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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Observational Study

Fibrinogen-to-albumin ratio predicts overall survival of hepatocellular carcinoma

Hao Sun, Jie Ma, Jian Lu, Zhi-Hong Yao, Hai-Liang Ran, Hai Zhou, Zhong-Qin Yuan, Yun-Chao Huang, Yuan-Yuan Xiao

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Abstract

BACKGROUND

Fibrinogen-to-albumin ratio (FAR) has been found to be of prognostic significance for several types of malignant tumors. However, less is known about the association between FAR and survival outcomes in hepatocellular carcinoma (HCC) patients.

AIM

To explore the association between FAR and prognosis and survival in patients with HCC.

METHODS

A total of 366 histologically confirmed HCC patients diagnosed between 2013 and 2018 in a provincial cancer hospital in southwestern China were retrospectively selected. Relevant data were extracted from the hospital information system. The optimal cutoff for baseline serum FAR measured upon disease diagnosis was established using the receiver operating characteristic (ROC) curve. Univariate and multivariate Cox proportional hazards models were used to determine the crude and adjusted associations between FAR and the overall survival (OS) of the HCC patients while controlling for various covariates. The restricted cubic spline (RCS) was applied to estimate the dose-response trend in the FAR-OS association.

RESULTS

The optimal cutoff value for baseline FAR determined by the ROC was 0.081. Multivariate Cox proportional hazards model revealed that a lower baseline

serum FAR level was associated with an adjusted hazard ratio of 2.43 (95% confidence interval: 1.87–3.15) in the OS of HCC patients, with identifiable dose-response trend in the RCS. Subgroup analysis showed that this FAR-OS association was more prominent in HCC patients with a lower baseline serum aspartate aminotransferase or carbohydrate antigen 125 level.

CONCLUSION

Serum FAR is a prominent prognostic indicator for HCC. Intervention measures aimed at reducing FAR might result in survival benefit for HCC patients.

Key Words: Fibrinogen-to-albumin ratio; Hepatocellular carcinoma; Overall survival; Survival analysis; Cox proportional hazards model

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Core Tip: It is important to explore the affecting factors of survival for hepatocellular carcinoma (HCC) patients. A receiver operating characteristic curve was used to establish the optimal cutoff value for baseline serum fibrinogen-to-albumin ratio (FAR) in disease diagnosis. Univariate and multivariate Cox proportional risk models were employed to determine the correlation between FAR and overall survival (OS) in HCC patients. Restricted cubic spline was used to estimate dose-response trends in FAR-OS associations. Serum FAR is an important prognostic index of HCC. Effective FAR reduction may benefit HCC patient survival.

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INTRODUCTION

As one of the most common malignant tumors of the digestive system, liver cancer is a burden on human health and social economy due to its insidious onset and poor prognosis. The latest global cancer data released by the International Agency for Research on Cancer in 2020 showed that liver cancer accounted for 4.7% of all new cancer cases and 8.3% of all cancer-related deaths worldwide[1]. In China, liver cancer accounted for 9.0% and 13.0% of new cancer cases and cancer deaths in 2020, respectively[1]. Early diagnosis and treatment of cancer patients are critical. However, since patients with liver cancer only experience minor clinical symptoms in the early stages of the disease, only a minority of them can achieve early diagnosis. A 2018 study noted that the one, three, and five-year survival rates of liver cancer patients in Asian countries were 34.8%, 19%, and 18.1%, respectively, which were comparatively lower than those in the European and North American countries[2].

Considering the less optimistic survival rates of liver cancer patients, it is imperative to explore its potential prognostic factors, especially those that are easy to monitor and allow for a possible intervention. Hepatocellular carcinoma (HCC) is the predominant histological type of liver cancer and accounts for 75%–85% of all liver cancer cases[3,4]. Major risk factors for HCC include viral hepatitis B or C, consumption of aflatoxin-contaminated food, alcohol abuse, and metabolic and endocrine diseases[5,6]. HCC prognosis is related to various factors, such as clinical stage, tumor size, portal vein invasion, and non-alcoholic fatty liver disease[7-9].

In recent years, serum markers and their significance in cancer survival have gradually attracted considerable research interest in the field of cancer epidemiology, probably due to their easy accessibility and low cost. Many serum indicators had been found to be associated with HCC prognosis, such as blood profiling indexes [total bilirubin (TBIL), platelets, and albumin][10], serum enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl aminotransferase, and alkalinephosphatase][11], systemic inflammatory indicators (neutrophil-to-lymphocyte ratio, systemic immune-inflammatory index)[12], and tumor biomarkers [carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and carbohydrate antigen 19-9 (CA19-9)][10,13-15].

