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ORIGINAL ARTICLE

Low albumin-to-creatinine ratio: a novel predictor of 90-day mortality in hepatocellular carcinoma with liver cirrhosis

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ABSTRACT

BACKGROUND

Despite recent advances in the treatments of hepatocellular carcinoma (HCC), the prognosis of HCC patients remains controversial. Lowered serum albumin in hepatocellular carcinoma, an advanced stage of liver cirrhosis, indicates a worsening condition. Hepatorenal syndrome, marked by increased serum creatinine, is a key mortality indicator. The aim of this study was to determine the serum albumin-to-creatinine ratio (sACR) as a predictor of mortality in patients with HCC and liver cirrhosis.

METHODS

This retrospective cohort study included 37 patients with HCC and liver cirrhosis. Patient characteristics, sACR, model of end-stage liver disease (MELD) score, and Child-Turcotte-Pugh (CTP) score were obtained from medical records. The optimal cut-off point for the sACR was determined using receiver operating characteristic (ROC) analysis to evaluate its predictive ability for 90-day mortality. Survival analysis was conducted using the Kaplan-Meier method with a log-rank test, and Cox regression was employed to obtain hazard ratios (HR) to estimate the patient's prognosis.

RESULTS

A low sACR cut-off of 2.32 was identified. Kaplan-Meier analysis confirmed that sACR met the proportional hazard assumption. sACR <2.32 was a significant predictor of 90-day mortality (HR 6.52; 95% CI 1.80-23.63; p=0.004), comparable to MELD 40 (HR 41.3; 95% CI 1.98-862.90; p=0.016) and CTP category (HR =2.19;95%CI: 0.79-6.06;p=0.131).

CONCLUSION

The sACR is a novel predictor of 90-day mortality in HCC patients with liver cirrhosis. Lower sACR is associated with overall survival and may help to design strategies to personalize management approaches among patients with HCC and liver cirrhosis.

Keywords: Hepatocellular carcinoma, liver cirrhosis, serum albumin-to-creatinine ratio, 90-day mortality predictor

INTRODUCTION

Albumin, the predominant protein in the human body, typically ranges in concentration from approximately 3.5 g/dL to 5 g/dL.[1] Albumin is synthesized by liver hepatocytes and then directly released into the bloodstream. Its main functions include regulating oncotic pressure and serving as a transporter for various drugs.[1,2] Albumin also plays a role in regulating the body's acid-base balance due to its electrically negative charge and functions as an antioxidant to combat free radicals.[3,4] In addition to its role in drug transport, albumin is crucial for the transport of bilirubin, fatty acids, hormones, and minerals throughout the body.[5] In certain clinical conditions, albumin serves as a therapeutic agent, such as in cases of hypovolemia, hypoalbuminemia, and chronic liver disease.[6] Besides being found in the human body, albumin can also be sourced from egg whites, commonly known as albumen.[7,8]

Liver cirrhosis and chronic liver disease rank as the 10th leading cause of death worldwide. Death is often caused by decompensation of the cirrhosis. One of the decompensations that occurs is hypoalbuminemia, resulting from decreased albumin production and increased excretion.[9,10]

On the other hand, cirrhotic patients often progress to cancer. Liver cirrhosis can undergo malignant transformation through a multistep process, beginning with cirrhosis, progressing to low-grade dysplastic nodules (LGDN), then to high-grade dysplastic nodules (HGDN), and subsequently advancing to early HCC and advanced HCC. This pathogenesis is influenced by telomere length and telomerase reactivation, with telomerase reactivation required at stages of HCC development. Telomerase reactivation occurs in over 90% of HCC patients. However, among all HCC cases, in some instances HCC does not develop from infectious diseases, such as hepatitis B or C, or from alcohol abuse. Rather, it can emerge through the transformation of hepatic adenoma.[11-13] Additionally, the hypermetabolic state in cancer patients causes increased breakdown of albumin, leading to hypoalbuminemia. Albumin is transported into proliferating cancer cells and degraded into its component amino acids. This condition is exacerbated by malnutrition in cancer patients. [14-16] Reduced serum albumin levels in HCC patients can serve as an indicator of disease progression in liver cirrhosis.

