 45 was defined as a low PNI. [22] According to the baseline SCr levels, for males, a SCr level < 0.6 mg/dL was considered as low, a SCr level of 0.6–1.2 mg/dL was considered as normal, and a SCr level ≥ 1.2 mg/dL was considered as high; for females, a SCr level < 0.5 mg/dL was considered as low, a SCr level of 0.5–1.0 mg/dL was considered as normal, and a SCr level ≥ 1.0 mg/dL was considered as high. [23] Preoperative platelet counts < 100×10^9/L were considered low preoperative platelet counts. [24].

Statistical analysis

All the statistical analyses were performed with SPSS 27.0 (SPSS Company, Chicago, IL) for Windows. Continuous variables were compared via one-way analysis of variance, whereas categorical variables were compared using the $\chi 2$ test or Fisher's exact test. The Kaplan–Meier method was used to determine overall survival (OS) rates, which were compared by the log-rank test. Multivariate analysis was carried out using logistic regression analysis to identify the risk factors independently associated with TO. Cox regression analysis was performed to identify the risk factors independently contributing to OS. The preoperative baseline characteristics of patients with low and high SCr levels were balanced with those of patients with normal SCr levels by 1:1 propensity score matching (PSM) analysis. All variables with a P value < 0.05 in the univariate analysis were included in the multivariate analysis. P values < 0.05 were considered significant.

Results

A total of 3857 eligible patients, including 3293 (85.4%) males and 564 (14.6%) females, were enrolled in this study (Fig. 1). The median SCr level of the whole cohort was 0.82 mg/dL (interquartile range: 0.72–0.93). According to the definition, 196 (5.1%), 3526 (91.4%) and 135 (3.5%) patients were divided into low, normal and high SCr groups, respectively. The mean age of the participants in this study was 52.5 ± 11.7 years. A total of 282 (7.3%) patients were in Barcelona clinical liver cancer stage (BCLC) 0, 2906 (75.3%) patients were in BCLC stage A, 295 (7.7%) patients were in BCLC stage B, and 374 (9.7%) patients were in BCLC stage C. Microvascular invasion (MVI) was detected in 1413 (36.6%) patients. High preoperative AFP levels were found in 1424 (36.9%) patients, whereas low platelet counts were observed in 1044 (27.1%) patients. There were 2737 (71.0%) and 1120 (29.0%) patients with ALBI grades 1 and 2, respectively. There were no patients with ALBI grade 3.

We compared the baseline clinicopathological characteristics of patients in the low, normal and high SCr groups. As shown in Table 1, compared with the normal-SCr group, the low-SCr group had more female patients, larger tumor sizes, more multiple tumors, more poorly differentiated tumors, more patients with a PNI < 45, low albumin levels, low hemoglobin levels, ALBI grade 2 and advanced BCLC stages, whereas the high-SCr group had more older patients, female patients, a lower proportion of patients with poor tumor differentiation and positive results for HBV-DNA.

Comparison of outcomes of patients in the low, normal and high SCr groups

In the whole cohort of the current study, 2403 (62.3%) patients achieved TO. The incidence of TO in the normal SCr group was 63.4%, which was significantly greater than that in the low SCr group (48.5%, $P < 0.001$) and high SCr group (53.3%, $P = 0.017$).

Table 2 compares the six individual outcome variables that were included in the definition of non-TO discordance among the low, normal and high SCr groups. The postoperative length of hospital stay was significantly longer in the low- and high-SCr groups than in the normal-SCr group. Additionally, compared with the normal SCr group, the low SCr group had a significantly greater incidence of perioperative blood transfusion.

Because the baseline characteristics of the three groups were not comparable, we used PSM to balance the baseline characteristics of the three groups. We compared the outcomes between patients with low and normal SCr levels. After PSM, 196 well-balanced pairs were available for outcome comparisons between the low and normal SCr groups (Supplementary Table 1). The incidence of TO was 61.7% for patients with normal SCr levels and 48.5% for patients with low SCr levels in the matched cohort. A significant difference was observed ($P = 0.008$).

When comparing the outcomes between patients with normal and high SCr levels, after PSM, 135 patients were selected for both the high and normal SCr groups (Supplementary Table 2). In the matched cohort, the incidence of TO in patients with normal SCr levels (74.8%) was also significantly better than that in patients with high SCr levels (53.3%; $P < 0.001$).