Fibrinogen is a glycoprotein synthesized by hepatic epithelial cells. Elevated plasma fibrinogen level has been shown to be associated with poorer survival in various malignancies[16]. Albumin is also produced by the liver and is generally used to assess nutritional status. In the advanced stage of cancer, malnutrition and inflammation jointly inhibit albumin synthesis[17]. Therefore, a significant decrease in serum albumin level can predict compromised cancer prognosis[18]. It has been reported that the composite index of fibrinogen and albumin, fibrinogen-to-albumin ratio (FAR), is an independent prognostic factor for progression-free-survival and overall survival (OS) in patients with head and neck squamous cell carcinoma[19]. In another newly published study, Yang *et al*[20] have found that FAR was also related to disease-free survival (DFS) and OS in triple-negative breast cancer patients, with longer median DFS and OS observed in patients with a lower FAR.

In two previously published studies, scholars have evaluated the association between FAR and survival outcomes in early-stage HCC patients who underwent curative resection and found that an elevated FAR was significantly associated with poorer survival and higher risk of recurrence[21]. Nevertheless, the general prognostic significance of serum FAR measured upon disease diagnosis in HCC patients remains unknown. The present study explores this issue in a large sample of HCC patients. The independent association between serum FAR and OS in HCC patients was analyzed and its dose-response trend was estimated.

MATERIALS AND METHODS

Study design

Patients with histologically confirmed HCC between January 1, 2013 and December 31, 2018 at the Third Affiliated Hospital of Kunming Medical University (Yunnan Provincial Cancer Hospital) were retrospectively identified. The hospital had a well-established hospital information system, including a digital clinical information system and a computer-assisted telephone interview follow-up system. In the digital clinical information system, all data related to the clinical practice of inpatients and outpatients are recorded and updated on a daily basis. The following information was extracted from the clinical information system in the present study: Gender, age at diagnosis, ethnicity, cigarette smoking status, alcohol drinking status, body mass index (BMI), clinical stage, and serum indicator levels measured at diagnosis (fibrinogen, albumin, AST, ALT, alpha-fetoprotein (AFP), TBIL, neutrophil-to-lymphocyte ratio (NLR), CEA, CA125, and CA19-9). Information about patient death, such as date and cause, was obtained from the follow-up system. HCC patients with complete required information were included in the final study analysis. The study protocol was approved by the Ethics Review Committee of Kunming Medical University. The requirement for informed consent was waived by the committee due to the retrospective study design.

Variables and definitions

The OS served as the study outcome. Survival interval was defined as the time from the histological diagnosis to the date of death from any cause or the end of follow-up (December 31, 2018), whichever came first. Baseline serum FAR was calculated as serum fibrinogen level divided by serum albumin level measured around the date of disease diagnosis (within seven days prior to or post diagnosis). Because no commonly used cutoffs have been proposed for serum FAR, the receiver operating characteristic (ROC) curve was used to establish the best cutoff value. Other baseline blood indicators to be controlled for, including AST, ALT, AFP, TBIL, NLR, CEA, CA125, and CA19-9, were also extracted from the system using the same time requirements as those for serum FAR. The most commonly adopted cutoffs were employed to dichotomize these blood indicators as follows: 40 U/L for AST and ALT, 17.1 $\mu\text{mol/L}$ for TBIL, 400 ng/mL for AFP[22,23], 5 U/L for CEA, 35 U/L for CA125, and 37 U/L for CA19-9. BMI and serum NLR were dichotomized using their medians.

Statistical analysis

Descriptive statistics were used to illustrate and compare the general characteristics of the participants. The Kaplan-Meier survival curves were plotted for HCC patients based on different baseline FAR levels and compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were employed to evaluate the crude and adjusted associations between baseline serum FAR and the OS of HCC patients. Variables that achieved a less strict significance level ($P < 0.10$) in univariate analyses were incorporated into the subsequent multivariate model. Considering the quantitative nature of FAR, the dose-response trend in its association with the OS of HCC patients was subsequently estimated using the restricted cubic spline (RCS). A two-tailed probability of < 0.05 was deemed statistically significant. Subgroup analyses based on clinical stage, AST level, and CA125 level were further performed. All statistical analyses were carried out in R software (version 4.2.2).