Elevated serum creatinine levels are frequently observed in cirrhotic patients due to acute kidney injury (AKI) or chronic kidney disease (CKD). The current diagnostic criteria for AKI in cirrhosis include an acute rise in serum creatinine by at least 0.3 mg/dL or an increase of 50% or more from baseline levels.[17] Acute kidney injury plays a critical role in predicting the prognosis of patients with cirrhosis and is linked to decreased overall survival in these individuals.[18] Acute kidney injury is also a prognostic determinant in HCC patients, with the hazard ratio value depending on the stage of AKI.[19] Therefore, serum creatinine levels in patients with HCC and liver cirrhosis can serve as a predictor of mortality.

Combining hypoalbuminemia and elevated serum creatinine levels in patients with HCC and cirrhosis can improve the accuracy of mortality prediction. A previous study has shown that markers such as urine albumin-to-creatinine ratio (uACR) ≥30 mg/g are associated with poorer survival outcomes compared to lower uACR levels ($p = 0.053$).[20] By assessing serum albumin-to-creatinine ratio (sACR), this research study explores the prognostic significance of sACR in liver cirrhosis, offering a new perspective on mortality prediction in these patients. One retrospective study involving 409 patients initially diagnosed with HCC showed that pretreatment albumin to C-reactive protein (ACR) ratio is a convenient and useful parameter for HCC patients predicting overall survival and disease-free survival. High ACR is associated with better outcome in HCC patients.[21] A meta-analysis demonstrated that elevated pre-treatment C-reactive protein (CRP) to albumin ratio (CAR) is an independent predictor of poor survival in HCC patients.[22] However, the sACR ratio, also considered as the inflammatory-nutritional index (INI), is seldom reported with a prognosis of HCC with liver cirrhosis. This study aimed to assess the prognostic value of sACR in predicting mortality among patients with HCC and liver cirrhosis.

METHODS

Research design

This study was a retrospective cohort analysis conducted on patients diagnosed with hepatocellular carcinoma (HCC) and liver cirrhosis. Patient identification was conducted through the medical record database Ngoerah Hospital, Denpasar, Bali from December 2022 to January 2024.

Study subjects

The study subjects comprised 45 patients diagnosed with HCC and liver cirrhosis between December 2022 and January 2024. However, 4 patients were excluded due to diabetes mellitus, and 4 additional patients were excluded due to chronic kidney disease (CKD). This left a total of 37 patients who were eligible and included in the final analysis.

The inclusion criteria for this study were: (a) adult patients, both male and female, over 18 years of age with HCC and liver cirrhosis, (b) patients hospitalized at RSUP IGNG Prof. Ngoerah Hospital, Denpasar, Bali, (c) liver cirrhosis diagnosed using transient elastography, with results of Metavir F-4 liver biopsy in certain cases. Hepatocellular carcinoma (HCC) diagnosed using contrast-enhanced CT scans or liver biopsy, (d) mortality status collected from patients that were monitored for 90 days to determine their mortality status, whether the patient was deceased or alive. The exclusion criteria included the following: (a) patients with a history of comorbid conditions such as chronic kidney disease (CKD), and (b) patients with a history of diabetes mellitus.

Demographic, clinical, and laboratory parameters of the study

The demographic data collected included age and sex. Age was categorized into two groups: greater than 60 years as a risk factor and 60 years or younger. Clinical data included the etiology of liver cirrhosis, which was divided into three categories: HBV, HCV, and unknown; hepatic encephalopathy; Child-Turcotte-Pugh (CTP) score, [23] classified into three categories: A, B, and C; ascites, classified into four grades: 0, 1, 2, and 3; and Barcelona Clinic Liver Cancer (BCLC) stage,[24] categorized into four groups: A, B, C, and D. Laboratory data were used to calculate the model of end-stage liver disease (MELD) score, which included total bilirubin, albumin, and International Normalized Ratio (INR) on hospital admission as baseline values. The MELD score was determined using the following formula: MELD score = 9.57 × log e(SCr) + 3.78 × log e(total bilirubin) + 11.2 × log e(INR) + 6.43. The score was categorized into five ranges: <10, 10-19, 20-29, 30-39, and ≥40.[25] The serum albumin-to-creatinine ratio (sACR) was determined by dividing serum albumin (g/dL) by serum creatinine (mg/dL).

