Prognostic value of preoperative serum ferritin in hepatocellular carcinoma patients undergoing transarterial chemoembolization

MI FAN[1,2*], TINGTING NIU[1,2*], BINWEI LIN[1], FENG GAO[1], BANGXIAN TAN[2] and XIAOBO DU[1,2]

[1]Departmant of Oncology, NHC Key Laboratory of Nuclear Technology Medical Transformation (Mianyang Central Hospital), Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology, Mianyang, Sichuan 621000; [2]Department of Oncology, Affiliated Hospital of North Sichuan Medical College, Nan Chong, Sichuan 637000, P.R. China

Received August 16, 2023; Accepted January 8, 2024

DOI: 10.3892/mco.2024.2720

Abstract. The present study investigated the prognostic impact of preoperative serum ferritin (SF) levels on the survival of patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE). Clinicopathological characteristics and laboratory biomarkers of 223 patients with HCC who underwent TACE were retrospectively reviewed. The Kaplan-Meier method was used to calculate the overall survival (OS), and the log-rank test was used to evaluate statistical significance. Univariate and multivariate analyses were performed using Cox proportional hazards regression to evaluate the prognostic impact of SF in these patients. The present findings identified extrahepatic metastases [hazard ratio (HR)=0.490,95%; confidence interval (CI)=0.282-0.843; P=0.010)] and vascular invasion (HR=0.373; 95% CI=0.225-0.619; P<0.0001) as independent prognostic factors for OS. However, preoperative SF levels could not independently predict OS when compared with other prognostic factors (HR=0.810; 95% CI=0.539-1.216; P=0.309). In conclusion, preoperative SF level is an unreliable biochemical predictor of survival in patients with HCC undergoing TACE.

Introduction

Liver cancer is one of the most common types of cancer worldwide, with the highest incidence rates reported in Asia and Africa. Hepatocellular carcinoma (HCC) mainly includes hepatocellular liver cancer, cholangiocarcinoma and mixed cell carcinoma (1). Of these, HCC accounts for 75-85% of all liver cancers (2). The annual worldwide incidence of HCC is increasing by 3-9% annually (3). Liver cancer has a poor prognosis and is the second leading cause of cancer-related deaths (4), with a 5-year overall survival (OS) rate of <10% (5). Treatment options for early stage liver cancer include liver resection, radio frequency ablation (RFA) and liver transplantation. However, due to its insidious onset, >50% of patients are diagnosed during the middle or late disease stages of the disease, missing the opportunity for curative treatment. Consequently, transcatheter arterial chemoembolization (TACE) has become the first-line treatment for intermediate and advanced-stage liver cancer (6).

Survival times among patients receiving TACE exhibit significant differences due to the heterogeneity of the disease. This is a challenging task for the duplication or cessation of space therapy (7-9). To provide the best individualized treatment to patients with cancer, it is necessary to identify biomarkers that can effectively predict the survival outcomes. Currently, alpha-fetoprotein (AFP) is the most commonly used marker for predicting the onset and recurrence of liver cancer. However, ~1/3 of patients with liver cancer are AFP-negative (10). Various studies have attempted to develop risk prediction models to predict treatment outcomes, including specially designed nomograms and post-TACE prognostic scoring systems (11-13). These models revealed the influence of liver function and the baseline tumor characteristics on the survival of TACE-treated patients with liver cancer. Tumor characteristics such as pathological type, differentiation, tumor size, number of tumors and vascular invasion are the main indicators for predicting prognosis (14-16). Biochemical indicators such as liver function, serum gamma-glutamyl transferase, serum vascular endothelial growth factor, C-reactive protein and novel metabolism-related gene have also attracted significant attention and research (17-19). However, these biomarkers are insufficient for accurately predicting prognosis, with reported inaccuracies in 45% of cases (12,20,21). Furthermore, the scoring system is complex, and its clinical application is difficult to promote. Therefore, such biomarkers are not widely used in clinical practice at present (22).