RESULTS

Patient characteristics

A total of 366 histologically confirmed HCC patients were retrospectively identified between 2013 and 2018. The ROC curve determined an optimal cutoff of 0.081 for baseline FAR (Supplementary Figure 1). Therefore, the patients were dichotomized into higher ($\text{FAR} \geq 0.081$) and lower ($\text{FAR} < 0.081$) FAR groups. General characteristics of the HCC patients are represented and compared in Table 1. Except for age at diagnosis, alcohol drinking status, BMI, and baseline CEA, all other characteristics were statistically different in HCC patients with different baseline serum FAR levels. The median survival time for all patients was 645.00 d (interquartile range: 757.25 d). Compared to patients with a lower baseline FAR level, HCC patients with higher baseline FAR levels ($\text{FAR} \geq 0.081$) had a significantly shorter median survival length (947.50 *vs.* 530.50 d).

Baseline serum FAR and OS in HCC patients

Figure 1 represents an overview of the OS for HCC patients with higher (≥ 0.081) and lower (< 0.081) baseline FAR levels. Patients with a lower baseline FAR had a superior OS (log-rank = 47.8, $P < 0.01$). The results of univariate and multivariate Cox proportional hazard model fitting results are shown in Table 2. Baseline FAR remained a significant

Table 1 General characteristics of the 366 hepatocellular carcinoma patients

Characteristics	All patients (n = 366)			P value
Gender				
Male	312 (85.24) ^c	113 (81.88) ^c	199 (87.28) ^c	0.16
Female	54 (14.76) ^c	25 (18.12) ^c	29 (12.72) ^c	
Age at diagnosis	54.59 (10.60) ^a	52.98 (10.83) ^a	55.56 (10.36) ^a	0.02
Cigarette smoking				
No	129 (35.24) ^c	54 (39.19) ^c	75 (32.89) ^c	0.23
Yes	237 (64.76) ^c	84 (60.81) ^c	153 (67.11) ^c	
Alcohol drinking				
No	161 (43.99) ^c	64 (46.38) ^c	97 (42.54) ^c	0.47
Yes	205 (56.01) ^c	74 (53.62) ^c	131 (57.46) ^c	
BMI (kg/m ²)	21.55 (2.71) ^b	21.93 (2.70) ^b	21.32 (2.70) ^b	0.04
Stage				< 0.01
I-II	68 (18.58) ^c	53 (38.41) ^c	15 (6.58) ^c	
III	166 (45.35) ^c	52 (37.68) ^c	114 (50.00) ^c	
IV	132 (36.07) ^c	33 (23.91) ^c	99 (43.42) ^c	
Survival length (d)	645.00 (757.25) ^b	947.50 (1002.25) ^b	530.50 (683.50) ^b	< 0.01
AST (U/L)	66.35 (75.22) ^b	46.50 (48.08) ^b	80.15 (81.30) ^b	< 0.01
ALT (U/L)	43.80 (38.68) ^b	38.95 (28.10) ^b	50.05 (40.93) ^b	0.01
AFP (ng/mL)	593.35 (9018.82) ^b	315.20 (483.18) ^b	743.25 (10910.73) ^b	0.53
TBIL (μmol/L)	17.40 (14.00) ^b	16.35 (13.55) ^b	19.45 (14.13) ^b	0.81
NLR (unit free)	2.75 (2.09) ^b	1.93 (1.29) ^b	3.30 (2.18) ^b	< 0.01
CEA (U/L)	2.80 (3.10) ^b	2.90 (3.11) ^b	2.73 (3.14) ^b	0.56
CA125 (U/L)	34.77 (83.51) ^b	19.63 (30.11) ^b	55.96 (104.58) ^b	0.01
CA19-9 (U/L)	29.50 (67.38) ^b	21.56 (36.71) ^b	36.56 (81.11) ^b	0.09
FAR (unit free)	0.09 (0.05) ^b		-	

^amean ± SD;^bMedian with interquartile range (IQR);^cFrequency with proportion (%).

AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CA125: Carbohydrate antigen 125; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; FAR: Fibrinogen-to-albumin ratio; NLR: Neutrophil-to-lymphocyte ratio; TBIL: Total bilirubin.

prognostic factor after adjusting for possible covariates, while HCC patients with higher FAR levels showed a hazard ratio (HR) of 2.43 [95% confidence interval (95%CI): 1.87–3.15].