The median follow-up was 42.03 months in the whole cohort. The 5-year OS rates were 51.1%, 67.6%, and 66.4% for the low-, normal- and high-SCr groups, respectively, in the whole cohort. As shown in Fig. 2, the OS of the low-SCr group was significantly lower than that of the normal- ($P_{\text{low vs. normal}}<0.001$) and high- ($P_{\text{low vs. high}}=0.020$) SCr groups. The OS rates were similar between the normal- and high-SCr groups ($P_{\text{normal vs. high}}=0.697$). As shown in Supplementary Fig. 1, after PSM, the OS of the low-SCr group was still significantly worse than that of

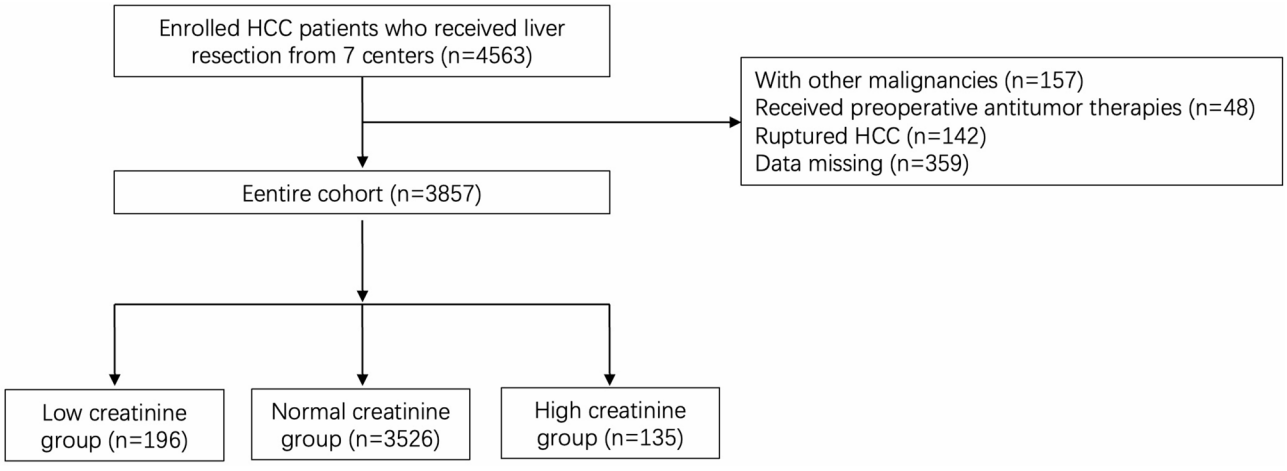


Fig. 1 The flowchart of this study

Table 1 Comparisons of clinical characteristics among the three groups according to preoperative serum creatinine levels