Serum ferritin (SF) is an iron storage protein composed of 24 subunits and was first discovered by the French

Correspondence to: Professor Xiaobo Du, Departmant of Oncology, NHC Key Laboratory of Nuclear Technology Medical Transformation (Mianyang Central Hospital), Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology, 12 Changjiaxiang Road, Mianyang, Sichuan 621000, P.R. China
E-mail: duxiaobo2005@126.com

*Contributed equally

Key words: hepatocellular carcinoma, serum ferritin, transarterial chemoembolization, biomarker, prognosis

scientist Laufberger in 1937 (23). SF is the oldest known protein involved in iron metabolism and plays essential roles in cell proliferation, angiogenesis, immunosuppression and iron transport (24). Abnormal SF levels have been shown to be closely associated with tumor progression and poor prognosis (25). Some studies have suggested that SF levels may reflect the extent of liver inflammation and fibrosis, and SF may be a poor prognostic risk factor for survival and recurrence after percutaneous RFA in patients with HCC (26). Furthermore, preoperative SF is an independent prognostic factor for liver cancer after liver resection (27). Despite this, there is limited research on the impact of ferritin levels on the prognosis of patients with HCC, and the current results are conflicting. In addition, the prognostic value of SF in HCC patients undergoing TACE is unclear. Therefore, the present study aimed to investigate the impact of preoperative SF levels on the survival outcomes of patients with HCC undergoing TACE treatment, and to determine whether preoperative SF levels can serve as an independent prognostic biomarker for these patients.

Patients and methods

Patients and study design. Clinical data of 223 patients were collected and reviewed from the case database of the Mianyang City Center Hospital (Mianyang, China) between February 2006 and March 2022. The follow-up time was limited to 50 months. These patients were diagnosed with unresectable or inoperable liver cancer and underwent TACE. The inclusion criterion was a diagnosis of unresectable HCC, which was based on clinical imaging, AFP levels, medical history, or confirmed histology. Only patients who underwent TACE as their first-line treatment were included. Patients with combined HCC with and other tumors, recurrent HCC, resectable primary HCC, and those with incomplete data were excluded. The present study was conducted in accordance with the principles of the Declaration of Helsinki revised in 2013, and was approved (approval no. S20230320-02) by the Medical Ethics Committee of Mianyang Central Hospital (Mianyang, China). The data were analyzed anonymously; thus, informed consent was not obtained from the participants.

Demographic and clinicopathological characteristics and biochemical indicators of the included patients were investigated. Demographic and clinicopathological characteristics included sex, age, tumor size, number of tumors, cirrhotic Child-Pugh stage, presence of extrahepatic metastases, tumor necrosis, vascular invasion and previous treatment history. Laboratory tests included preoperative SF, preoperative AFP, alanine aminotransferase, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), albumin, as well as total bilirubin levels, and biochemical indicators such as the presence of hepatitis B or hepatitis C viral infection. Clinical staging was performed using the BCLC system. The frequency of TACE treatment performed during the follow-up period until the last follow-up date was also recorded.

OS. OS was defined as the time from the first day of initial treatment to death. Where a patient was lost to follow-up or death records was unavailable, the patient was censored. Survival time in censored patients was defined as the duration from the commencement of treatment to the last day of follow-up or the date when their survival status was last confirmed.

Statistical analysis. Categorical variables are presented as counts and percentages, and comparisons were performed using Pearson's chi-square or Fisher's exact test. Continuous data are expressed as the median and range, and were compared using the Mann-Whitney U test. If the survival time was incomplete, right censoring was used in the survival analysis. Survival curves were plotted using the Kaplan-Meier method, and were compared using the log-rank test. Single- and multi-factor analyses of independent prognostic factors for OS were performed using the Cox proportional hazards model. Statistical analysis was performed using the SPSS 26.0 software (IBM Corp.), and $P<0.05$ based on a two-tailed test was considered to indicate a statistically significant difference.

Results

Patient characteristics. The pathological characteristics and laboratory indicators of the included patients are summarized in Table I. Among the 223 patients, 183 (82.1%) were male, and 162 (72.6%) were aged >50 years. Most patients (54.7%) underwent a single treatment. The vast majority of patients either had a solitary tumor (81.6%) or a tumor diameter >5 cm (65%). A total of 134 patients (60.1%) had cirrhosis, 172 (77.1%) had tumor necrosis, 85 (38.1%) had pathological vascular invasion and 33 (14.8%) had extrahepatic metastases. Among them, 162 patients (72.6%) belonged to Child-Pugh class A, 151 (67.7%) were classified as BCLC stage B, and 55 (24.7%) were designated as BCLC stage C.

Correlation between SF and clinicopathological variables. According to the upper limit of the normal reference value for SF, the 223 patients were divided into the low (SF ≤274 ng/ml) and high SF (SF >274 ng/ml) groups. Next, the relationship between preoperative SF levels and clinicopathological parameters was studied. As demonstrated in Table II, some factors were associated with SF. Specifically, HBV infection, AST, ALT and GGT were significantly correlated with preoperative SF levels, while other laboratory indicators were not. Additionally, there was a discernible correlation between preoperative SF levels and sex, cirrhosis and tumor number. Details of the relationship between clinicopathological variables and preoperative SF levels are summarized in Table II.