To verify the reliability and determine the trend of this association, HCC patients were further divided into four groups based on their baseline serum FAR quartiles as follows: Group 1 (FAR < 0.071), group 2 (0.071 ≤ FAR < 0.093), group 3 (0.093 ≤ FAR < 0.131), and group 4 (FAR ≥ 0.131). After adjustment for potential covariates identified in the previous univariate model, the adjusted HRs for groups 2 to 4 compared to group 1 were 1.07 (95%CI: 0.73–1.57), 1.62 (95%CI: 1.10–2.39), and 1.37 (95%CI: 0.92–2.04), respectively (Figure 2). The RCS fitting results showed that after controlling for the same potential confounders as those in the multivariate Cox proportional hazards model, a nonlinear relationship between baseline FAR levels and HR was observed, with the overall risk of death in HCC patients arising with an increasing baseline FAR. Furthermore, the risk of death was significantly higher when the baseline FAR exceeded 0.093 (Figure 3).

Subgroup analysis

A series of subgroup analyses were performed separately using three important characteristics of the HCC patients, including baseline serum AST, CA125, and clinical stage (Figure 4). Among the three stratified factors, baseline serum AST and CA125 levels presented as noticeable effect modifiers. Specifically, the FAR-OS association tended to be much

Table 2 Univariate and multivariate Cox proportional hazards model fitting results

Covariates	Univariate Cox model		Multivariate Cox model	
	Crude HR (90%CI)	P value	Adjusted HR (95%CI)	P value
Sex: Male	1.74 (1.30, 2.35)	< 0.01		
Age at diagnosis: + 5 yr	1.01 (0.96, 1.06)	0.72		
Cigarette smoking: Yes	1.51 (1.23, 1.87)	< 0.01		
Alcohol drinking: Yes	1.23 (1.01, 1.50)	0.08		
BMI: + 1 kg/m ²	0.97 (0.93, 1.00)	0.14		
Stage (Ref: I-II)				
III	3.49 (2.46, 4.96)	< 0.01	2.14 (1.37, 3.35)	< 0.01
IV	4.86 (3.40, 6.95)	< 0.01	2.33 (1.45, 3.74)	< 0.01
AST: 40 U/L	2.74 (2.12, 3.53)	< 0.01	1.50 (1.01, 2.22)	0.04
ALT: 40 U/L	1.72 (1.41, 2.10)	< 0.01		
AFP: 400 ng/mL	1.93 (1.58, 2.36)	< 0.01	1.53 (1.19, 1.96)	< 0.01
TBIL: 17.1 μmo/L	1.81 (1.49, 2.20)	< 0.01		
NLR: + 5	1.72 (1.45, 2.05)	< 0.01		
CEA: 5 U/L	1.26 (1.01, 1.57)	< 0.01		
CA125: 35 U/L	2.89 (2.36, 3.55)	< 0.01	1.72 (1.30, 2.27)	< 0.01
CA19-9: > 37 U/L	1.95 (1.60, 2.37)	< 0.01		
FAR: 0.081	2.43 (1.95, 3.02)	< 0.01	1.39 (1.05, 1.83)	< 0.01

90%CI: 90% confidence interval; 95%CI: 95% confidence interval; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CA125: Carbohydrate antigen 125; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; FAR: Fibrinogen-to-albumin ratio; HR: Hazard ratio; NLR: Neutrophil-to-lymphocyte ratio; TBIL: Total bilirubin.

stronger for HCC patients with lower baseline serum AST or CA125 levels.

DISCUSSION

The present retrospective study examined the prognostic role of serum FAR measured upon diagnosis for the OS in 366 HCC patients. As a result, a higher baseline FAR was related to significantly inferior OS in HCC. Further analysis using either FAR quartiles or the RCS revealed a prominent dose-response trend in this association. Subgroup analysis revealed that the FAR-OS association was more significant in patients with lower baseline serum AST or CA125 Levels. These findings may have potential clinical significance in guiding the HCC treatment.

FAR is a composite index. It increases along with an increase in serum fibrinogen level or a decrease in serum albumin level. Elevated serum fibrinogen level may be associated with increased fibrinogen deposition in tumor tissue[24]. It has been found that fibrinogen has strong adhesion to tumor cells. With the help of thrombin, fibrinogen is converted into fibrin, which forms a physical barrier around tumor cells, helps them survive, and plays an important role in cancer progression[25]. Serum albumin has been recognized as not only an important indicator of nutritional status in cancer patients[26,27], but also a tumor suppressor that inhibits matrix metalloproteinase (MMP)-induced invasion and metastasis of HCC by modulating urokinase plasminogen activator surface receptor signaling[28]. In the advanced stages of cancer, albumin level also decreases with the increase in concentrations of other acute phase proteins[29]. These mechanisms can justify the positive connection between elevated serum FAR and compromised OS in HCC patients identified in the present study.

