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ORIGINAL RESEARCH

Prognostic Significance of Elevated Preoperative Serum CA125 Levels After Curative Hepatectomy for Hepatocellular Carcinoma

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Objective: The aim of this study was to investigate predictive and prognostic significance of elevated carbohydrate antigen 125 (CA125) serum level preoperatively.

Methods: A total of 3440 HCC patients were retrospectively enrolled into this study, and all of them underwent curative hepatectomy. The clinical and pathological variables together with CA125, AFP serum level were collected at diagnosis and postoperative care stages. A chi-square test was used to compare the differences between variables. Overall survival (OS) and recurrence-free survival (RFS) were measured with the Kaplan–Meier method. To estimate prognostic factors, a multivariate Cox regression analysis was performed.

Results: Of the 3440 enrolled patients, 409 (11.9%) exhibited elevated preoperative serum CA125 level, and high preoperative serum CA125 level was significantly associated with younger age, female, higher ALBI grade, higher serum AFP level, blood transfusion, more operative bleeding loss, larger tumor size, multiple tumor, increased macro- or micro-vascular invasion, Edmondson grade III–IV, absence of tumor capsular, satellite nodules, liver cirrhosis, more advanced TNM stages and BCLC stages. HCC patients with high preoperative serum CA125 level usually had a shorter OS rate and experienced a higher probability of recurrence than those with normal preoperative serum level of CA125 ($p<0.0001$). The multivariate analysis suggested that elevated serum CA125 level serves as an independent predictor of OS and RFS in HCC patients after surgical resection.

Conclusion: Elevated preoperative serum CA125 correlated with many malignant characterizations of HCC and served as an independent prognostic factor of OS and RFS.

Keywords: CA125, hepatocellular carcinoma, prognosis, hepatectomy

Introduction

As the fifth most common and malignant tumor in the world, hepatocellular carcinoma (HCC) is deemed as the second cause of cancer-related death.[1,2] In China more than 400 million persons are suffering from liver disease,[3,4] contributing to 450,000 new cases of HCC and 383,000 patients death each year.[3,5] During the past decades, curative hepatectomy has been widely applied and considered as the first choice to treat HCC.[6] However, HCC patients frequently subject to recurrence/metastasis postoperatively in clinical practice. So that, only 25–40% patients survive more than 5 years, and 70% of them suffers from recurrence in 5 years after curative hepatectomy.[7–9] Therefore, it remains valuable to discover and identify novel biomarker and prognostic factor to diagnosis or predict the outcome of HCC patients postoperatively. Carbohydrate antigen 125

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(CA125) is one of the widely accepted serum cancer biomarkers and has been identified to be associated with worse prognosis in ovarian cancer, gastric cardia cancer,[10] pancreatic adenocarcinoma,[11] colorectal cancer,[12] and uterine cancer.[13] In clinic, elevated serum CA125 is frequently identified in hepatocellular carcinoma. Unfortunately, the prognostic significance of serum CA125 has not been well elucidated so far. Therefore, investigating the clinical significance of serum CA125 and evaluating its prognostic value are helpful to identify a new prognostic predictor of HCC patients after hepatectomy.

Methods

Patients and Study Design

This study was conducted to the ethical guideline of the 1975 Declaration of Helsinki and was approved by the institutional ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University. Informed consent was obtained from each patient for their data to be used for research purposes. HCC patients who underwent hepatectomy between January 2008 and December 2015 were extracted from primary liver cancer big data (PLCBD) by an IT engineer, and then was verified by three independent researchers (Yao Huang, Jianxing Zeng, Teng Liu) in this study. Patient information included demographic information, surgical factors, laboratory parameters and tumor characteristics.

The inclusion criteria were set as follows: (1) 0 to 1 score of performance status;[14] (2) well liver function; (3) no evidence of extrahepatic metastasis and distant metastasis; (4) no history of preoperative anticancer treatment; (5) no history of other malignancies, and (6) curative hepatectomy with tumor-negative resection margins (R0 resection).[15] Meanwhile, patients who received palliative tumor resection, received recurrent tumor resection, had incomplete clinical data, died of severe surgical complications, and lost to follow-up within 60 days after discharge were excluded.