Determination of prognostic factors for OS. Single-factor analysis was used to determine the predictive factors for proportional hazards regression multivariate analysis. Regarding clinicopathological factors, the presence of extrahepatic metastasis, vascular invasion and cirrhosis were significantly associated with poor survival outcomes. In terms of laboratory factors, increased AST (AST >40 IU/l), elevated GGT (GGT >60 IU/l), high AFP (AFP >400 ng/ml) and elevated total bilirubin (bilirubin >26 μmol/l) were significantly associated with poor survival outcomes. There was no significant correlation between preoperative SF levels and patient survival (P=0.309) (Table III).

For multivariate analysis, a Cox proportional hazards model that included all significant factors from the univariate analysis was used to determine the independent predictive

Table I. Baseline demographic and clinicopathological characteristics of patients.

Clinicopathological characteristics	Number (total n=223)	Percentage (%)
Age, years		
≤50	61	27.4
>50	162	72.6
Sex		
Male	183	82.1
Female	40	17.9
TACE frequency		
1/2/3/4/5/6/7/8/9	122/39/27/16/4/5/6/1/2	54.7/17.5/12.1/7.2/1.8/2.2/2.7/0.4/0.9
Serum ferritin (ng/ml)		
≤274	120	53.8
>274	103	46.2
HBV infection		
Absent	65	29.1
Present	158	70.9
HCV infection		
Absent	206	92.4
Present	17	7.6
ALT (IU/l)		
≤50	119	53.4
>50	104	46.6
AST (IU/l)		
≤40	45	20.2
>40	180	79.8
GGT (IU/l)		
≤60	43	19.3
>60	180	80.7
AFP (ng/ml)		
≤400	148	66.4
>400	75	33.6
Total bilirubin (μmol/l)		
≤26	16	72.2
>26	62	27.8
Albumin (g/l)		
≤35	64	28.7
>35	159	71.3
Cirrhosis		
Absent	89	39.9
Present	134	60.1
Tumor size (cm)		
≤5	78	35
>5	145	65
Tumor necrosis		
Absent	51	22.9
Present	172	77.1
Tumor number		
Single	182	81.6
Multiple	41	18.4
Extrahepatic metastases		
Absent	190	85.2
Present	33	14.8
Vascular invasion		
Absent	138	61.9
Present	85	38.1
Child-Pugh class		
A	162	72.6
B	60	26.9
C	1	0.4
BCLC stage		
0	4	1.8
A	12	5.4
B	151	67.7
C	55	24.7
D	1	0.4

TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transferase; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

factors for OS. In this model, the significant independent prognostic factors affecting survival model included the presence of extrahepatic metastasis and vascular invasion. Specifically, extrahepatic metastasis (HR=0.490; 95% CI=0.282-0.843; P=0.010) and vascular invasion (HR=0.373; 95% CI=0.225-0.619; P<0.0001) emerged as independent prognostic factors for OS (Table IV).

Survival analysis. A total of 98 patients died during the follow-up period. The median OS was 17 months. The 1-, 3-, and 5-year OS rates were 92, 83 and 77%, respectively. The median OS of patients did not significantly differ between the low (≤274 ng/ml) and high (>274 ng/ml) SF groups (Fig. 1A). The presence of vascular invasion (P<0.0001) and extrahepatic metastasis (P=0.010) significantly shortened the survival time of patients (Fig. 1 B and C).

Discussion

Liver cancer is the second leading cause of cancer-related deaths in China. For most patients with unresectable or inoperable HCC, TACE is considered the first-line treatment option. TACE is considered to cause tumor necrosis by creating a hypoxic environment and producing cytotoxic effects on tumor cells by concentrating high doses of chemotherapy drugs locally on the tumor (28). TACE can improve the quality of life and extend the survival of patients in intermediate or advanced HCC stages (29,30).

SF is a group of proteins that play an important role in iron storage, and is primarily found in the liver, spleen and bone

Table II. Association of preoperative SF level with clinicopathological parameters.