Subgroup analysis suggested that the FAR-OS association appeared to be stronger in patients with lower serum AST or CA125 Levels. AST is an enzyme that reflects liver damage and is often used to evaluate the progression of liver-related diseases. The clearance of serum AST decreases as liver function declines, causing elevated serum AST levels[30]. Elevated serum AST levels have been found to be independently related to inferior survival rates of HCC patients[31]. CA125 is a macromolecular glycoprotein synthesized and stored in the somatic cavity of epithelial cells and is not normally accessible to the circulation. Elevation in this indicator reflects various tumor behaviors that may be associated with severe cell damage, angiogenesis, vascular invasion, and destruction[32]. In some previously published studies, a higher serum CA125 level has been demonstrated to be prominently related to compromised prognosis of liver cancer patients[33]. These findings suggest that even if the reduction in serum FAR can be manipulated, little survival benefit

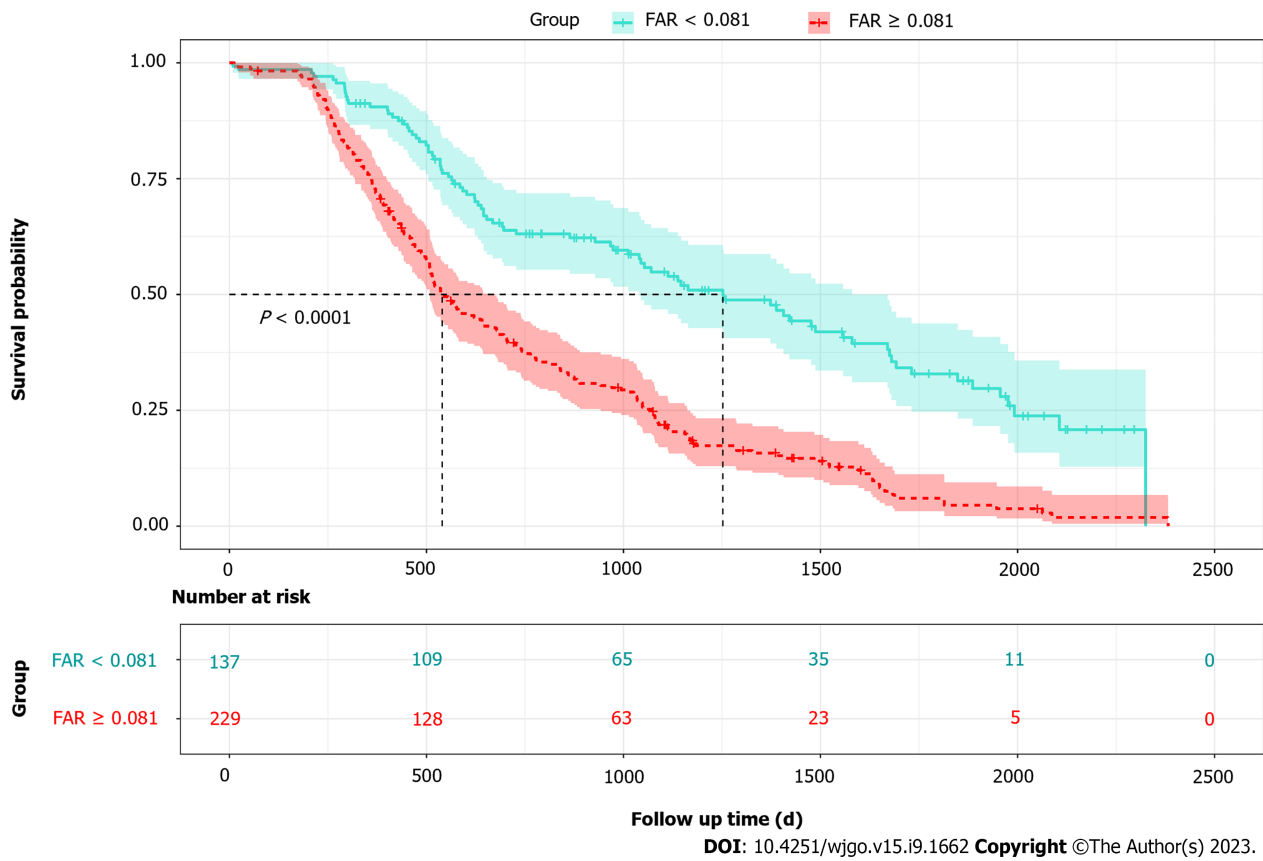


Figure 1 Kaplan-Meier survival curves for hepatocellular carcinoma patients with different baseline fibrinogen-to-albumin ratio levels. FAR: Fibrinogen-to-albumin ratio.

