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Low serum creatine kinase level is associated with poor prognosis in patients with hepatocellular carcinoma: A retrospective single-center study

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Abstract. Previous studies have reported low serum creatine kinase (s-CK) levels as a poor prognostic factor in various cancers. However, there have been no reports on its significance in hepatocellular carcinoma. The present study aimed to evaluate the association of the preoperative s-CK levels with clinicopathologic features and their prognostic impact on survival in patients with hepatocellular carcinoma. This retrospective study included 163 patients with hepatocellular carcinoma (127 male and 36 female patients; median age, 69 years) who underwent radical liver resection between January 2004 and December 2021. A cutoff preoperative s-CK level of 91 U/l determined by receiver operating characteristic curve analysis was used to evaluate the significance of s-CK in predicting overall and recurrence-free survival. In addition, the prognostic impact of s-CK was evaluated using univariate and multivariate analysis. s-CK level was not associated with clinicopathologic factors. Overall survival and recurrence-free survival of the low s-CK group were significantly worse compared with the high s-CK group (P=0.043 and P=0.029, respectively). By multivariate analysis, low s-CK was an independent risk factor for poor overall survival and recurrence-free survival (P=0.019 and P=0.014, respectively). This trend was the same for male patients, but no significant difference was observed for female patients. Low preoperative s-CK level might be a poor prognostic biomarker in patients with hepatocellular carcinoma.

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Abbreviations: s-CK, serum creatine kinase; HCC, hepatocellular carcinoma; ICG, indocyanine green retention; AFP, α-fetoprotein; PIVKA-II, vitamin K absence or antagonist-II; ROC, receiver operating characteristic curve; OS, overall survival; RFS, recurrence-free survival

Key words: serum creatine kinase, hepatocellular carcinoma, prognosis

Introduction

Serum creatine kinase (s-CK) is one of the routine blood tests in patients with cancer. s-CK is an enzyme consumed in energy metabolism in various tissues and has been reported to be involved in cell division and the immune system (1,2). Importantly, studies have reported low s-CK levels as a poor prognostic factor in esophageal (3), gastric (4), breast (5), and lung cancers (6,7).

The mechanisms of low s-CK activity in patients with cancer are not fully understood. Tumor cells may consume s-CK to generate energy needed for increased proliferation, leading to a decline in s-CK levels. Cancer-related inflammation and cachexia may also lead to the loss of muscle mass, and muscle wasting in patients with cancer is considered to impact the decrease in s-CK levels.

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related deaths (8). The prognosis of patients with HCC is unsatisfactory because of the high incidence of tumor recurrence and distant metastasis (9). Early detection of HCC recurrence is associated with improved prognosis due to the better response of smaller tumors to potentially curative treatments such as liver resection, radiofrequency ablation, and transcatheter arterial chemoembolization (10-12). Therefore, the development of biomarkers that can predict HCC recurrence is important (13). s-CK has long been known to be highly active in cancers, including HCC, suggesting its potential as a prognostic factor (14). However, no report to date has demonstrated the clinicopathologic and prognostic significance of s-CK in patients with HCC.

Based on our hypothesis that low s-CK level was associated with adverse outcomes in HCC, we aimed to evaluate the prognostic significance of preoperative s-CK levels in patients with HCC.

Materials and methods

Study population. This was a retrospective study including 163 patients (127 male and 36 female patients) with a median age of 69 (range, 40-88) who were diagnosed with HCC and underwent radical liver resection between January 2004 and December 2021 in Toho University Omori Medical Center. This study protocol was approved by the Ethics Committee of Toho University Omori Medical Center (The approval number is M22223, the approval date is November 30, 2022.) and conducted in accordance with the Declaration of Helsinki. Information about the study was disclosed on the institutional website and the potential participants were given the opportunity to opt-out.

Study design. The following clinicopathologic factors were included to evaluate their association with preoperative and postoperative s-CK levels: age, sex, presence of cirrhosis, tumor size, stage [Japanese Classification of Hepatocellular Carcinoma; 2019 (The 6th Edition)], indocyanine green retention (ICG) rate at 15 min, white blood cell, platelet counts, levels of α-fetoprotein (AFP) and levels of protein induced by vitamin K absence or antagonist-II (PIVKA-II).