All enrolled patients received routine serological examination, imaging examination, and histopathological diagnosis. Histologic grading of HCC was based on the Edmondson-Steiner classification.[16] The criterion of the American Association for the Study of Liver Diseases was used for preoperative clinical diagnosis of HCC.[17] All patients were staged using the American Joint Committee on Cancer (AJCC) staging system[17] and Barcelona Clinic Liver Cancer (BCLC) staging classification.[18]

The cut-off of CA125 was based on normal reference value. We defined CA125 $\leq$ 35kU/L as normal CA125 group (N-CA125) and CA125 >35kU/L as high CA125 group (H-CA125). The clinicopathological features and the prognosis of HCC patients in N-CA125 group were compared with those in H-CA125 group.

Follow-Up

Patients' follow-up was strictly performed every 3 months in the first 2 years after surgery and later every 3 to 6 months. In each time of the follow-up, patients still received the following examination: liver function, serum AFP and imaging. The diagnostic criteria for tumor recurrence were the same as for the initial diagnosis.[17] The follow-up was censored on 30th October 2018. The endpoints of the study were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the interval between the date of surgery and the date of death or the last follow-up. And RFS was calculated as the time ranged from the date of surgery to the date of recurrence or death, or the date of last follow-up.

Statistical Analysis

Categorical variables were grouped on the basis of normal reference value or clinical judgment. Categorical variables were compared using the chi-square test or Fisher exact test. Continuous variables were compared using the Student's *t*-test for variables with a normal distribution or Mann–Whitney *U*-test for variables with an abnormal distribution. Kaplan–Meier method was used to estimate the OS and RFS rate, and differences between two groups were analyzed by Log-rank test. Subgroup analyzes were conducted based on the Cox model. All statistical tests were 2-tailed and a p-value of less than 0.05 was considered statistically significant. All statistical analysis was performed with R version 3.5.2 (http://www.r-project.org/).

Categorical variables are presented as no. (%); the continuous variables with normal distribution were presented with Mean (SD); and the continuous variables with abnormal distribution were showed as median (interquartile range).

Results

Comparison of Clinicopathological Features Among HCC Patients with Normal and High Serum CA125 Levels

During the study period, there were a total of 6623 patients with HCC. 3183 patients were excluded because of

extrahepatic metastasis (n=207), preoperative anticancer treatment (n =464), recurrent tumor resection (n=256), history of other malignancies (n =56), palliative tumor resection (n=174), incomplete clinical data (n=1739), perioperative death (n=33), and early loss to follow-up after discharge (n=254) (Figure 1).

According to our inclusion and exclusion criteria, 3440 patients with median age of 50.0 years old (ranged from 41 to 60 years old) were enrolled in this study. Among these patients, 3031 HCC patients were divided into N-CA125 group, whereas 409 HCC patients were distributed to H-CA125 group.

As summarized in Table 1, HCC patients in H-CA125 group were younger and higher probability of female comparing to the patients in N-CA125 group. Moreover, higher serum CA125 level was significantly associated with higher ALBI grade, higher serum AFP level, blood transfusion, more operative bleeding loss, larger tumor size, multiple tumor, increased macro- or micro-vascular invasion, Edmondson grade III–IV, absence of tumor capsulation, satellite nodules, liver cirrhosis, more advanced TNM stages and BCLC stages.

Comparison of Prognosis Between Normal CA125 and High CA125 HCC Patients

Kaplan–Meier survival curve was applied to evaluate the survival state of enrollments in this study. As shown in

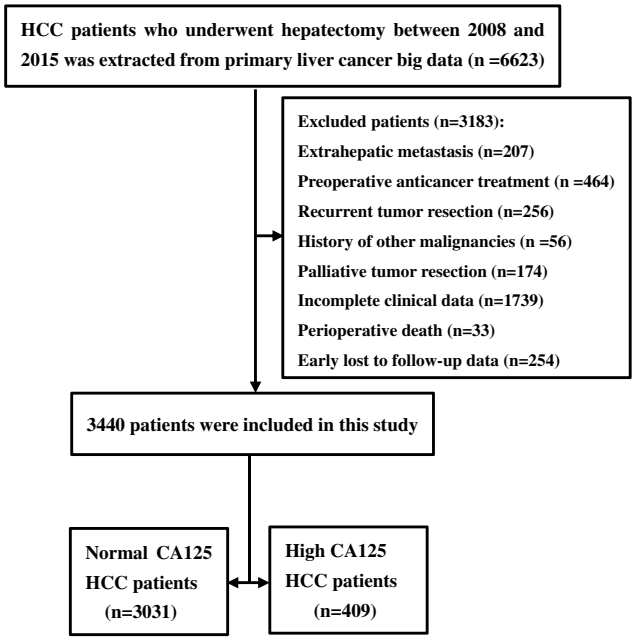

Figure 1 The flow chart of selected patients.
Abbreviations: HCC, hepatocellular carcinoma; CA125, carbohydrate antigen 125.