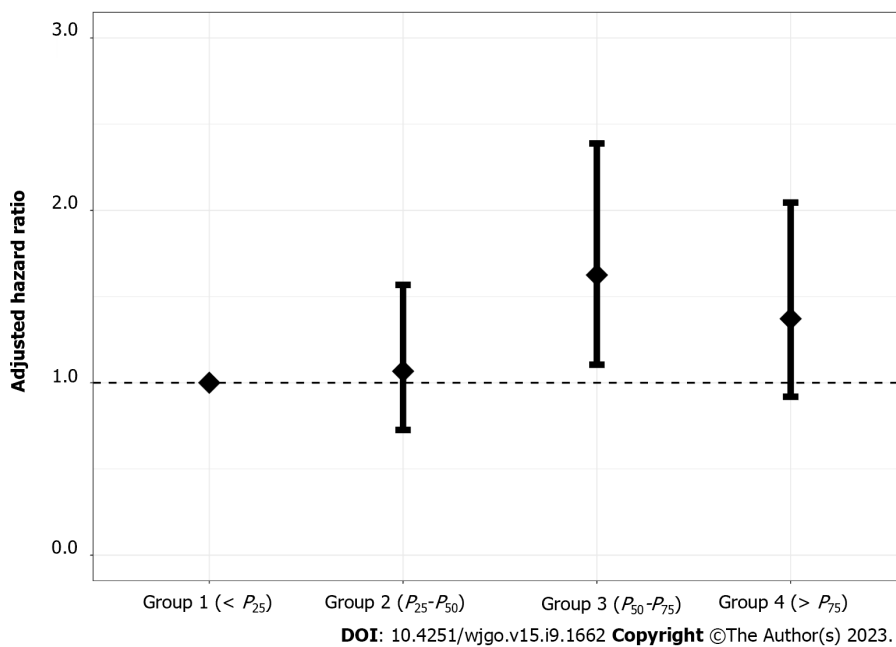


Figure 2 Dose-response association between baseline fibrinogen-to-albumin ratio and the overall survival of hepatocellular carcinoma by using the quartiles.