Preoperative s-CK levels measured during routine blood tests within seven days before surgery and postoperative s-CK levels measured at discharge or at one-month follow-up after surgery were included in the present study. Cut-off preoperative and postoperative s-CK levels were determined using receiver operating characteristic curve (ROC) analysis, with death due to any case as the dependent variable. Then, patients were categorized into those with high and low preoperative s-CK levels based on the cutoff preoperative s-CK level to evaluate the association of preoperative s-CK levels with clinicopathologic factors, overall survival (OS), and recurrence-free survival (RFS).

In the present study, OS was defined as the interval from the date of surgery to the date of death or last follow-up. RFS was defined as the interval from the date of surgery to the date of known recurrence.

Statistical analysis. Student's t-test (unpaired) and Fisher's exact probability tests were used for two-group comparisons. OS and RFS were calculated using the Kaplan-Meier method, and differences between the groups were evaluated using the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression. All statistical analyses were performed using EZR (15). A two-sided P-value of <0.05 was considered to denote statistical significance.

Results

Patient categorization according to preoperative s-CK levels. Based on the cutoff preoperative s-CK level of 91 U/l according to the ROC analysis (Fig. 1A), the 127 males were divided into the high CK group (n=85) and low CK group (n=42). The 36 females were divided into the high CK group (n=26) and the low CK group (n=10) (Fig. 1B).

Association of preoperative s-CK levels with clinicopathologic factors.

Four patients did not undergo the ICG test because of allergy to the contrast medium. No clinicopathological factors were significantly associated with the rate of patients with low preoperative s-CK levels (Table I).

Comparison of OS between patients with low and high preoperative s-CK levels. In the overall cohort, the OS was significantly worse in the low preoperative s-CK group than in the high preoperative s-CK group (P=0.043, Fig. 2A). Similarly, the OS was significantly worse in the low preoperative s-CK group than in the high preoperative s-CK group among the male patients (P=0.011, Fig. 2B). However, a significant difference in OS was not found between the female patients with low and high preoperative s-CK levels (P=0.785, Fig. 2C).

Univariate analysis revealed that the OS was significantly worse in patients with low preoperative s-CK levels, those aged over 65 years, those with an ICG retention rate of ≥10% at 15 min, and those with high α-fetoprotein and PIVKA-II levels compared to others (P<0.05, Table II). Multivariate analysis revealed that a low preoperative s-CK level, ICG retention rate of ≥10% at 15 min, and high PIVKA-II level were independent poor prognostic factors for OS (P<0.05, Table II).

Comparison of RFS between patients with low and high preoperative s-CK levels. The RFS of the low preoperative s-CK group was significantly worse than that of the high preoperative s-CK group in the overall cohort (P=0.028, Fig. 2D) and among the male patients (P=0.011, Fig. 2E). Similar to our findings regarding OS, the RFS did not significantly differ between the female patients with low and high preoperative s-CK levels (P=0.688, Fig. 2F).

Univariate analysis revealed that the RFS was significantly worse in patients with low preoperative s-CK levels, those with an ICG retention rate of ≥10% at 15 min, and those with high PIVKA-II levels compared to others (P<0.05, Table III). Multivariate analysis revealed that low preoperative s-CK level, an ICG retention rate of ≥10% at 15 min, and high PIVKA-II level were independent poor prognostic factors for RFS (P<0.05, Table III).

Discussion

In the present study, although preoperative s-CK level was not associated with any clinicopathological factors, low preoperative s-CK level was an independent risk factor for poor OS and RFS in patients with HCC.