Table 1 Comparison of Clinicopathological Features Between Normal CA125 and High CA125 HCC Patients Who Underwent Curative Hepatectomy

Variables	Normal CA125 HCC Patients (n=3031)	High CA125 HCC Patients (n=409)	p-value
Age, years			
Median [IQR]	52.0 [45.0, 60.0]	48.0 [41.0, 58.0]	<0.001
Gender			
Female	397 (13.1%)	78 (19.1%)	0.00133
Male	2634 (86.9%)	331 (80.9%)	
Etiology			
HBV	2657 (87.7%)	364 (89.0%)	0.709
HCV	44 (1.5%)	6 (1.5%)	
NBNC	330 (10.9%)	39 (9.5%)	
ALBI grade			
Grade 1	2400 (79.2%)	260 (63.6%)	<0.001
Grade 2	631 (20.8%)	148 (36.2%)	
Grade 3	0 (0%)	1 (0.2%)	
AFP			
≤20ng/mL	1184 (39.1%)	107 (26.2%)	<0.001
>20ng/mL	1847 (60.9%)	302 (73.8%)	
Blood transfusion			
No	2807 (92.6%)	327 (80.0%)	<0.001
Yes	224 (7.4%)	82 (20.0%)	
Operative bleeding loss			
<800mL	2852 (94.1%)	345 (84.4%)	<0.001
≥800mL	179 (5.9%)	64 (15.6%)	
Tumor diameter, cm			
Median [IQR]	4.90 [3.20, 7.40]	9.10 [5.30, 12.6]	<0.001
Tumor number			
Solitary	2476 (81.7%)	299 (73.1%)	<0.001
Multiple	555 (18.3%)	110 (26.9%)	
Microscopic vascular invasion			
No	1928 (63.6%)	195 (47.7%)	<0.001
Yes	1103 (36.4%)	214 (52.3%)	
Macroscopic vascular invasion			
No	2693 (88.8%)	313 (76.5%)	<0.001
Yes	338 (11.2%)	96 (23.5%)	

(*Continued*)

Table 1 (Continued).

Variables	Normal CA125 HCC Patients (n=3031)	High CA125 HCC Patients (n=409)	p-value
Edmondson grade			
I–II	359 (11.8%)	19 (4.6%)	<0.001
III–IV	2672 (88.2%)	390 (95.4%)	
Tumor capsular			
No	603 (19.9%)	112 (27.4%)	<0.001
Yes	2428 (80.1%)	297 (72.6%)	
Satellite nodules			
No	1767 (58.3%)	207 (50.6%)	0.00376
Yes	1264 (41.7%)	202 (49.4%)	
Liver cirrhosis			
No	882 (29.1%)	95 (23.2%)	0.0158
Yes	2149 (70.9%)	314 (76.8%)	
BCLC stage			
0/A	2316 (76.4%)	241 (58.9%)	<0.001
B	377 (12.4%)	72 (17.6%)	
C	338 (11.2%)	96 (23.5%)	
AJCC TNM stage			
I	1666 (55.0%)	145 (35.5%)	<0.001
II	804 (26.5%)	108 (26.4%)	
IIIA	223 (7.4%)	60 (14.7%)	
IIIB	338 (11.2%)	96 (23.5%)	

Abbreviations: HCC, hepatocellular carcinoma; CA125, carbohydrate antigen 125; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastases; IQR, interquartile range.