Clinicopathological characteristics	Level of preoperative SF, number (percentage %)		P-value
	Low SF Group (≤274 ng/ml) (n=120)	High SF Group (>274 ng/ml) (n=103)	
Age, years			1.000
≤50	91 (75.8%)	78 (75.7%)	
>50	35 (24.1%)	29 (24.3%)	
Sex			0.001
Male	89 (74.2%)	94 (90.4%)	
Female	31 (25.8%)	9 (9.6%)	
TACE frequency			0.574
1/2/3/4/5/6/7/8/9	64 (53.3%)/20 (16.6%)/16 (13.3%)/7 (5.8%)/32 (26.6%)	58 (56.3%)/19 (18.4%)/11 (10.7%)/9 (8.7%)/2 (1.9%)/1 (0.9%)/1 (0.9%)/1 (0.9%)/1 (0.9%)	
HBV infection			0.039
Absent	28 (23.3%)	37 (36%)	
Present	92 (76.7%)	66 (64%)	
HCV infection			0.349
Absent	109 (90.8%)	97 (94.2%)	
Present	11 (9.2%)	6 (5.8%)	
AST (IU/l)			0.009
≤40	32 (26.7%)	13 (12.7%)	
>40	88 (73.3%)	90 (87.3%)	
ALT (IU/l)			0.016
≤50	73 (60.8%)	46 (44.7%)	
>50	47 (39.2%)	57 (55.3%)	
GGT (IU/l)			
≤60	36 (30.0%)	7 (6.8%)	<0.0001
>60	84 (70.0%)	96 (93.2%)	
AFP (ng/ml)			0.215
≤400	84 (70.0%)	64 (62.1%)	
>400	36 (30.0%)	39 (37.9%)	
Total bilirubin (μmol/l)			0.276
≤26	83 (69.2%)	78 (75.7%)	
>26	37 (30.8%)	25 (24.3%)	
Albumin (g/l)			0.643
≤35	36 (30.0%)	28 (27.2%)	
>35	84 (70.0%)	75 (72.8%)	
Cirrhosis			0.07
Absent	38 (31.7%)	51 (49.5%)	
Present	82 (68.3%)	52 (50.5%)	
Tumor size (cm)			0.772
≤5	43 (35.9%)	35 (34%)	
>5	77 (64.1%)	68 (66%)	
Tumor necrosis			0.076
Absent	33 (27.5%)	18 (17.4%)	
Present	87 (72.5%)	85 (82.5%)	
Tumor number			0.005
Single	106 (88.3%)	76 (73.8%)	
Multiple	14 (11.7%)	27 (26.2%)	
Extrahepatic metastases			0.774
Absent	103 (85.9%)	87 (84.5%)	
Present	17 (14.1%)	16 (15.5%)	

Table II. Continued.

Clinicopathological characteristics	Level of preoperative SF, number (percentage %) Low SF Group (≤274 ng/ml) (n=120)	High SF Group (>274 ng/ml) (n=103)	P-value
Vascular invasion			0.943
Absent	74 (61.7%)	64 (62.1%)	
Present	46 (38.3%)	39 (37.9%)	
Child-Pugh class			0.549
A	87 (72.5%)	75 (72.8%)	
B	33 (27.5%)	27 (26.2%)	
C	0	1 (0.9%)	
BCLC stage			0.676
0	2 (1.6%)	2 (1.9%)	
A	5 (4.2%)	7 (6.7%)	
B	81 (67.5%)	70 (68%)	
C	32 (26.7%)	32 (31.1%)	
D	0	1 (0.9%)	

SF, serum ferritin; TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transferase; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