In the previous reports, cutoff values have varied by cancer type, and there seems to be no unified view regarding how the cutoff should be determined. The cutoff values have varied by the median value (3), the ROC curve (4), the mean value (5), and the upper or lower limit of normal (6). Our study first examined cutoff values based on the ROC curve, median, and quartile. Among them, only the cutoff value based on the ROC curve showed significant differences both in the results of log-rank tests for OS and RFS and the results of univariate and multivariate analyses of prognostic factors for OS and RFS. The area under the curve in this ROC curve is 0.545, indicating low accuracy. Although this is a weak point of our study, further discussion of the cutoff value for s-CK in HCC is difficult because no other reports showed it. In the future, we plan to

Table I. Univariate analysis of clinicopathological factors of the low and high preoperative creatine kinase groups in patients with hepatocellular carcinoma.

Variables	Groups	No. of patients	Low preoperative (n=163) creatine kinase, <91 U/l (n=111)	High preoperative creatine kinase, ≥91 U/l (n=52)	P-value[a]
Sex	Female	36	26	10	0.686
	Male	127	85	42	
Age, years	<65	55	35	20	0.477
	≥65	108	76	32	
Cirrhotic liver	Negative	62	41	21	0.730
	Positive	101	70	31	
Tumor size, mm	<20	42	31	11	0.443
	≥20	121	80	41	
Stage	I/II	111	71	40	0.108
	III/IV	52	40	12	
ICG R15, %	<10	73	51	22	0.733
	≥10	86	57	29	
White blood cell, /μl	<8,000	154	105	49	1.000
	≥8,000	9	6	3	
Platelet, /μl	<150,000	69	49	20	0.614
	≥150,000	94	62	32	
AFP, ng/ml	Negative	105	72	33	0.863
	Positive	58	39	19	
PIVKA-II, mAU/ml	Negative	80	54	26	1.000
	Positive	83	57	26	

[a]Fisher's exact probability test. ICG R15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; PIVKA-II, vitamin K absence or antagonist-II.