Figure 2A, the OS ratio at 1, 3, 5 year was 70.8%, 45.3% and 29.5%, respectively, for HCC patients in H-CA125 group and 87.9%, 66.2% and 48.4%, respectively, for HCC patients in N-CA125 group (p<0.0001, Figure 2A). Additionally, the RFS ratio at 1, 3, 5 year was 45.0%, 28.0% and 17.8%, respectively, for HCC patients in H-CA125 group and 66.8%, 44.0% and 30.2%, respectively, for HCC patients in N-CA125 group (p<0.0001, Figure 2B). These data reflected that HCC patients in H-CA125 group usually suffered from a worse OS and RFS than the patients in N-CA125 group after surgery.

After stratification according to AFP levels, HCC patients in H-CA125 group had a significantly worse prognosis than the patients in N-CA125 group (Figure 3).

Risk Factors Associated with Overall Survival and Tumor Recurrence After Curative Hepatectomy

Fifteen variables were statistically analyzed as risk factors for overall survival and tumor recurrence using a univariate analysis (Table 2). The multivariate model identified 10 variables together with serum CA125 as independent prognostic factors associated with overall survival (Table 3). Eleven variables including CA125 were the independent risk factors associated with tumor recurrence by multivariate analysis (Table 3). The multivariate analysis revealed that HCC patients in N-CA125 group had a significantly better OS and RFS rate than the patients in H-CA125 group [hazard ratio (HR) for OS = 1.267; 95% confidence interval (CI): 1.104–1.454; p = 0.001; hazard ratio (HR) for RFS = 1.172; 95% confidence interval (CI): 1.036–1.327; p = 0.012].

Discussion

Serum CA125 is a "classical" biomarker of ovarian cancer, but its diagnostic and prognostic value in HCC has not been well clarified. In the present study, a statistical analysis of a big cohort of HCC patients with long term follow-up was performed and indicated that preoperative serum CA125 is closely associated with OS and RFS of HCC patients after curative hepatectomy.

CA125 was discovered for the first time and identified as a tumor marker of ovarian cancer in 1981 by Niloff et al.[19] Nowadays, serum CA125 is not only used in the diagnosis of many kinds of tumors, but also an effective biomarker to predict the prognosis of tumors. It can predict the recurrence of various cancers, such as ovarian cancer,[20] breast cancer,[21] lung cancer,[22] and gastric cancer.[23,24] Therefore, the clinical significance of CA125 has extensively accepted, which indicated that CA125 might also be a HCC biomarker.

CA125 is a macromolecule glycoprotein synthesized and stored in coelomic epithelial cells, which is produced by MUC16 gene and contains 22,000 amino acids. It normally cannot enter the blood circulation due to the blocking action of the basement membrane and the connection between cells. However, when the tissue undergoes malignant transformation, intracellular CA125 concentrates on the edge of cells, depolarizes local cell membranes and is released off the cells.

Theoretically, there are two possible reasons for the increase of serum CA125. One is that the production of CA125 is increased during the development and progression of malignant tumors. It is well known that hypoxia