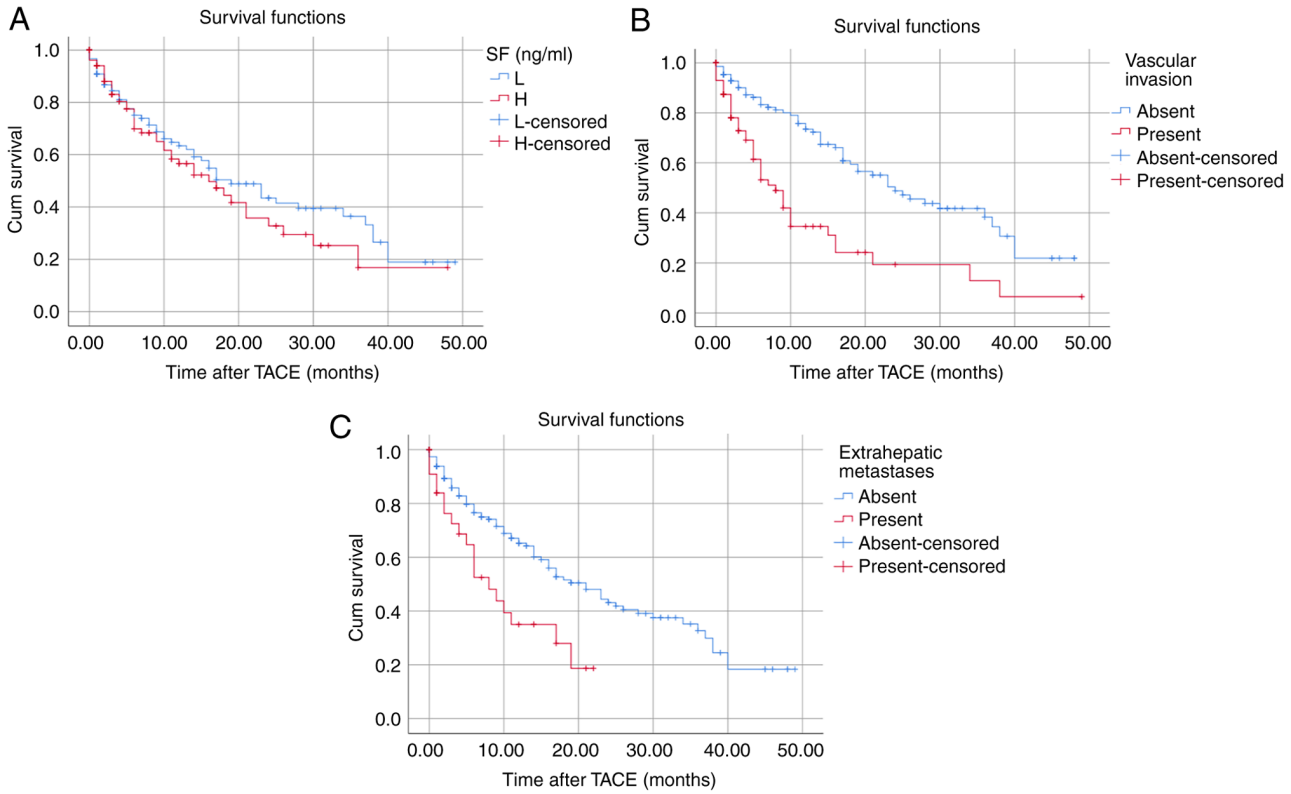

Figure 1. Overall survival of patients with HCC after TACE. (A) Low (≤274 ng/ml) or high (>274 ng/ml) serum ferritin. (B) With or without vascular invasion. (C) With or without extrahepatic metastasis.

marrow. Under normal physiological conditions SF is mainly composed of light (L) chains; however, in numerous malignant tumors the ratio of heavy (H) ferritin and H/L ferritin increases (31). The reasons for the increase in SF in liver cancer are as follows (32): i) Liver cancer cells can synthesize and secrete ferritin or hetero-ferritin; ii) the uptake and clearance of ferritin in liver cancer tissue are affected; and iii) hepatocyte damage and necrosis cause the release of stored ferritin

Table III. Univariate analysis of potential prognostic factors for survival.

Clinicopathological characteristics	Hazard ratio (95% confidence interval)	P-value
Sex	1.137 (0.684-1.891)	0.620
Male		
Female		
Age, years	1.184 (0.745-1.883)	0.474
≤50		
>50		
Serum ferritin (ng/ml)	0.810 (0.539-1.216)	0.309
≤274		
>274		
HBV infection	1.342 (0.885-2.036)	0.166
Absent		
Present		
HCV infection	0.810 (0.421-1.560)	0.529
Absent		
Present		
ALT (IU/l)	0.764 (0.512-1.139)	0.186
≤50		
>50		
AST (IU/l)	0.520 (0.303-0.893)	0.018
≤40		
>40		
GGT (IU/l)	0.527 (0.304-0.915)	0.023
≤60		
>60		
AFP (ng/ml)	0.559 (0.398-0.901)	0.014
≤400		
>400		
Total bilirubin (μmol/l)	0.678 (0.442-1.039)	0.045
≤26		
>26		
Albumin (g/l)	1.465 (0.959-0-2.238)	0.078
≤35		
>35		
Cirrhosis	0.631 (0.406-0.982)	0.041
Absent		
Present		
Tumor size (cm)	0.717 (0.469-1.095)	0.124
≤5		
>5		
Tumor necrosis	0.850 (0.532-1.357)	0.495
Absent		
Present		
Tumor number	1.045 (0.633-1.726)	0.863
Single		
Multiple		
Extrahepatic metastases	0.456 (0.273-0.764)	0.003
Absent		
Present		
Vascular invasion	0.376 (0.249-0.568)	<0.0001
Absent		
Present		
Child-Pugh class	0.703 (0.703-1.603)	0.776
A		
B		
C		
BCLC stage	1.214 (0.864-1.705)	0.264
0		
A		
B		
C		
D		

HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transferase; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Table IV. Multivariate analysis of potential prognostic factors for overall survival.