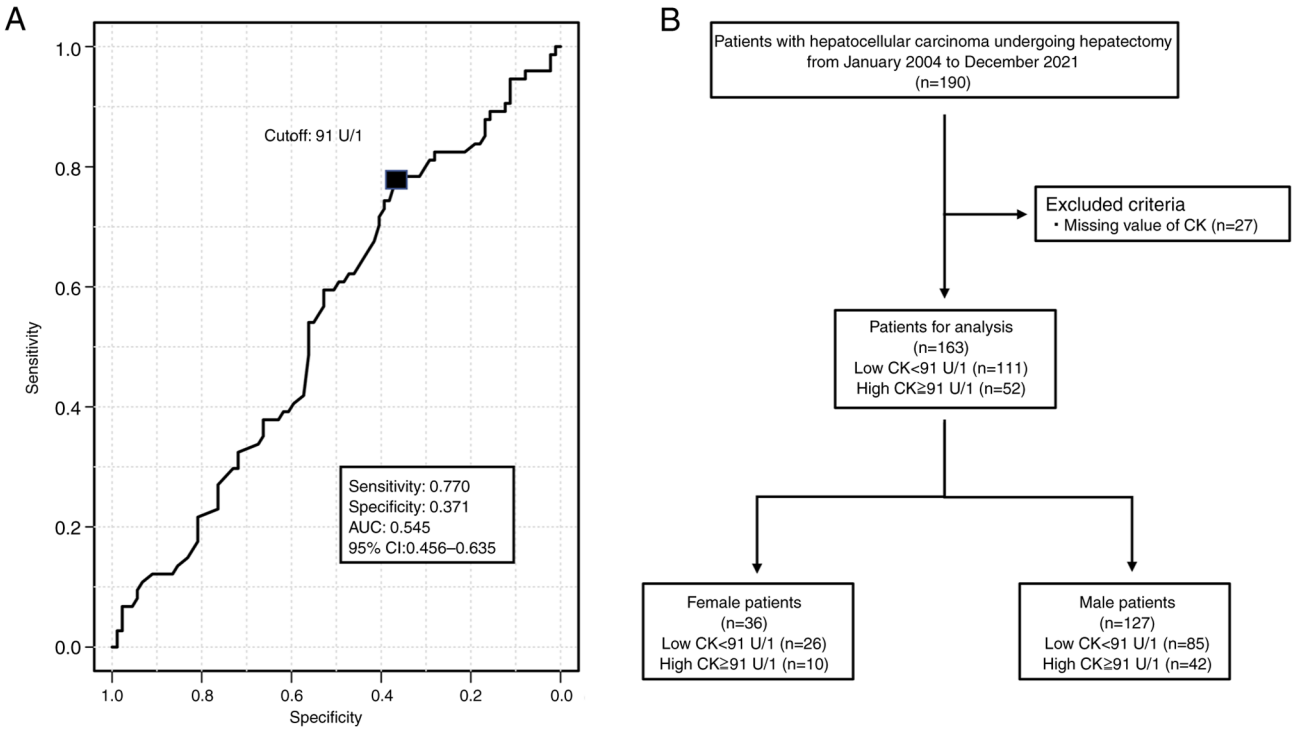

Figure 1. (A) Receiver operating characteristic curve predicting overall survival of all patients by preoperative s-CK and (B) a flow chart of patients analyzed in the study. AUC, the area under the curve; CI, confidence interval; CK, creatine kinase.

Table II. Univariate and multivariate analysis of clinicopathological factors for predicting overall survival of patients with hepatocellular carcinoma.

		Univariate analysis		Multivariate analysis	
Variables	No. patients (n=163)	Hazard ratio (95% confidence interval)	P-value[a]	Hazard ratio (95% confidence interval)	P-value[a]
Sex					
Male/Female	127/36	1.756 (0.946-3.259)	0.074		
Age (years)					
≥65/<65	108/55	1.744 (1.031-2.950)	0.038	1.502 (0.884-2.552)	0.133
Cirrhotic liver					
Positive/negative	101/62	0.897 (0.559-1.437)	0.650		
Tumor size, mm					
≥20/<20	121/42	1.262 (0.724-2.198)	0.412		
Stage					
I II/III IV	111/52	0.781 (0.483-1.263)	0.313		
ICG R15, %					
≥10/<10	86/73	1.996 (1.223-3.258)	0.005	2.077 (1.264-3.414)	0.004
White blood cell, /μl					
≥8,000/<8,000	9/154	0.618 (0.195-1.969)	0.416		
Platelet, /μl					
≥150,000/<150,000	94/69	1.221(0.769-1.936)	0.397		
AFP, ng/ml					
Positive/negative	58/105	1.668 (1.053-2.643)	0.029	1.336 (0.819-2.179)	0.247
PIVKA-II, mAU/ml					
Positive/negative	83/80	2.389 (1.473-3.875)	0.001	2.115 (1.263-3.541)	0.004
Preoperative serum creatine kinase, U/l					
<91/≥91	111/52	1.739 (1.017-2.973)	0.043	1.946 (1.115-3.397)	0.019

[a]Cox proportional hazard regression analysis. ICG R15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; PIVKA-II, vitamin K absence or antagonist-II.

conduct a multi-center collaborative study by recruiting other facilities that agree with this paper's objectives.

Regarding to the clinicopathological significance of s-CK level, low s-CK level was related to the tumor progression in other cancers. Reduction of s-CK level was found in the deep tumor in esophageal (3) and gastric cancer (4), large tumor in breast cancer (5), and bone and lymph node metastases in lung cancer (7). However, in the present study on HCC, preoperative s-CK levels were not associated with any of the analyzed clinicopathologic factors. These findings suggest that clinicopathologic factors might have limited association with prognosis in HCC and that the malignancy potential of the tumor itself might be related to prognosis.

Regarding to the OS, the low and high s-CK groups showed similar survival curves until five years after surgery. However, the survival difference appeared at five years after surgery in OS. This observation was not previously reported in other cancer types and might be unique to HCC. This difference might be due to the availability of various treatment options for HCC recurrence, including repeat liver resection, radiofrequency ablation, transcatheter arterial chemoembolization, chemotherapy, and immune checkpoint inhibitors, which might have contributed to improved survival after recurrence for up to five years. Although the tendency of RFS was similar to that of OS, the differences in RFS between the two groups were obvious even within five years. The RFS was significantly different between the patients with low and high preoperative s-CK levels five years after liver resection.