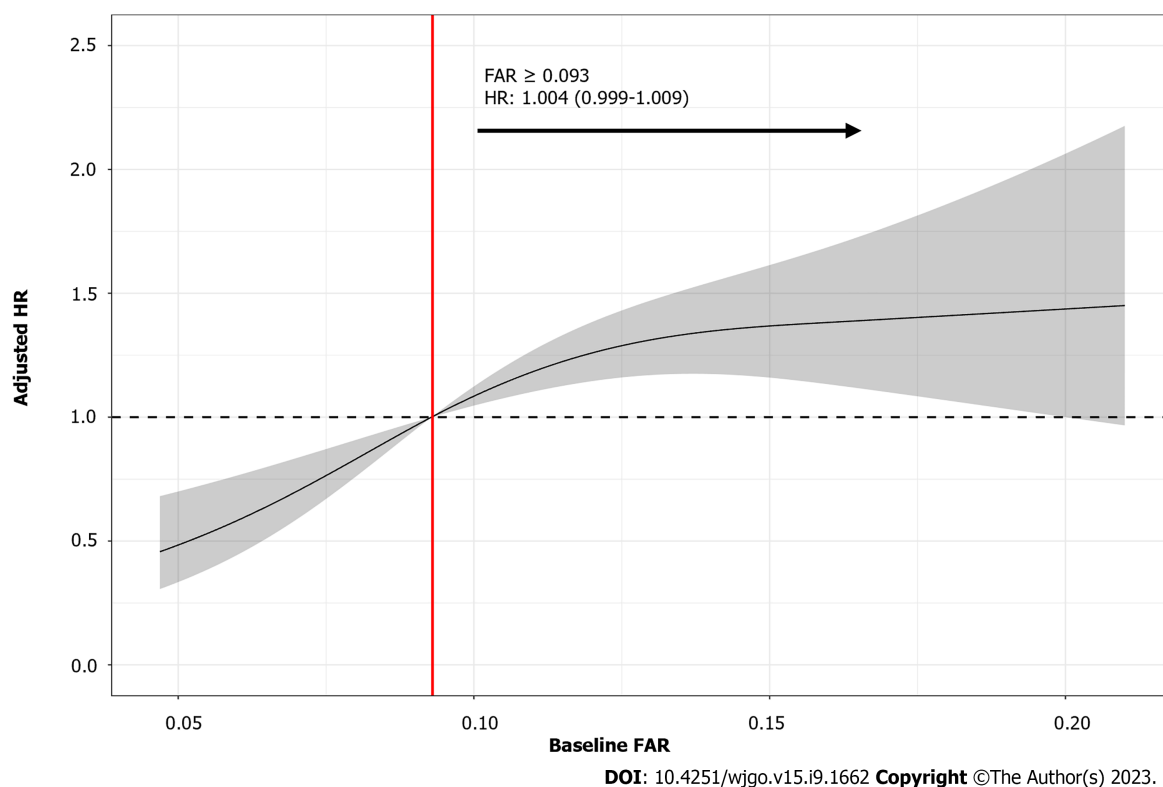


Figure 3 Dose-response relationship between quantitative baseline fibrinogen-to-albumin ratio and the overall survival of hepatocellular carcinoma patients by using the restricted cubic spline. FAR: Fibrinogen-to-albumin ratio; HR: Hazard ratio.

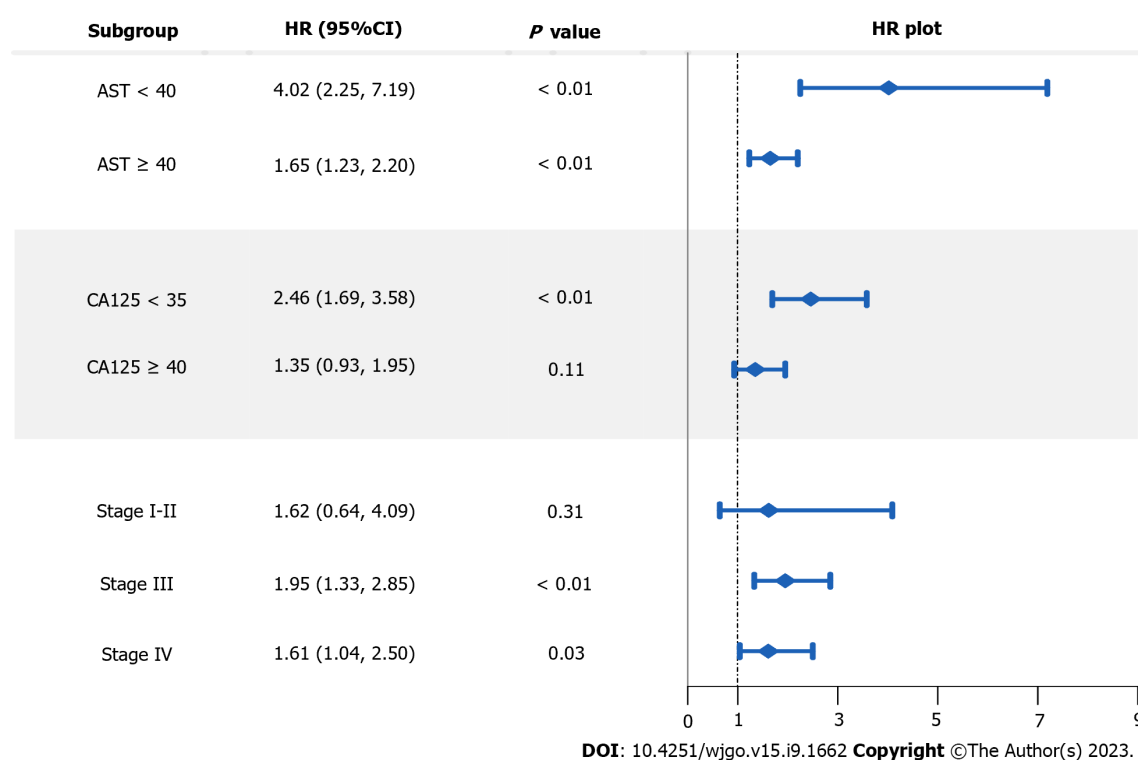


Figure 4 Subgroup analysis stratified by aspartate aminotransferase, carbohydrate antigen 125 and clinical stage. 95%CI: 95% confidence interval; AST: Aspartate aminotransferase; CA125: Carbohydrate antigen 125; HR: Hazard ratio.

can be achieved in HCC patients with higher AST or CA125 levels.