Statistical analysis

Statistical analysis was performed using SPSS software version 26.0. Continuous data were presented as mean ± standard deviation for variables that followed a normal distribution ($p > 0.05$); otherwise, they were presented as median (minimum, maximum) if the data were not normally distributed. The samples were divided into two groups: deceased and censored. The term "censored" was used when patients were alive or lost to follow-up. The analysis began by determining the optimal sACR cutoff using receiver operating characteristic (ROC) analysis for the 90-day mortality outcome. sACR was categorized into two groups: low sACR (< cutoff value) and high sACR (≥ cutoff value). Kaplan-Meier analysis, along with the log-rank test, was performed to assess the relationship between sACR as the independent variable and 90-day mortality as the dependent variable. If the Kaplan-Meier curve met the proportional hazards (PH) assumption, a multivariate Cox regression analysis was conducted. This analysis accounted for confounding variables such as age over 60 years, sex, and the Barcelona Clinic Liver Cancer (BCLC) stage. The adjusted hazard ratio (HR) for low sACR was then calculated to assess its impact on 90-day mortality in patients with HCC and liver cirrhosis.

Ethical clearance

This study was conducted based on ethical clearance No. 1740/UN14.2.2.VII.14/LT/2024. This study was approved by the Research Committee of the Faculty of Medicine at Udayana University and Ngoerah Hospital.

RESULT

Patient Characteristics

The clinical characteristics and demographics of the 37 HCC cases are shown in Table 1. The majority of the patients included in this study were male (n=27 or 72.9%), and 24 patients (64.8%) were <60 years old. HCC patients were dominated by CTP C (454.1%). A total of 19 (51.3%) patients had MELD 10-19 and 22 (59.5%) patients had BCLC D. Out of 37 patients diagnosed with HCC and liver cirrhosis, 16 (43.2%) had an sACR <2.32 and 14 (37.8%) had hepatic encephalopathy.

Table 1. Demographics and clinical characteristics of HCC patients with liver cirrhosis (n=37)

Variable	n (%)
Age (years)	
≤ 60	24 (64.8)
> 60	13 (35.2)
Gender	
Male	27 (72.9)
Female	10 (27.1)
CTP	
A	15 (40.5)
B	2 (5.4)
C	20 (54.1)
Hepatic encephalopathy	
Yes	14 (37.8)
No	23 (62.2)
MELD	
<9	7 (18.9)
10-19	19 (51.3)
20-29	7 (18.9)
30-39	3 (8.1)
40	1 (0.8)
BCLC	
A	3 (8.1)
B	4 (10.8)
C	8 (21.6)
D	22 (59.5)
sACR	
< 2.32	16 (43.2)
≥ 2.32	21 (56.8)
Etiology	
HBV	21 (56.7)
HCV	8 (21.6)
Unknown	8 (21.6)

Data presented as n(%); CTP: Child-Turcotte-Pugh; MELD: model of end-stage liver disease; BCLC: Barcelona Clinic Liver Cancer; sACR: serum albumin creatinine ratio

Definition of cut-off value

Area under the curve (AUC) analysis was utilized to identify the optimal cutoff point for the serum albumin-to-creatinine ratio (sACR) in predicting 90-day mortality among patients with HCC and liver cirrhosis. The analysis identified 2.32 as the most effective cutoff value for sACR, with an area under the curve (AUC) of 0.484. The sensitivity of the cutoff was 60.9%, and the specificity was 50%. An sACR value below 2.32 was found to be a significant predictor of 90-day mortality in these patients (Figure 1).