The potential role of estrogen should be considered regarding the observed sex difference in the impact of low preoperative s-CK levels on OS. In females, estrogen, a major female hormone, stabilizes skeletal fascia by suppressing the release of s-CK into the bloodstream (16,17). Therefore, s-CK levels are lower in females than in males, and the difference in OS between the female patients with low and high s-CK levels could have been similar to the difference in OS observed between the male patients in the absence of estrogen's effect on s-CK levels. Because our study included only 36 females, prognostic factors were not examined separately for males and females. Estrogen suppression of s-CK release may have the

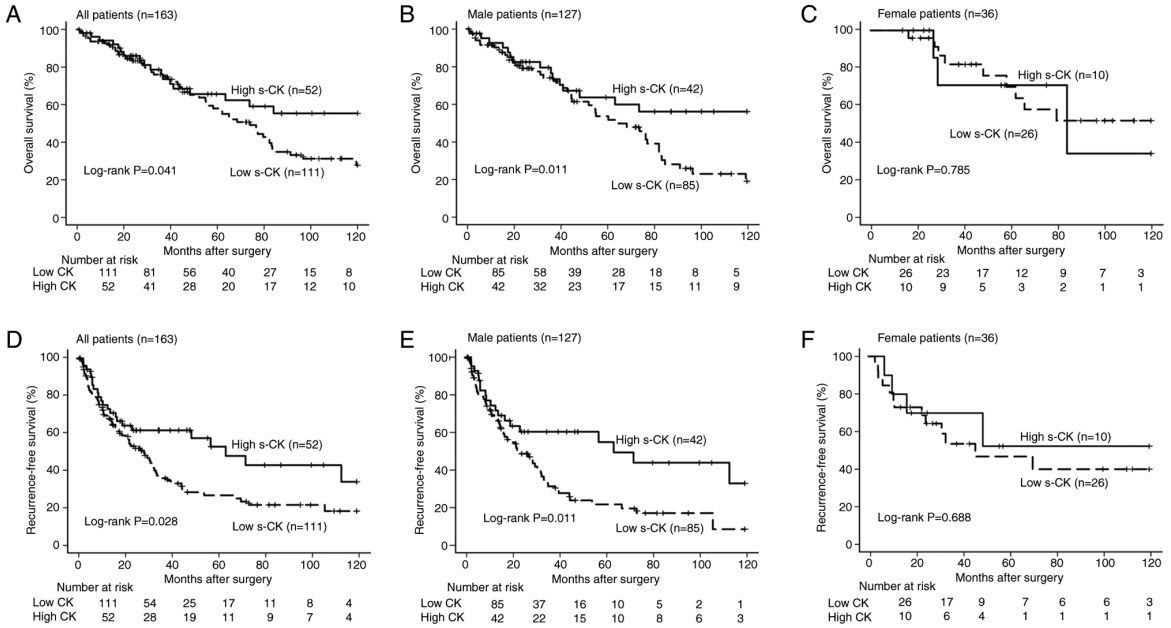

Figure 2. Comparisons of overall survival curves between low s-CK group and high s-CK group for (A) all patients, (B) male patients and (C) female patients. Comparisons of recurrence-free survival curves between the low s-CK group and the high s-CK group for (D) all patients, (E) male patients and (F) female patients. s-CK, serum creatine kinase.