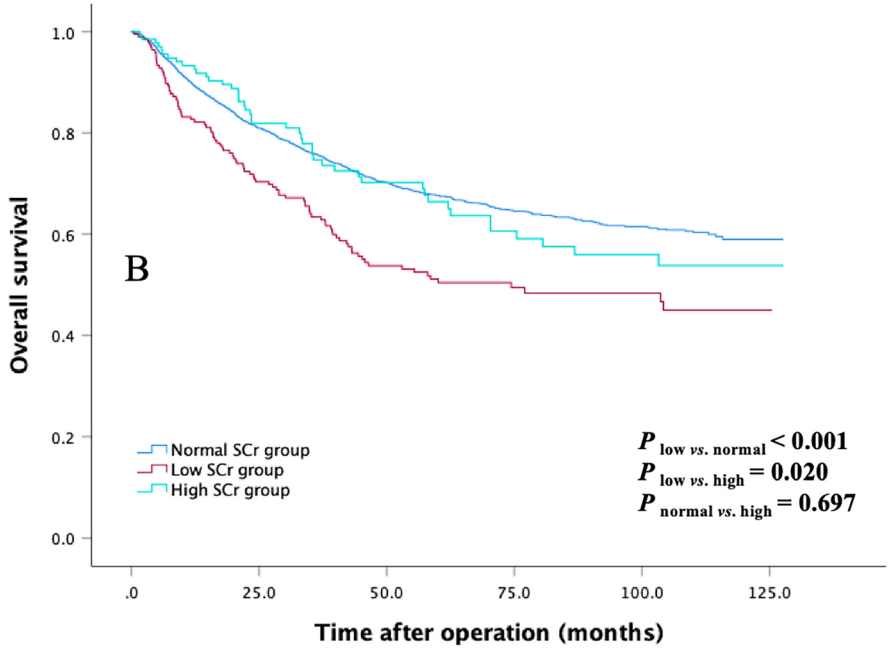
Variables	Overall (*N* = 3857)	Low SCr (*N* = 196)	Normal SCr (*N* = 3526)	High SCr (*N* = 135)	*P* values (low vs. normal SCr)	*P* values (high vs. normal SCr)
Age > 65 years	654(17.0)	29(14.8)	585(16.6)	40(29.6)	0.510	< 0.001
Gender (male)	3293(85.4)	145(74.0)	3401(86.2)	107(79.3)	< 0.001	0.022
BMI (low/normal/high)	215(5.6)/2556(66.2)/1086(28.2)	13(6.6)/139(71.0)/44(22.4)	193(5.5)/2333(66.1)/1000(28.4)	9(6.7)/84(62.2)/42(31.1)	0.183	0.610
Tumor size > 5 cm	1849(47.9)	130(66.3)	1657(47.0)	62(45.9)	< 0.001	0.807
Multiple tumor	391(10.1)	34(17.3)	342(9.7)	15(11.1)	< 0.001	0.587
Poor differentiation	423(11.0)	31(15.8)	387(11.0%)	5(3.7)	0.037	0.007
Presence of MVI	1413(36.6)	85(43.4)	1275(36.2)	53(39.3)	0.041	0.462
AFP > 400 ng/mL	1424(36.9)	85(43.4)	1291(36.6)	48(35.6)	0.057	0.802
Low platelet counts	1044(27.1)	60(30.6)	947(26.9)	37(27.4)	0.249	0.888
HBV-DNA positive	1514(39.3)	78(39.8)	1395(39.6)	41(30.4%)	0.948	0.032
PNI < 45	657(17.0)	63(32.1)	574(16.3)	20(14.8)	< 0.001	0.651
PLR > 150	574(14.9)	34(17.3)	522(14.8)	18(13.3)	0.331	0.636
NLR > 3	884(22.9)	51(26.0)	798(22.6)	35(25.9)	0.271	0.370
Albumin < 40 g/L	1067(27.7)	86(43.9)	950(26.9)	31(23.0)	< 0.001	0.306
Hemoglobin < 120 g/L	273(7.1)	22(11.2)	236(6.7)	15(11.1)	0.015	0.046
ALBI grade 2	1120(29.0)	91(46.4)	1000(28.4)	29(25.1)	< 0.001	0.081
BCLC stage (0/A/B/C)	282(7.3)/2906(75.3)/295(7.7)/374(9.7)	9(4.6)/132(67.3)/29(14.8)/26(13.3)	269(7.6)/2667(75.6)/252(7.2)/338(9.6)	4(3.0)/107(79.2)/14(10.4)/10(7.4)	< 0.001	0.088

Abbreviations:ALBI grade Albumin-bilirubin, *AFP* Alpha-fetoprotein, *BCLC stage* Barcelona clinical liver cancer stage, *BMI* Body mass index, *HBV* Hepatitis B virus, *MVI* Microvascular invasion, *NLR* Neutrophil-to-lymphocyte ratio, *PLR* Platelet-to-lymphocyte ratio, *PNI* Prognostic Nutritional Index, *SCr* Serum creatinine

Table 2 Comparison of each type of non-TO among the three groups according to preoperative serum creatinine levels