Survival analysis

Survival analysis revealed that an sACR level <2.32 significantly increased mortality in patients with HCC and liver cirrhosis, with a mean survival of 6.7 ± 2.08 days in the sACR <2.32 group compared to 15.7 ± 3.47 days in the sACR ≥2.32 group (p=0.037) (Table 2). Cox regression analysis was performed to obtain the hazard ratio (HR), controlling for confounders such as sex, age >60 years, BCLC stage, etiology, and hepatic encephalopathy. In the final Cox regression analysis, an sACR value below 2.32 emerged as a significant predictor of mortality, with a hazard ratio (HR) of 6.52 (95% confidence interval (95%CI): 1.80-23.63; p=0.004) (Table 3).

The Kaplan-Meier curve shows that patients with sACR <2.32 have a significantly higher mortality rate within 90 days compared to those with sACR ≥2.32. This visual representation highlights the impact of sACR on patient survival, emphasizing the increased risk associated with lower sACR levels (Figure 2).

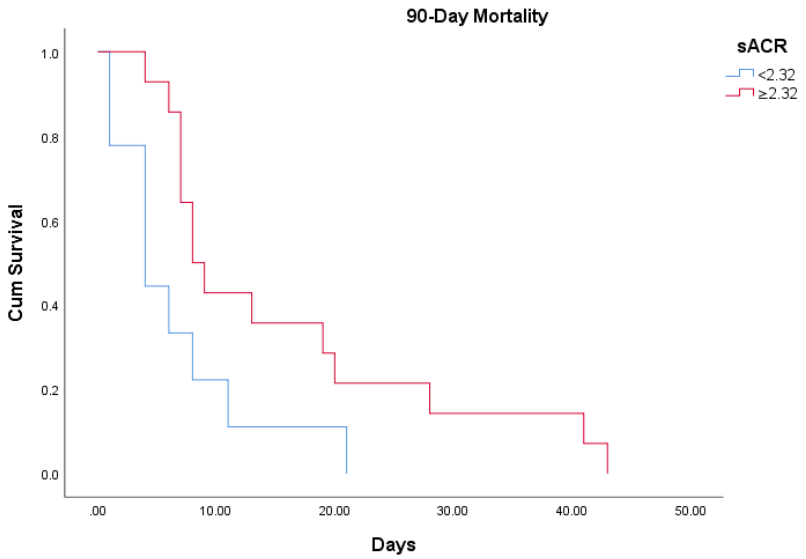

Figure 1. ROC curve for optimal cutoff of sACR
Note sACR = serum albumin creatinine ratio

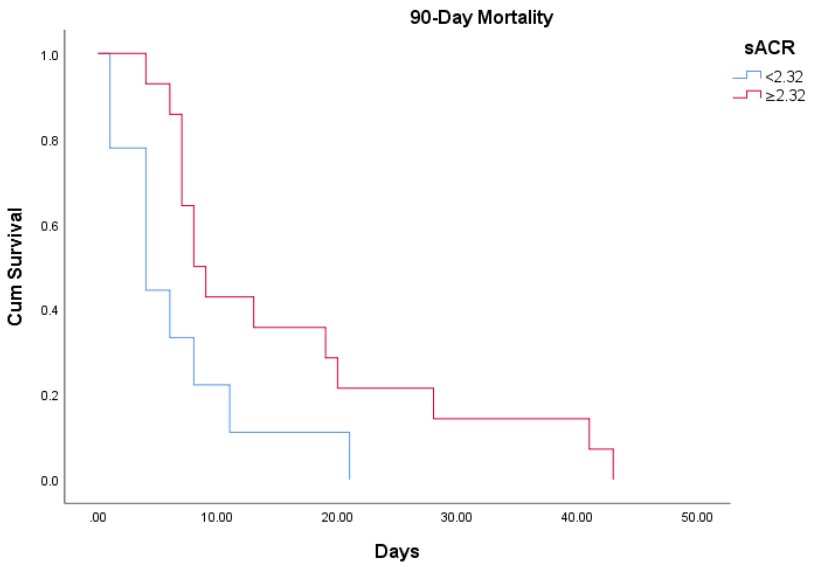

Figure 2. Kaplan-Meier curve of sACR for 90-day mortality

Table 2. Kaplan Meier analysis (Log Rank Test) of sACR

sACR	Mean ± SD	95%CI		Log Rank
		Lower	Upper	
sACR < 2.32	6.7 ± 2.08	2.587	10.747	0.037
sACR ≥ 2.32	15.7 ± 3.47	8.908	22.521	
Overall	12.17 ± 2.42	7.437	16.911	