Clinicopathological characteristics	Hazard ratio (95% confidence interval)	P-value
Extrahepatic metastases	0.490 (0.282-0.843)	0.010
Absent		
Present		
Vascular invasion	0.373 (0.225-0.619)	<0.0001
Absent		
Present		

in the hepatocyte cytoplasm into the bloodstream. Elevated SF levels have also been reported in malignant tumors of the blood system (33), as well as non-tumor diseases, including hemochromatosis, chronic kidney disease, diabetes (34-36), rheumatoid arthritis and adult Still's disease (37). Multiple pathological factors influence the levels of SF, and its instability leads to a lack of specificity. Therefore, predicting prognosis based on SF is challenging.

In the present study, it was determined that 274 ng/ml was the cut-off point for SF. By contrast, Wu *et al* (27) used 267 ng/ml as the optimal SF cut-off point. The cut-off point for SF in a Korean study cohort was 150 ng/ml, whereas an Italian study reported that the optimal prognostic threshold for SF was 244 ng/ml (26,38). These variations suggested that the normal range of SF may be influenced by factors such as differences in laboratory equipment, region and ethnicity. Thus, the currently published data on SF as a prognostic tool for liver cancer lack generalizability and applicability. Furthermore, SF levels can

also be affected by the batch of experimental reagents and equipment. Thus, the accuracy of preoperative SF levels in predicting the prognosis of liver cancer may be compromised.

The correlation between SF levels and clinicopathological variables was then studied, and it was found that HBV infection, AST, ALT and GGT were significantly correlated with preoperative SF levels, while being unrelated to other laboratory parameters. Increased preoperative SF levels were also positively correlated with sex and cirrhosis. AST, ALT and GGT are indicators of liver cell injury. The presence of HBV infection and cirrhosis suggests the impairment of liver function. The destruction of normal liver cells and the presence of liver cancer cells can both lead to the release of ferritin into the bloodstream, resulting in increased SF levels. The correlation between SF levels and clinicopathological variables was also investigated. Wu *et al* (27) reported that in HCC patients undergoing liver resection TNM and BCLC stages closely correlated with preoperative SF levels while remaining unrelated to other clinicopathological variables. By contrast, Facciorusso *et al* (26) reported that in HCC patients undergoing RFA treatment, no significant correlation was found between SF levels and other prognostic factors. It was inferred that the different treatments employed may explain this inconsistency in the results.

In the present study, univariate analysis revealed that the presence of extrahepatic metastasis, vascular invasion, cirrhosis, and AST, GGT, AFP and total bilirubin levels were predictors of OS. However, the multivariate Cox analysis refined the number of predictors for OS, focusing on the presence of extrahepatic metastasis and vascular invasion. The presence of extrahepatic metastasis and vascular invasion both indicate tumor progression and are associated with increased mortality. However, the present findings indicated that preoperative SF levels are not an independent predictor of mortality in patients with HCC undergoing TACE. A recent study found limited prognostic value for SF in patients with decompensated cirrhosis, suggesting it may not be an independent predictor of mortality (39). Consequently, the value of SF for liver disease prognosis remains controversial.

The present study had certain limitations that should be acknowledged. First, the analysis did not include changes in SF levels after TACE. Second, no distinction was made between various interventional embolization methods, although research has revealed that drug-eluting bead-transarterial chemoembolization has no advantage over conventional transarterial chemoembolization in patients with unresectable HCC (40). Furthermore, the extended time span of the study means there are no mature guideline for earlier cases as a reference. According to BCLC, the study might not have been suitable candidates for TACE. Fourth, the present study was designed as a retrospective single-group analysis, with a relatively small sample size, which could introduce bias; therefore, its conclusions may require further validation through randomized controlled trials or large-scale prospective cohort studies. Finally, imaging follow-up data were unavailable for numerous patients, resulting in cases where only OS data were available without corresponding disease-free survival data.

In conclusion, this single-center study demonstrated that preoperative SF levels in patients with HCC undergoing TACE was not significantly correlated with prognosis. The present findings indicated that SF has limited utility as a prognostic indicator for patients with HCC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