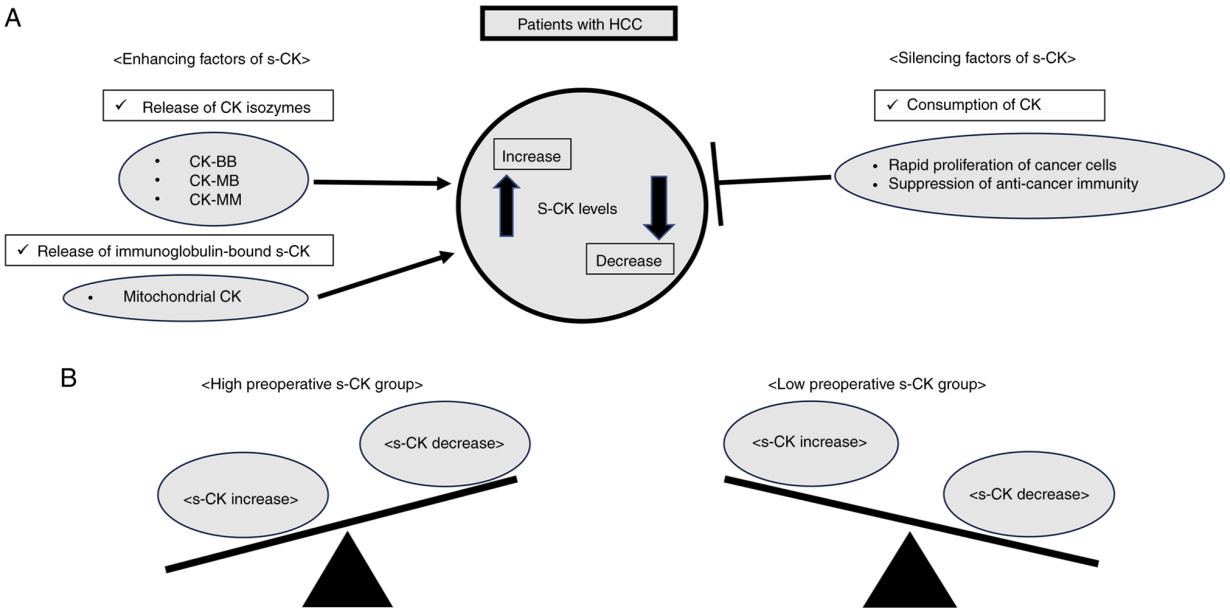

Figure 3. Mechanism of regulations of s-CK in patients with HCC. (A) Details of factors that increase and decrease preoperative s-CK levels in patients with HCC. (B) Diagram of the balance of s-CK in the low and high preoperative s-CK groups. s-CK, serum creatine kinase; HCC, hepatocellular carcinoma.

same effect as in gastric cancer (4), but the small number of female cases makes it difficult to draw a definite conclusion. Further research is necessary to determine if s-CK is a potential prognostic factor in females.

Our multivariate analysis also revealed that low preoperative s-CK level was an independent poor risk factor OS and RFS, similar to that observed in esophageal (3) and gastric cancers (4). Although low s-CK levels were associated with disease progression in esophageal and gastric cancers, a similar finding was not previously reported in HCC. We speculate that tumor volume might be associated with s-CK consumption in esophageal and gastric cancers. However, we did not observe an association between tumor volume and low s-CK levels in the current cohort of patients with HCC and low s-CK levels in HCC might strongly reflect malignant potential. It was suggested that the higher the cancer cells consume s-CK, the higher the malignant potential.

Based on our present study, in the patients with HCC, various factors are supposed to effect s-CK levels. There were several factors that increased or decreased s-CK in the patients with HCC (Fig. 3A). According to Yan YB's report (1), enhancing factors of s-CK include CK isozymes

Table III. Univariate and multivariate analysis of clinicopathological factors for predicting recurrence-free survival of patients with hepatocellular carcinoma.