Distribution of non-TO	Overall	Low-SCr group (*N* = 196)	Normal-SCr group (*N* = 3526)	High-SCr group (*N* = 135)	*P* values (low vs. normal SCr)	*P* values (high vs. normal SCr)
Overall	2403 (62.3%)	95(48.5%)	2236(63.4%)	72(53.3%)	< 0.001	0.017
Postoperative 30-day severe morbidity	209(5.4%)	16(8.2%)	184(5.2%)	9(6.7%)	0.075	0.460
Postoperative 90-day mortality	56(1.5%)	3(1.5%)	51(1.4%)	2(1.5%)	0.924	0.973
Non-R0 resection	146(3.8%)	12(6.1%)	128(3.6%)	6(4.4%)	0.074	0.621
Perioperative blood transfusion	270(7.0%)	23(11.7%)	240(6.8%)	7(5.2%)	0.009	0.461
Readmission within 30-day after discharge	25(0.6%)	0(0%)	23(0.7%)	2(1.5%)	0.257	0.251
Prolonged length of postoperative hospital stay	1146(29.7%)	78(39.8%)	1016(28.8%)	52(38.5%)	0.001	0.015

Abbreviations:SCr Serum creatinine, *TO* Textbook outcome



No. at risk						
Low SCr	196	135	84	51	29	2
Normal SCr	3526	2517	1487	864	362	34
High SCr	135	93	58	40	26	4

Fig. 2 Comparison of overall survival among patients in the three groups

the normal-SCr group ($P = 0.004$). However, after PSM, the OS of patients with normal SCr levels was similar to that of patients with high SCr levels (Supplementary Fig. 2, $P = 0.103$).

Factors independently associated with non-TO

As presented in Table 3, univariate analysis suggested that a tumor size > 5 cm, a preoperative AFP > 400 ng/mL, MVI, ALBI grade 2, a PNI < 45, a PLR > 150, an NLR > 3, albumin levels < 40 g/L, an advanced BCLC stage and SCr level were potential factors contributing to non–TO achievement. The multivariate logistic regression confirmed a tumor size > 5 cm (OR = 1.738, 95% CI = 1.506–2.007, $P < 0.001$), a preoperative AFP > 400 ng/mL (OR = 1.216, 95% CI = 1.055–1.401, $P = 0.007$), MVI (OR = 1.242, 95% CI = 1.071–1.439, $P = 0.004$), a PNI < 45 (OR = 1.564, 95% CI = 1.233–1.984, $P < 0.001$), an NLR > 3 (OR = 1.214, 95% CI = 1.032–1.428, $P = 0.019$),

Table 3 Factors associated with not achieving TO in HCC patients after liver resection

Variables	UV OR 95% CI	UV *P*	MV OR 95% CI	MV *P*
Male	1.140 (0.946–1.374)	0.170		
Age > 65 years	0.942 (0.791–1.122)	0.504		
Tumor size > 5 cm	2.147 (1.880–2.452)	< 0.001	1.738 (1.506–2.007)	< 0.001
Multiple tumors	1.007 (0.812–1.250)	0.947		
AFP > 400 ng/mL	1.431 (1.251–1.636)	< 0.001	1.216 (1.055–1.401)	0.007
Poor tumor differentiation	1.125 (0.915–1.383)	0.263		
Presence of MVI	1.635 (1.429–1.870)	< 0.001	1.242 (1.071–1.439)	0.004
HBV-DNA positive	1.020 (0.893–1.165)	0.772		
ALBI grade 2	1.906 (1.654–2.196)	< 0.001		
PNI < 45	2.333 (1.968–2.766)	< 0.001	1.564 (1.233–1.984)	< 0.001
PLR > 150	1.378 (1.152–1.649)	< 0.001		
NLR > 3	1.551 (1.332–1.806)	< 0.001	1.214 (1.032–1.428)	0.019
Albumin < 40 g/L	1.993 (1.727–2.301)	< 0.001	1.429 (1.171–1.745)	< 0.001
Low platelet counts	1.008 (0.871–1.167)	0.914		
Normal BMI	Ref.			
Low BMI	0.796 (0.592–1.069)	0.129		
High BMI	0.960 (0.829–1.111)	0.581		
Normal SCr	Ref.			
Low SCr	1.843 (1.381–2.459)	< 0.001	1.413 (1.045–1.910)	0.025
High SCr	1.517 (1.074–2.142)	0.018	1.583 (1.109–2.260)	0.011
BCLC (B/C vs. 0/A)	1.723 (1.456–2.038)	< 0.001	1.300 (1.085–1.559)	0.005