Note : sACR : serum albumin creatinine ratio

Table 3. Multivariate Cox-regression analysis to identify the risk factors for the 90-day mortality in HCC with liver cirrhosis

Variable	HR	95%CI		p value
		Lower	Upper	
Step 1				
sACR < 2.32	6.09	1.57	23.56	0.009
Age > 60 years	0.76	0.24	2.39	0.641
Male Gender	4.03	0.55	29.23	0.167
Etiology (Unknown)	1.00	1.00	1.00	0.864
Etiology (HBV)	0.57	0.05	6.52	0.656
Etiology (HCV)	0.60	0.08	4.17	0.606
BCLC A	1.00	1.00	1.00	0.071
BCLC D	11.59	0.96	139.83	0.054
BCLC C	40.85	1.68	988.81	0.022
Hepatic Encepalopathy	3.11	0.98	9.85	0.053
Step 3				
ACR < 2.32	6.52	1.80	23.63	**0.004**
Male Gender	4.22	1.23	14.40	0.022
BCLC A	1.00	1.00	1.00	0.030
BCLC D	7.79	0.97	62.23	0.053
BCLC C	32.56	2.46	430.10	0.008
Hepatic encepalopathy	2.83	0.96	8.39	0.059

Note: HR: hazard ratio; BCLC: Barcelona Clinic Liver Cancer; sACR: serum albumin creatinine ratio; HCC: hepatocelullar carcinoma

Table 4. Multivariate Cox proportional hazards regression of prognostic factors for the 90-day mortality in HCC with liver cirrhosis

Variable	HR	95%CI		p value
		Lower	Upper	
sACR < 2.32	6.52	1.80	23.63	0.004
MELD 40	41.30	1.98	862.90	0.016
CTP category	2.19	0.79	6.06	0.131

Note : HR : hazard ratio; sACR : serum albumin creatinine ratio, MELD: Model for End-Stage Liver Disease, CTP : Child-Turcotte Pugh,HCC: hepatocellular carcinoma

The predictive value of sACR <2.32 was compared with MELD and CTP score categories. MELD scores were categorized into five groups: 0-9, 10-19, 20-29, 30-39, and 40. CTP scores were categorized into three groups: A, B, and C. MELD scores of 40 were significantly predictive of 90-day mortality, with HR of 41.30 (95% CI: 1.98-862.90; p=0.016). In contrast, the CTP score category was not a significant predictor of 90-day mortality (HR=2.19;95% CI: 0.79-6.06; p=0.131). Thus, sACR can be considered a competitive predictor of 90-day mortality alongside the MELD score (Table 4).

DISCUSSION

This study found on survival analysis that an sACR <2.32 significantly increased mortality in HCC patients with liver cirrhosis. Multivariate analysis, controlling for confounding factors, identified sACR <2.32 as a predictor of mortality within 90 days after the first hospitalization, with a hazard ratio (HR) of 6.52.

A cohort study of HCC patients who were candidates for liver transplantation (LT) after one cycle of microwave ablation found that an albumin level <3.4 g/dL was a significant prognostic factor for time to progression (TTP) over 2 years, with a rate of 68% compared to 95% for levels ≥3.4 g/dL.[26] A systematic review of cirrhosis patients with renal failure revealed high mortality rates for patients with renal failure at 1-month and 12-month follow-ups, with respective rates of 58% and 63%. The pooled odds ratio for mortality in patients with renal failure versus those without was 7.6 (95% CI 5.4-10.8).[27] This underscores the important role of hypoalbuminemia and renal failure as prognostic factors in both HCC and liver cirrhosis patients.