		Univariate analysis		Multivariate analysis	
Variables	No. patients (n=163)	Hazard ratio (95% confidence interval)	P-value[a]	Hazard ratio (95% confidence interval)	P-value[a]
Sex					
Male/female	127/36	1.651 (0.974-2.798)	0.063		
Age, years					
≥65/<65	108/55	1.127 (0.732-1.737)	0.587		
Cirrhotic liver					
Positive/negative	101/62	1.356 (0.879-2.091)	0.587		
Tumor size, mm					
≥20/<20	121/42	1.085 (0.676-1.739)	0.736		
Stage					
I II/III IV	111/52	0.875 (0.566-1.354)	0.549		
ICG R15, %					
≥10/<10	86/73	1.514 (0.991-2.312)	0.050	1.625 (1.061-2.491)	0.026
White blood cell, /μl					
≥8,000/<8,000	9/154	0.803 (0.326-1.979)	0.634		
Platelet, /μl					
≥150,000/<150,000	94/69	1.452 (0.965-2.184)	0.073		
AFP, ng/ml					
Positive/Negative	58/105	1.295 0.850-1.972)	0.228		
PIVKA-II, mAU/ml					
Positive/Negative	83/80	1.746 (1.155-2.639)	0.008	1.802 (1.180-2.752)	0.006
Preoperative serum creatine kinase, U/l					
<91/≥91	111/52	1.689 (1.053-2.709)	0.029	1.843 (1.122-3.000)	0.014

[a]Cox proportional hazard regression analysis. ICG R15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; PIVKA-II, vitamin K absence or antagonist-II.

(e.g., CK-BB, CK-MB, CK-MM) and immunoglobulin-bound forms (e.g., mitochondrial CK), which may be associated with s-CK increase. On the other hand, silencing factors of s-CK include rapid cancer proliferation and decreased anti-cancer immunity, which may be associated with s-CK decrease. We think that the rapid proliferation of cancer cells and the suppression of anti-cancer immunity could be explained by cancer cells' enhancement of creatine metabolism (2). Highly active cancer cells need energy for rapid proliferation. Therefore, we assume cancer cells obtain energy by consuming s-CK and converting adenosine triphosphate to adenosine diphosphate. T cells play an essential role in anti-cancer defense. And creatine metabolism has the function of anti-tumor T-cell immunity (2). In rapidly proliferated cancer cells, T cells and cancer cells compete for creatine kinase in the blood. As a result, T cell production is reduced, leading to decreased anti-tumor immunity. The preoperative high s-CK group is a condition where CK increase exceeds decrease, and the preoperative low s-CK group is a condition where CK decrease exceeds increase (Fig. 3B). Therefore, the preoperative low s-CK group may reflect a highly malignant potential of HCC.

The present study has several limitations. First, since this was the first study to evaluate the association between s-CK levels and HCC, a cut-off value for S-CK was determined using a test cohort of all patients. We expect further reports from other centers on the validation cohort regarding the significance of the cut-off value in the future. Second, the sample size was relatively small in this single-center study and future studies with larger cohort sizes are warranted to confirm the current study findings. Third, CK has three isozymes: CK-MM, CK-MB, and CK-BB. A previous study reported that the CK-MB/total CK ratio was useful in detecting pancreatic adenocarcinoma (18), suggesting that the determination of all isozymes might be considered to more accurately evaluate the role of CK as a prognostic factor compared to total s-CK levels. Unfortunately, the retrospective study design precluded the determination of the levels of all three isozymes. Fourth, underlying diseases such as dermatomyositis and cardiovascular disease, which could potentially impact preoperative

s-CK levels, were not excluded. We aim to resolve these limitations in the future through a multicenter study.

In conclusion, low preoperative s-CK level was an independent risk factor for poor OS and RFS after surgery in patients with HCC. Our present study showed promising early findings regarding the association between low s-CK levels and poor OS in HCC. Further study with a larger sample size is required to make the findings more statistically reliable. Long-term follow-up of patients is crucial to ensure the impact of low s-CK levels on poor OS and RFS. Rigorous statistical analysis will ensure the strength of the conclusions drawn. It is also important to compare the prognostic value of low s-CK levels with existing standard treatments to establish their relative importance. These efforts will help determine whether low s-CK levels can be reliably used as a prognostic biomarker in the clinical management of HCC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YM and HS designed this study. YM, YO, RO, YI, KK, JI, TM, MT and KF were involved in its conception, design and data collection. YM, RO and YI confirm the authenticity of all the raw data. YM and HS wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Toho University Omori Medical Center (approval no. M22223; November 2022), and we provided means of opting out for patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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