Abbreviations: *ALBI grade* Albumin-bilirubin, *AFP* Alpha-fetoprotein, *BCLC stage* Barcelona clinical liver cancer stage, *BMI* Body mass index, *CI* Confidence interval, *HBV* Hepatitis B virus, *MV* Multivariate, *MVI* Microvascular invasion, *NLR* Neutrophil-to-lymphocyte ratio, *OR* Odds ratio, *PLR* Platelet-to-lymphocyte ratio, *PNI* Prognostic Nutritional Index, *SCr* Serum creatinine, *TO* Textbook outcome, *UV* Univariate

albumin levels < 40 g/L (OR = 1.429, 95% CI = 1.171–1.745, $P < 0.001$), an advanced BCLC stage (OR = 1.300, 95% CI = 1.085–1.559, $P = 0.005$) and a SCr level (normal SCr group for ref; low SCr: OR = 1.413, 95% CI = 1.045–1.910, $P = 0.025$; high SCr: OR = 1.583, 95% CI = 1.109–2.260, $P = 0.011$) independently associated with non-TO achievement.

Factors associated with overall survival in the whole cohort

We also wanted to analyze whether the preoperative creatinine level affects the long-term survival of HCC patients after liver resection. As listed in Table 4, a tumor size > 5 cm, multiple tumors, AFP levels > 400 ng/mL, poor tumor differentiation, MVI, a positive HBV-DNA, ALBI grade 2, a PNI < 45, a PLR > 150, an NLR > 3, preoperative albumin levels < 40 g/L, SCr level and BCLC stage were potential risk factors for mortality in the univariate analysis. However, a only tumor size > 5 cm (HR = 1.773, 95% CI = 1.566–2.008, $P < 0.001$), an AFP > 400 ng/mL (HR = 1.266, 95% CI = 1.128–1.420, $P < 0.001$), poor tumor differentiation (HR = 1.328, 95% CI = 1.135–1.555, $P < 0.001$), MVI (HR = 1.533, 95% CI = 1.358–1.730, $P < 0.001$), a positive HBV-DNA (HR = 1.368, 95% CI = 1.222–1.533, $P < 0.001$), ALBI grade 2 (HR = 1.165, 95% CI = 1.035–1.312, $P = 0.011$), SCr level (normal SCr for reference; low SCr: HR = 1.328, 95% CI = 1.076–1.639, $P = 0.008$; high SCr: HR = 1.173, 95% CI = 0.870–1.583, $P = 0.294$) and advanced BCLC stage (HR = 2.080, 95% CI = 1.830–2.364, $P < 0.001$) were independent risk factors for OS. As shown in Table 4, low SCr was independently associated with mortality, whereas high SCr was not an independent risk factor for OS.

Discussion

The SCr level is widely used to assess patient renal function. However, the SCr level can also reflect a patient's nutritional status. A low SCr level indicates that the patient may be malnourished. [9] A number of studies have revealed that HCC patients with malnutrition have a greater incidence of postoperative morbidity and lower long-term survival than do those without malnutrition. [21, 25, 26] For example, Hu et al. [25] confirmed that a low PNI, a marker of malnutrition, was associated with a low incidence of recurrence-free survival and OS in patients with HCC after liver resection. Li et al. [26] suggested that early postoperative control of the nutritional status score is associated with severe complications after hepatectomy in patients with HCC. In previous studies, these indicators of nutritional status involved multiple factors, but none of those included serum creatinine levels. BMI, the PNI and the serum albumin level are widely used to reflect a patient's nutritional status. Like some previous studies, our study also suggested that a low PNI and albumin level independently associated with non-TO in HCC patients after liver resection. [21] However, unlike the PNI, serum albumin level, and BMI, etc., because of creatinine is mostly found in muscle, some investigations have suggested that creatine can be used as a surrogate for muscle mass measurement. [27–29] Low SCr levels are often associated with sarcopenia status. [28, 30] Recently, many studies have confirmed that sarcopenia status is related to high postoperative morbidity

Table 4 Factors associated with the overall survival of patients with HCC after liver resection