The present study's major findings highlight the prognostic significance of serum FAR in HCC patients. The decrease in fibrinogen level or increase in albumin level, which result in reduced serum FAR, might be related to improved survival. Many drugs that lower serum fibrinogen level are currently available. For instance, fibrates directly reduce fibrinogen mRNA transcription *in vitro* and *in vivo* through their effect on peroxisome proliferator-activated receptor alpha[34]. It has been observed that benzofibrate significantly reduces serum fibrinogen level, which, in turn, is associated with the anti-tumor effect of benzofibrate as a biomarker or potential mediator[35]. In addition, MMPs and serine proteases contained in snake venom drugs also have a good fibrinogen-lowering effect[36]. Moreover, it has been reported that the median survival of HCC patients can be extended by taking low doses of aspirin[37]. Branched-chain amino acid (BCAA) supplementation is commonly used for correcting malnutrition issues in cancer patients, and it significantly increases serum albumin concentration[38]. It has been reported that BCAA supplementation can also alleviate the impairment of liver function in HCC patients after transarterial chemoembolization[39]. Some literature has reported that the administration of n-3 polyunsaturated fatty acids, especially eicosa-pentaenoic, can also help to maintain serum albumin level in cancer patients[40]. Nonetheless, the effect of either fibrinogen reduction or albumin supplementation aimed at improving the survival outcomes in HCC patients should be further validated by clinical experimental studies.

The main strengths of the present study include its comparatively large sample size. In addition, many potential confounders were simultaneously controlled for when analyzing the FAR-OS association. Furthermore, a dose-response trend revealed by the RCS further corroborated the stability of this FAR-OS association. However, some study limitations were present. First, analytical data were collected retrospectively, introducing a risk of information bias. Second, all HCC patients were from a single institution, which limits the ability to generalize the study results. Multi-centered longitudinal studies are needed to further validate the present study's major findings.

CONCLUSION

In this retrospective study of 366 histologically confirmed HCC patients, serum FAR measured at disease diagnosis was found to be significantly associated with the OS. Patients with a higher baseline FAR had an increased death hazard with a prominent dose-response trend. This FAR-OS association was more prominent in HCC patients with lower serum AST or CA125 levels. The study findings have important implications for clinical treatment of HCC, suggesting that intervention measures aiming at reducing FAR might provide a survival benefit for this group of patients. Prospective studies with more representative samples should be carried out.

ARTICLE HIGHLIGHTS

Research background

Fibrinogen-to-albumin ratio (FAR) has been found significantly associated with survival of some types of cancer. Less is known regarding to its association with prognosis for hepatocellular carcinoma (HCC) patients.

Research motivation

We intend to thoroughly discuss the association between baseline serum FAR and the overall survival (OS) for HCC patients.

Research objectives

To provide estimation for the association between baseline FAR and the OS of HCC patients, and to discuss potential effect modification by some important characteristics of the patients.

Research methods

Retrospective study design was used to identify qualified HCC patients from a provincial cancer hospital in China. Relevant information was extracted from the Hospital Information System. Kaplan-Meier survival curves were plotted to compare the OS of HCC patients with different baseline serum FAR levels. Cox proportional hazards models were applied to estimate the adjusted association between FAR and the OS of HCC patients. The Restricted Cubic Spline was used to further delineate the dose-response association.

Research results

A lower baseline serum FAR level was associated with an adjusted hazard ratio of 2.43 (95% confidence interval: 1.87–3.15) in the OS of HCC patients, with identifiable dose-response trend. The FAR-OS association was more prominent in HCC patients with a lower baseline serum aspartate aminotransferase or carbohydrate antigen 125 level.

Research conclusions

Serum FAR is a prominent prognostic indicator for HCC.

Research perspectives

Intervention measures which aiming at regulating serum FAR might of clinical interest for treating HCC patients.

FOOTNOTES

Author contributions: All authors contributed to the conception and design of the study; the data extraction conditions were determined by Huang YC and Xiao YY; data extraction was performed by Sun H, Ma J, Lu J, Yao ZH, Zhou H, Yuan ZQ; data analysis plan was determined by Xiao YY, and data analysis was performed by Sun H, Ma J, Tan HL; the first draft of the manuscript was written by Sun H and Ma J, and all the authors commented on the previous versions of the manuscript; all authors have read and approved the final manuscript.

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