XD and BT conceived and designed the study. MF, TN, BL and FG collected and analyzed the data. MF and TM drafted the manuscript. XD, BT, MF, TN, BL and FG contributed to the data interpretation and discussion. XD and BT confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. S20230320-01) by the Medical Ethics Committee of Mianyang Central Hospital (Mianyang, China). The data were analyzed anonymously; thus, informed consent was not obtained from the participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Gao YX, Yang TW, Yin JM, Yang PX, Kou BX, Chai MY, Liu XN and Chen DX: Progress and prospects of biomarkers in primary liver cancer (Review). Int J Oncol 57: 54-66, 2020.
2. Chen W, Chiang CL and Dawson LA: Efficacy and safety of radiotherapy for primary liver cancer. Chin Clin Oncol 10: 9, 2021.
3. Velázquez RF, Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorríos NG, Martínez I and Rodrigo L: Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology 37: 520-527, 2003.
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide:Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-E386, 2015.
5. Alisi A and Balsano C: Enhancing the efficacy of hepatocellular carcinoma chemotherapeutics with natural anticancer agents. Nutr Rev 65 (12 Pt 1): 550-553, 2007.
6. Han K and Kim JH: Transarterial chemoembolization in hepatocellular carcinoma treatment: Barcelona clinic liver cancer staging system. World J Gastroenterol 21: 10327-10335, 2015.