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* values	HR	95% CI	*P* values
Male	1.050	0.895–1.232	0.549			
Age > 65 years	0.936	0.802–1.093	0.405			
Tumor size > 5 cm	2.377	2.113–2.674	< 0.001	1.773	1.566–2.008	< 0.001
Multiple tumors	1.670	1.423–1.960	< 0.001			
AFP > 400 ng/mL	1.611	1.439–1.802	< 0.001	1.266	1.128–1.420	< 0.001
Poor tumor differentiation	1.655	1.416–1.933	< 0.001	1.328	1.135–1.555	< 0.001
Presence of MVI	2.245	2.006–2.512	< 0.001	1.533	1.358–1.730	< 0.001
HBV-DNA positive	1.548	1.384–1.732	< 0.001	1.368	1.222–1.533	< 0.001
ALBI grade 2	1.305	1.160–1.468	< 0.001	1.165	1.035–1.312	0.011
PNI < 45	1.358	1.186–1.554	< 0.001			
PLR > 150	1.569	1.363–1.806	< 0.001			
NLR > 3	1.338	1.180–1.517	< 0.001			
Albumin < 40 g/L	1.292	1.148–1.456	< 0.001			
Low platelet counts	0.998	0.880–1.131	0.969			
Normal BMI	Ref.					
Low BMI	1.003	0.791–1.273	0.979			
High BMI	0.973	0.856–1.105	0.669			
Normal SCr	Ref.			Ref.		
Low SCr	1.627	1.320–2.004	< 0.001	1.328	1.076–1.639	0.008
High SCr	1.066	0.791–1.436	0.675	1.173	0.870–1.583	0.294
BCLC (B/C vs. 0/A)	2.881	2.553–3.252	< 0.001	2.080	1.830–2.364	< 0.001

Abbreviations:ALBI grade Albumin-bilirubin, *AFP* Alpha-fetoprotein, *BCLC stage* Barcelona clinical liver cancer stage, *BMI* Body mass index, *CI* Confidence interval, *HBV* Hepatitis B virus, *HCC* Hepatocellular carcinoma, *HR* Hazard ratio, *MVI* Microvascular invasion, *NLR* Neutrophil-to-lymphocyte ratio, *PLR* Platelet-to-lymphocyte ratio, *PNI* Prognostic Nutritional Index, *SCr* Serum creatinine

and mortality in HCC patients after liver resection. [31–33] This may explain why HCC patients with low SCr levels had a poor prognosis in the present study. Our study revealed that low SCr was associated with both poor short-term and long-term outcomes in HCC patients. These results suggest that the preoperative SCr level should not be ignored in preoperative surgical risk assessment. Several studies have also reported the effects of creatinine levels on the prognosis of other tumors. [34, 35] Wang et al. [34] suggested that low SCr contributed to a high incidence of major postoperative complications in gynecologic oncology. A multicenter study performed by Yang et al. [36] reported significantly shorter OS in colorectal cancer patients with a low SCr level than in those with a normal SCr level.

Our study also confirmed that both preoperative low and high SCr levels could negatively impact the TO achievement of HCC patients after liver resection. As shown in Table 1, the baseline characteristics were different in the low, normal and high SCr groups. Compared with the normal SCr group, the low SCr group included more patients with poor liver function, advanced tumor stage, low albumin level and low hemoglobin level, whereas the high SCr group included more elderly patients and patients with low hemoglobin level. Previous studies have confirmed that low preoperative ALB levels, poor liver function, advanced age, low hemoglobin levels, advanced BCLC stage, etc., are significantly related to a high incidence of postoperative morbidity, perioperative blood transfusion, prolonged length of hospital stay, etc. [14, 37–39] Moreover, sarcopenia was often occurs in patients with low SCr levels. Yang et al. confirmed that sarcopenia was independently associated with a higher rate of postoperative major postoperative complications, blood transfusions and a longer LOS. [32] This could explain why patients with both low and high SCr levels were less likely to achieve TO than patients with normal SCr levels.

In this study, low SCr levels were associated with a poor OS compared with normal SCr levels. Moreover, unlike low SCr, high SCr was not an independent risk factor for OS in patients with HCC after liver resection in the current study. As shown in Table 2, more patients with low SCr levels than patients with normal SCr levels received blood transfusions. A number of studies have confirmed that blood transfusion could result in a decrease in OS. [40, 41] Furthermore, as listed in Table 1, more aggressive tumor biological characteristics, such as larger tumor size, poor liver function, poor tumor differentiation, and low albumin levels, were observed in the low-SCr group. Many previous investigations have confirmed that these factors are related to a high incidence of postoperative recurrence and mortality. [4, 42, 43] Furthermore, as we mentioned earlier, many patients with low SCr levels may