Another study identified initial performance status, Barcelona Clinic Liver Cancer (BCLC), Child-Turcotte-Pugh (CTP) score, and stage at diagnosis as prognostic indicators for overall survival in hepatocellular carcinoma (HCC) patients. In that study, CTP was a significant independent prognostic factor with an HR of 1.1.[28] However, our study yielded different results, in that CTP category was not a significant independent prognostic factor for mortality in patients with liver cirrhosis and HCC, with an HR of 2.19.

Laboratory parameters have also been shown to play a role as prognostic factors in HCC patients. For instance, in HCC patients after liver transplantation, albumin-bilirubin (ALBI) grade 1 was associated with better overall survival compared to grade 2.[29] The Fibrosis-4 index-TNM staging (FIB4-T) has also been useful in predicting 5-year survival in HCC patients, with FIB4-T scores of 0 to 5 showing survival rates ranging from 88% to 10%.[30] The albumin-to-C-reactive protein (CRP) ratio in hepatocellular carcinoma (HCC) patients prior to treatment has been shown to be a valuable predictor of both overall survival and disease-free survival. A lower albumin-to-CRP ratio was linked to more advanced TNM staging, larger tumor sizes, and higher alpha-fetoprotein (AFP) levels.[31] This demonstrates that laboratory parameters are crucial in determining patient prognosis.

Serum albumin and creatinine are commonly used parameters in liver cirrhosis studies. One study assessing the urine albumin-to-creatinine ratio (uACR) ≥30 mg/g found poorer survival outcomes compared to uACR <30 mg/g.[20] In this study, the albumin-to-creatinine ratio (sACR) was introduced as a novel parameter for predicting 90-day mortality in hepatocellular carcinoma (HCC) patients with liver cirrhosis. Additionally, sACR showed competitive predictive ability compared to the MELD score, for 90-day mortality in this patient population. MELD score is widely used in clinical applications for determining survival in HCC patients, especially those undergoing liver transplantation. Some studies have found that MELD scores ≥20 increase the incidence of septic

shock, but do not significantly differ in 1-, 3-, and 5-year survival compared to MELD scores <20.[32]

Patients with liver cirrhosis experience structural damage to liver cells, leading to reduced albumin synthesis and increased albumin excretion, ultimately resulting in hypoalbuminemia. Additionally, cancers, such as HCC, lead to hypermetabolic states and malnutrition, which further exacerbate hypoalbuminemia. Moreover, liver cirrhosis and HCC are often associated with hepatorenal syndrome, contributing to elevated serum creatinine levels. The ratio of these two factors (albumin and creatinine) can thus be used as a predictor of mortality in these patients. [19]

Serum albumin creatinie ratio is an emerging parameter for evaluating 90-day mortality in patients with HCC and liver cirrhosis. However, it still has some limitations. First, since it is a single-center cohort, this study needs a multi-center prospective design in a larger population to validate our results. Second, our study only analyzed the impact of some parameters on the survival in HCC patients, while other parameters such as prothrombin induced by vitamin K absence-II (PIVKA-II), carcinoembryonic antigen (CEA), the Barcelona Clinic Liver Cancer (BCLC) staging system, were not taken into account in this study. Further prospective analyses should be conducted with larger populations or multi-center cohorts.

CONCLUSIONS

The conclusion can be reached that a serum albumin-to-creatinine ratio (sACR) <2.32 can serve as a predictor of 90-day mortality in patients with HCC and liver cirrhosis. This parameter is straightforward and can rival or complement the MELD score in prognosticating patient outcomes.

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Conflict of Interest

Conflict of interest not declared.

Author Contributions

DAS and IKM collected the sample data; KMNP and PISLD analyzed the data; KMNP, PISLD, NLPYD, and NNGKD arranged the manuscript. All authors have read and approved the final manuscript.

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Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

Declaration of Use of AI in Scientific Writing

This research has been confirmed as not utilizing AI tools or methods in its development.

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