7. Raoul JL, Forner A, Bolondi L, Cheung TT, Kloeckner R and de Baere T: Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev 72: 28-36, 2019.
8. Lee SW, Peng YC, Lien HC, Ko CW, Tung CF and Chang CS: Clinical values of Barcelona Clinic Liver Cancer subgroup and up-to-7 criteria in intermediate stage hepatocellular carcinoma with transcatheter arterial chemoembolization. World J Clin Cases 10: 7275-7284, 2022.
9. Kotsifa E, Vergadis C, Vailas M, Machairas N, Kykalos S, Damaskos C, Garmpis N, Lianos GD and Schizas D: Transarterial chemoembolization for hepatocellular carcinoma: Why, when, how? J Pers Med 12: 436, 2022.
10. Samman BS, Hussein A, Samman RS and Alharbi AS: Common sensitive diagnostic and prognostic markers in hepatocellular carcinoma and their clinical significance: A review. Cureus 14: e23952, 2022.
11. Pinato DJ, Arizumi T, Jang JW, Allara E, Suppiah PI, Smirne C, Tait P, Pai M, Grossi G, Kim YW, *et al*: Combined sequential use of HAP and ART scores to predict survival outcome and treatment failure following chemoembolization in hepatocellular carcinoma: A multi-center comparative study. Oncotarget 7: 44705-44718, 2016.
12. Op den Winkel M, Nagel D, Op den Winkel P, Trojan J, Paprottka PM, Steib CJ, Schmidt L, Göller M, Stieber P, Göhring P, *et al*: Transarterial chemoembolization for hepatocellular carcinoma: development and external validation of the Munich-TACE score. Eur J Gastroenterol Hepatol 30: 44-53, 2018.
13. Ruf A, Dirchwolf M and Freeman RB: From Child-Pugh to MELD score and beyond: Taking a walk down memory lane. Ann Hepatol 27: 100535, 2022.
14. Xu L, Peng ZW, Chen MS, Shi M, Zhang YJ, Guo RP, Lin XJ and Lau WY: Prognostic nomogram for patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. J Hepatol 63: 122-130, 2015.
15. Mähringer-Kunz A, Weinmann A, Schmidtmann I, Koch S, Schotten S, Pinto Dos Santos D, Pitton MB, Dueber C, Galle PR and Kloeckner R: Validation of the SNACOR clinical scoring system after transarterial chemoembolisation in patients with hepatocellular carcinoma. BMC Cancer 18: 489, 2018.
16. Kadalayil L, Benini R, Pallan L, O'Beirne J, Marelli L, Yu D, Hackshaw A, Fox R, Johnson P, Burroughs AK, *et al*: A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol 24: 2565-2570, 2013.
17. Zhang JB, Chen Y, Zhang B, Xie X, Zhang L, Ge N, Ren Z and Ye SL: Prognostic significance of serum gamma-glutamyl transferase in patients with intermediate hepatocellular carcinoma treated with transcatheter arterial chemoembolization. Eur J Gastroenterol Hepatol 23: 787-793, 2011.
18. Xuan ZD, Zhou L, Wang Y and Zheng X: Prognostic value of the combination of serum levels of vascular endothelial growth factor, C-reactive protein and contrast-enhanced ultrasound in patients with primary liver cancer who underwent transcatheter arterial chemoembolization. Expert Rev Anticancer Ther 17: 1169-1178, 2017.
19. Yuan C, Yuan M, Chen M, Ouyang J, Tan W, Dai F, Yang D, Liu S, Zheng Y, Zhou C and Cheng Y: Prognostic implication of a novel metabolism-related gene signature in hepatocellular carcinoma. Front Oncol 11: 666199, 2021.
20. Rahimi-Dehkordi N, Nourijelyani K, Nasiri-Tousi M, Ghodssi-Ghassemabadi R, Azmoudeh-Ardalan F and Nedjat S: Model for End stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores: Ability to predict mortality and removal from liver transplantation waiting list due to poor medical conditions. Arch Iran Med 17: 118-121, 2014.
21. Peng Y, Qi X and Guo X: Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis:A systematic review and meta-analysis of observational studies. Medicine (Baltimore) 95: e2877, 2016.
22. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, *et al*: BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 76: 681-693, 2022.
23. Wang W, Knovich MA, Coffman LG, Torti FM and Torti SV: Serum ferritin: Past, present and future. Biochim Biophys Acta 1800: 760-769, 2010.
24. Plays M, Müller S and Rodriguez R: Chemistry and biology of ferritin. Metallomics 13: mfab021, 2021.
25. Guo Q, Li L, Hou S, Yuan Z, Li C, Zhang W, Zheng L and Li X: The role of iron in cancer progression. Front Oncol 11: 778492, 2021.
26. Facciorusso A, Del Prete V, Antonino M, Neve V, Crucinio N, Di Leo A, Carr BI and Barone M: Serum ferritin as a new prognostic factor in hepatocellular carcinoma patients treated with radiofrequency ablation. J Gastroenterol Hepatol 29: 1905-1910, 2014.
27. Wu SJ, Zhang ZZ, Cheng NS, Xiong XZ and Yang L: Preoperative serum ferritin is an independent prognostic factor for liver cancer after hepatectomy. Surg Oncol 29: 159-167, 2019.
28. Ghanaati H, Mohammadifard M and Mohammadifard M: A review of applying transarterial chemoembolization (TACE) method for management of hepatocellular carcinoma. J Family Med Prim Care 10: 3553-3560, 2021.
29. Manjunatha N, Ganduri V, Rajasekaran K, Duraiyarasan S and Adefuye M: Transarterial chemoembolization and unresectable hepatocellular carcinoma: A narrative review. Cureus 14: e28439, 2022.
30. Chung SW, Park MK, Cho YY, Park Y, Lee CH, Oh H, Jang H, Kim MA, Kim SW, Nam JY, *et al*: Effectiveness of transarterial chemoembolization-first treatment for advanced hepatocellular carcinoma: A propensity score matching analysis. J Hepatocell Carcinoma 8: 587-598, 2021.
31. Alkhateeb AA and Connor JR: The significance of ferritin in cancer: Anti-oxidation, inflammation and tumorigenesis. Biochim Biophys Acta 1836: 245-254, 2013.
32. Nielsen P, Günther U, Dürken M, Fischer R and Düllmann J: Serum ferritin iron in iron overload and liver damage: Correlation to body iron stores and diagnostic relevance. J Lab Clin Med 135: 413-418, 2000.
33. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J and Janka G: HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohisti-ocytosis. Pediatr Blood Cancer 48: 124-131, 2000.
34. Kalantar-Zadeh K and Lee GH: The fascinating but deceptive ferritin: To measure it or not to measure it in chronic kidney disease? Clin J Am Soc Nephrol 1 (Suppl 1): S9-S18, 2006.
35. Wang X, Fang X, Zheng W, Zhou J, Song Z, Xu M, Min J and Wang F: Genetic support of a causal relationship between iron status and type 2 diabetes: A mendelian randomization study. J Clin Endocrinol Metab 106: e4641-e4651, 2021.
36. Suárez-Ortegón MF, Ensaldo-Carrasco E, Shi T, McLachlan S, Fernández-Real JM and Wild SH: Ferritin, metabolic syndrome and its components: A systematic review and meta-analysis. Atherosclerosis 275: 97-106, 2018.
37. Jia J, Wang M, Meng J, Ma Y, Wang Y, Miao N, Teng J, Zhu D, Shi H, Sun Y, *et al*: Ferritin triggers neutrophil extracellular trap-mediated cytokine storm through Msrl contributing to adult-onset Still's disease pathogenesis. Nat Commun 13: 6804, 2022.
38. Lee S, Song A and Eo W: Serum ferritin as a prognostic biomarker for survival in relapsed or refractory metastatic colorectal cancer. J Cancer 7: 957-964, 2016.
39. Guo G, Sun M, Li Y, Yang W, Wang X, Yu Z, Li C, Hui Y, Fan X, Jiang K and Sun C: Serum ferritin has limited prognostic value on mortality risk in patients with decompensated cirrhosis: A propensity score matching analysis. Lab Med 54: 47-55, 2023.
40. Facciorusso A, Di Maso M and Muscatiello N: Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. Dig Liver Dis 48: 571-577, 2016.