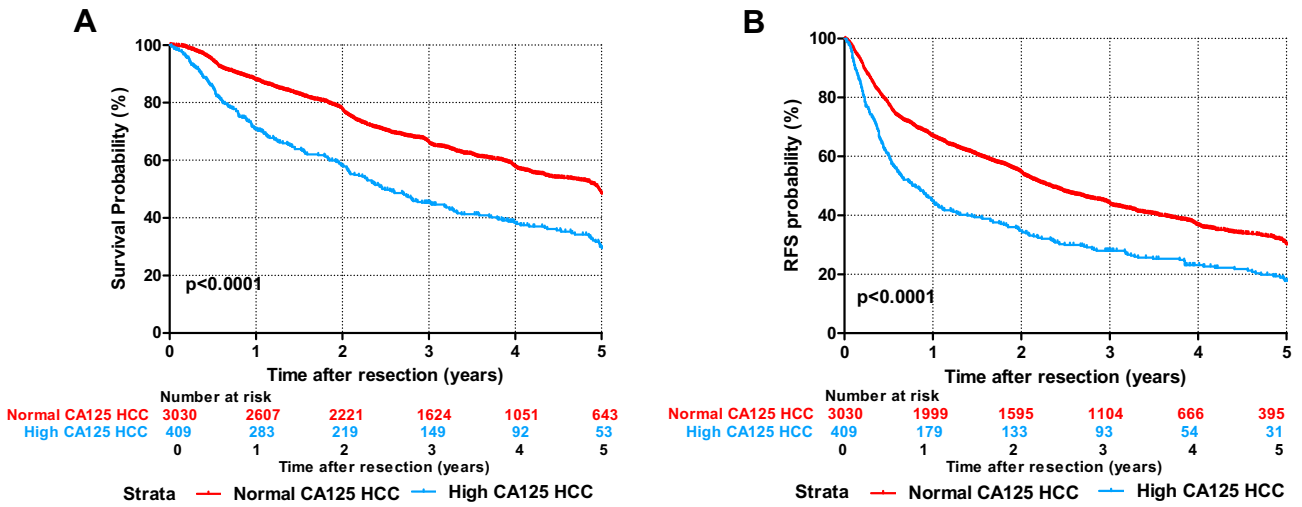

Figure 2 Comparison of prognosis after curative hepatectomy between normal CA125 and high CA125 HCC groups. (**A**) Overall survival. (**B**) Recurrence-free survival.
Abbreviations: HCC, hepatocellular carcinoma; CA125, carbohydrate antigen 125; RFS, recurrence-free survival.