suffer from sarcopenia. Many studies have revealed that patients with sarcopenia have high incidences of postoperative recurrence and mortality after liver resection. [33, 44] These findings may explain why patients in the low-SCr group had a poor OS. Unlike low SCr levels, the influence of poor renal function on the surgical prognosis of patients with HCC is controversial. [10, 11] Orri et al. [10] reported that HCC patients with renal failure had a lower OS rate than those with normal renal function. However, Sakamoto et al. [11] suggested that poor renal function was only associated with a high incidence of postoperative bleeding and surgical site infection, whereas the OS rates were comparable between patients with poor and normal renal function. In the present study, we included patients with high preoperative SCr levels. However, this does not mean that all patients with high SCr levels need renal dialysis. In contrast, the current study included only a very small number of patients who required renal dialysis. This may be another explanation for why high SCr was not independently associated with OS in the current study.

Many other markers, such as the estimated glomerular filtration rate and cystatin C level, are used to evaluate renal function. [10, 45] However, only the SCr level can reflect a patient's nutritional status and muscle mass. The focus of this study was not on the impact of renal function on the prognosis of patients with HCC after liver resection. A low SCr level does not indicate poor renal function but rather poor nutritional status and sarcopenia. In clinical practice, we often pay more attention to the impact of poor renal function on patient prognosis but often ignore the influence of low SCr on patient outcomes after liver resection. Our study confirmed that low SCr could adversely affect both the short-term and long-term outcomes of HCC patients.

There were also several limitations in this study. Although this was a multicenter study, it was a retrospective study. The results need to be validated by prospective studies. There have been few studies on the definitions of low and high SCr levels. This study was based on a definition from a previous study. [23] However, many other definitions have been used in previous studies. [12, 34] The cutoff value for low SCr levels in the present study was lower than that reported in other studies. [12, 36] This is also an explanation for why the incidence of low SCr levels in the present study was lower than that in other studies. [35, 36] We acknowledge that more investigations are needed to clarify the optimal cutoff value to define low SCr in the future. Moreover, whether preoperative improvement in low-SCr status improves patient prognosis is not clear. In our clinical practice, we do not perform any treatments for patients with low SCr before surgery. However, this is an interesting topic. We believe that a prospective study could be conducted to explore whether short-term treatment would improve outcomes in patients with low preoperative SCr levels.

Conclusion

Both low and high SCr levels could affect TO achievement, while low SCr levels further affect OS from liver resection in HCC patients. The results of this study remind us not to ignore the effect of low preoperative SCr levels on the prognosis of patients with HCC after liver resection.

Abbreviations

(ALBI) grade	Albumin-bilirubin
AFP	Alpha-fetoprotein
(BCLC) stage	Barcelona clinical liver cancer
BMI	Body mass index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
MVI	Microvascular invasion
NLR	Neutrophil-to-lymphocyte ratio
OS	Overall survival
PLR	Platelet-to-lymphocyte ratio
PNI	Prognostic nutritional index
SCr	Serum creatinine
TO	Textbook outcome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04422-9.

Supplementary Material 1

Supplementary Material 2. Supplementary Fig. 1. Comparison of overall survival between patients with low and normal SCr levels after PSM.

Supplementary Material 3. Supplementary Fig. 2. Comparison of overall survival between patients with high and normal SCr levels after PSM

Acknowledgements

Not applicable.

Authors' contributions

Li C proposed this study. Qin L, Qiu ZC, Xie F, Zhang Y, Yu Y, Leng SS, Chen TH, Wang ZX and XU YQ collected the data. Li C, Qin L, Qiu ZC, and Dai JL analyzed the data. Qin L wrote the first draft of the manuscript. Li C, Wen TF made critical revision to the paper.

Funding

This study was supported by a grant from the Natural Science Foundation of Sichuan Province (No. 2024NSFSC0637).

Data availability

The data supporting the findings of this study are available from the correspondingauthor upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (No. 2024 – 1723) and was conducted under the tenets of the Declaration of Helsinki. The data were collected retrospectively and analysed anonymously, and the requirement for informed consent was therefore waived.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 22 October 2024 / Accepted: 24 October 2025
Published online: 13 November 2025

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