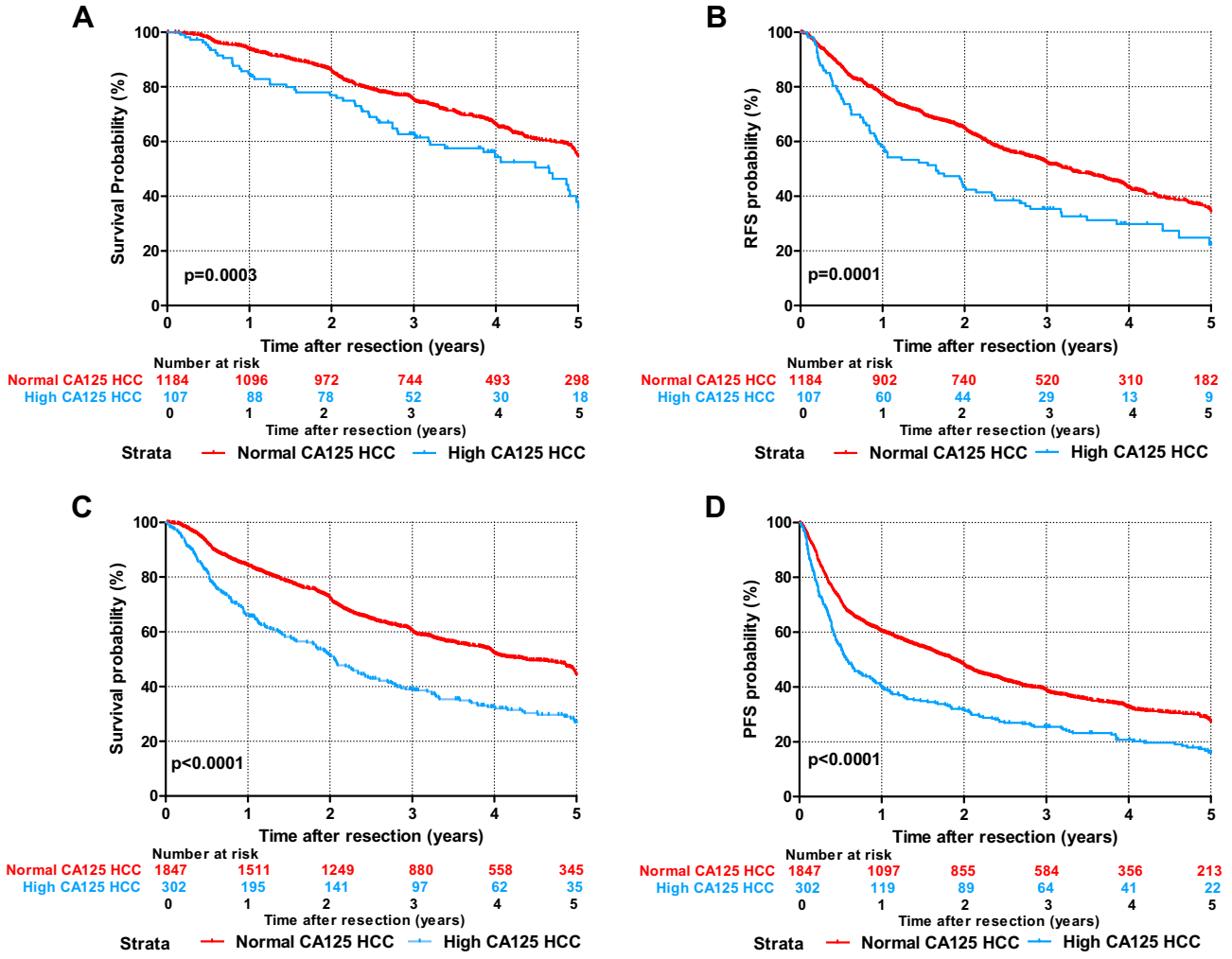

Figure 3 Comparison of prognosis after curative hepatectomy between normal CA125 and high CA125 HCC groups. Survival prognosis was stratified by AFP. (**A**) Overall survival in normal AFP subgroup. (**B**) Recurrence-free survival in normal AFP subgroup. (**C**) Overall survival in high AFP subgroup. (**D**) Recurrence-free survival in high AFP subgroup.
Abbreviations: HCC, hepatocellular carcinoma; CA125, carbohydrate antigen 125; AFP, alpha-fetoprotein; RFS, recurrence-free survival.

Table 2 Univariate Analysis of Factors Associated with Overall Survival and Tumor Recurrence After Curative Hepatectomy

Variables	Overall Survival			Tumor Recurrence		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Age, years	0.995	0.991–0.999	0.028	0.995	0.991–0.999	0.01
Gender						
Male versus Female	1.056	0.918–1.213	0.446	1.197	1.061–1.35	0.004
Etiology						
HCV versus HBV	0.902	0.607–1.135	0.609	1.002	0.718–1.399	0.992
NBNC versus HBV	0.968	0.827–1.339	0.691	0.825	0.717–0.947	0.006
CA125						
>35 versus ≤35 kU/L	1.899	1.666–2.164	<0.001	1.648	1.465–1.853	<0.001
AFP						
>20 versus ≤20ng/mL	1.612	1.456–1.786	<0.001	1.459	1.34–1.588	<0.001
Blood transfusion						
Yes versus No	1.794	1.547–2.081	<0.001	1.759	1.543–2.005	<0.001
Operative bleeding loss						
≥800 versus <800mL	1.775	1.505–2.093	<0.001	1.734	1.498–2.008	<0.001
Tumor diameter, cm	1.112	1.1–1.124	<0.001	1.09	1.08–1.101	<0.001
Tumor number						
Multiple versus solitary	1.764	1.578–1.971	<0.001	1.763	1.601–1.941	<0.001
Microscopic vascular invasion						
Yes versus No	2.194	1.994–2.415	<0.001	1.886	1.737–2.047	<0.001
Macroscopic vascular invasion						
Yes versus No	3.729	3.305–4.207	<0.001	3.032	2.713–3.388	<0.001
Edmondson grade						
III–IV versus I–II	2.333	1.937–2.809	<0.001	1.783	1.548–2.053	<0.001
Tumor capsular						
Yes versus No	0.575	0.516–0.641	<0.001	0.657	0.597–0.723	<0.001
Satellite nodules						
Yes versus No	1.762	1.601–1.939	<0.001	1.65	1.521–1.79	<0.001
Liver cirrhosis						
Yes versus No	1.074	0.966–1.195	0.186	1.124	1.026–1.231	0.012

Abbreviations: CA125, carbohydrate antigen 125; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, Non-B non-C; CI, confidence interval.

accelerates malignant tumors to proliferate and production of MUC16, which cause synthesizing more CA125. The other reason is that more CA125 may be released into the blood circulation due to various tumor behaviors of severe cell damage, angiogenesis, vascular invasion and destruction.[25] On the other hand, the liver is the main site for degrading glycoproteins derived from the blood circulation.[26] It is proved that serum CA125 levels are higher in HCC patients with liver cirrhosis and hepatitis due to weak metabolic ability in dysfunctional liver.[27] Thus, elevated serum CA125 might indicate that the tumor has broken through the capsulation, stayed at an advanced stage and the patients subjected to worse liver function. About 11.9% (409/3440) of enrolled patients in this study had elevated preoperative serum CA125 levels. It is not a high proportion, probably because that the enrolled patients are all resectable and have well liver function.

The results of this study showed that preoperative serum CA125 was significantly associated with many

Table 3 Multivariate Analysis of Factors Associated with Overall Survival and Tumor Recurrence After Curative Hepatectomy

Variables	Overall Survival			Tumor Recurrence		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Age, years	1.005	1.001–1.01	0.024	–	–	–
Gender						
Male versus Female	–	–	–	1.155	1.021–1.306	0.022
CA125						
>35 versus ≤35 kU/L	1.267	1.104–1.454	0.001	1.172	1.036–1.327	0.012
AFP						
>20 versus ≤20ng/mL	1.179	1.058–1.314	0.003	1.087	1.035–1.142	0.001
Tumor diameter, cm	1.076	1.063–1.089	<0.001	1.059	1.048–1.071	<0.001
Tumor number						
Multiple versus Solitary	1.21	1.062–1.378	0.004	1.301	1.164–1.454	<0.001
Microscopic vascular invasion						
Yes versus No	1.343	1.199–1.505	<0.001	1.301	1.164–1.454	<0.001
Macroscopic vascular invasion						
Yes versus No	1.996	1.738–2.293	<0.001	1.738	1.527–1.977	<0.001
Edmondson grade						
III–IV versus I–II	1.5	1.237–1.819	<0.001	1.251	1.079–1.45	0.003
Tumor capsular						
Yes versus No	0.729	0.648–0.818	<0.001	0.823	0.742–0.912	<0.001
Satellite nodules						
Yes versus No	1.171	1.038–1.32	0.01	1.164	1.052–1.287	0.003
Liver cirrhosis						
Yes versus No	–	–	–	1.145	1.044–1.256	0.004

Abbreviations: CA125, carbohydrate antigen 125; AFP, alpha-fetoprotein; CI, confidence interval.

clinicopathological factors in patients with HCC who underwent curative hepatectomy, including larger tumor size, multiple tumor, increased macro- or micro-vascular invasion, absence of tumor capsulation, satellite nodules, more advanced TNM stages and BCLC stages. These indicators all point to more advanced HCC. This correlation may contribute to the fact that CA125 was a valuable tool to predict the prognosis of HCC after curative hepatectomy.

The results of this study showed that the patients with HCC who had elevated preoperative serum CA125 had lower RFS and OS after curative hepatectomy. Moreover, multivariate analysis revealed that preoperative serum CA125 was an independent prognostic factor after curative hepatectomy for hepatocellular carcinoma. The result suggests that, to the patients with HCC who had elevated preoperative serum CA125 levels, more effective anti-recurrence therapy and closer follow-up are required after curative hepatectomy.

The ability of serum CA125 to predict tumor prognosis appears to be superior to many commonly used tumor indicators. For example, although CA19-9 is most commonly used in pancreatic cancer, serum CA125 is approved more efficient than CA19-9 in predicting resectability of pancreatic cancer.[28,29] In lung cancer, serum CA125 shows a better performance than CEA in predicting the prognosis.[30] Studies have confirmed that preoperative serum CA125 is an independent prognostic factor for overall survival of colon cancer, rather than CEA.[31] Serum AFP is the most common tumor marker for HCC, following with elevated serum AFP among 2/3 of HCC patients. A markedly elevated serum AFP level usually indicates a poor prognosis of HCC.[32] However, the role of serum CA125 level in the prognosis of HCC has been

underestimated for a long time. The stratified results of this study showed that the patients of HCC with elevated preoperative serum CA125 levels suffered from worse prognosis, regardless of whether serum AFP level was normal or elevated, which further demonstrate the powerful ability of CA125 to predict cancer prognosis.

However, the prediction of the prognosis of patients with HCC after curative hepatectomy should not depend on a certain tumor mark or technique. Combining various prediction methods provide wiser options for the clinical prediction.

Conclusion

The current study demonstrated that elevated preoperative serum CA125 level as an ideal HCC biomarker is significantly associated with many malignant factors of HCC, which is also an effective and valuable prognostic factor of OS and RFS in HCC.

Abbreviations

HCC, hepatocellular carcinoma; CA125, carbohydrate antigen 125; OS, overall survival; RFS, recurrence-free survival; N-CA125, normal CA125; H-CA125, high CA125; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastases; IQR, interquartile range; CI, confidence interval.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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