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ORIGINAL RESEARCH

Prognostic Significance of Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score in Hepatocellular Carcinoma

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Purpose: HALP score consisting of hemoglobin content, albumin content, lymphocyte count, and platelet count can comprehensively evaluate the inflammatory response and nutritional status. Many researchers have indicated that the HALP score is an effective predictor of the overall prognosis of various tumors. However, there is no relevant research to suggest whether the HALP score can predict the prognosis of patients with hepatocellular carcinoma (HCC).

Patients and Methods: We retrospectively analyzed 273 HCC patients who underwent surgical resection. Hemoglobin content, albumin content, lymphocyte count, and platelet count in peripheral blood were measured for each patient. The relationship between the HALP score and overall survival (OS) was investigated.

Results: With a mean of 56.69 ± 1.25 months follow-up, the 1-, 3-, and 5-year OS was 98.9%, 76.9%, and 55.3% for all patients, respectively. HALP scores (HR=1.708, 95% CI=1.192–2.448, P=0.004) were significant independent risk factors of OS. The 1-, 3-, and 5-year OS were 99.3%, 84.3%, and 63.4% for patients with high HALP scores; and 98.6%, 69.8%, and 47.5% for patients with low HALP scores, respectively (P=0.018). In TNM I–II stage patients, compared with high HALP scores, low HALP scores have worse OS (P=0.039). In AFP positive patients, compared with high HALP scores, low HALP scores have worse OS (P=0.042).

Conclusion: Our research showed the preoperative HALP score is an independent predictive factor of overall prognosis, and a low HALP score indicates a worse prognosis in HCC patients who underwent surgical resection.

Keywords: hepatocellular carcinoma, survival, HALP score, surgical resection, prognostic marker

Introduction

HCC is the most common pathological type of primary liver cancer[1] and one of the most common cancers in the world.[2] Because of the high recurrence rate and high metastasis rate, its treatment and management are still a big challenge today. There are many ways to treat HCC.[3] As we know, hepatectomy is one of the effective methods to treat HCC. Child-Pugh classification consisting of serum albumin, serum bilirubin, prothrombin time, ascites and hepatic encephalopathy is a practical tool to assess the prognosis of patients with liver cirrhosis.[4] It is generally believed that the earlier the grading, the better the prognosis. Hepatectomy can be used as the first-line curative treatment for HCC patients with Child-Pugh A.[5] Besides surgical resection, there are liver transplantation,[6] local area therapy,[7] targeted therapy[8,9] and immunotherapy,[10] etc. But the overall prognosis of HCC is not optimistic.

The inflammatory reaction and immune state of the body are both very important for the prognosis of the tumor. The tumor immune microenvironment is critical to the occurrence and development of liver cancer.[11] Many inflammatory markers based on hematology have been proven to be prognostic factors of HCC.[12,13] As we all know, nutritional status plays a critical role in the occurrence, development, and prognosis of many diseases, and HCC is no exception.[14–16] HALP score consisting of hemoglobin content, albumin content, lymphocyte count, and platelet count can comprehensively evaluate the inflammatory response and nutritional status. There is no relevant research to suggest whether the

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HALP score can predict the overall survival of HCC patients who underwent hepatectomy. However, many researchers have shown that the HALP score is an effective predictive factor of the overall prognosis of various tumors,[17] such as pancreatic cancer,[18] gastrointestinal stromal tumor,[19] esophageal cancer,[20] etc.

Non-invasive laboratory markers gamma-glutamyl transpeptidase-to-platelet ratio (GPR) and fibrosis-4 (Fib-4) are related to the level of liver fibrosis.[21,22] They are also important indexes to evaluate the occurrence of HCC.[23–26] In practical work, their acquisition methods are simple and easy for patients to accept. And they are considered to have important clinical significance. GPR is an effective factor to indicate the prognosis of liver cancer.[27,28] Studies have suggested that Fib-4 is related to complications such as liver failure[29] and varicose veins[30] in liver cancer. Studies have shown that the level of Fib-4 can indicate the OS of patients with HCC,[31] but others have shown that Fib-4 has no such effect.[32,33]

Our main purpose is to explore the impact of the preoperative HALP score on the overall prognosis of HCC patients who underwent hepatectomy. And the predictive value of other important clinicopathological features and controversial markers in OS of patients with HCC was also evaluated.

Patients and Methods

Our study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). We retrospectively analyzed HCC patients who underwent surgical resection in Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, from May 2016 to June 2017. All included patients met the following requirements: (1) primary liver cancer patients; (2) patients underwent surgical resection for the first time; (3) hepatocellular carcinoma was confirmed by postoperative pathological examination. Exclusion criteria: (1) combined with other malignant tumors; (2) anticancer treatment before operation; (3) under eighteen; (4) metastatic liver cancer; (5) recurrent liver cancer.

Clinical Variables

All the test results were taken from routine tests within 1 week before surgery. HALP score, GPR and Fib-4 were calculated using the following formulas, respectively: $\mathrm{Fib}-4=[\mathrm{age(year)}*\mathrm{AST(U/L)}]/[\mathrm{platelet}(*10^9/\mathrm{L})*\sqrt{\mathrm{ALT(U/L)}}]$. $\mathrm{GPR}=\gamma-\mathrm{glutamyl\ transpeptidase(g/L)/platelet}(*10^9/\mathrm{L})$.[28]

$\mathrm{HALP\ score}=\mathrm{hemoglobin(g/L)}*\mathrm{albumin(g/L)}*\mathrm{Lymphocyte}(*10^9/\mathrm{L})/\mathrm{platelet}(*10^9/\mathrm{L})$.[18]

Follow-Up

The electronic medical record system was used to screen the inpatients in our hospital according to the above criteria. Telephone and electronic medical record systems were used for postoperative follow-up.

Statistical Analysis

Univariate analysis and multivariate analysis were performed using Cox regression analysis. Independent risk factors of OS were determined by multivariate analysis. In the univariate analysis, the variable that $P<0.05$ was further included in the multivariate analysis. We used the Kaplan–Meier method to identify OS, and compared them with the Log rank test. Using the Kolmogorov–Smirnov test to evaluate the normality of the continuous variables. The mean ± standard deviation expressed the continuous variables that conformed to the normal distribution and the median (interquartile range) expressed the continuous variables with a skewed distribution. The categorical variables have expressed the frequency and percentage. All statistical analyses were performed using MedCalc 20.0 and SPSS 25.0. P values <0.05 were considered statistically significant.

Results

We enrolled 273 HCC patients who met the study conditions during the study period. There were 238 (87.2%) male and 35 (12.8%) female patients. The mean age was 53.99 ± 10.74 years (Table 1). With a mean of 56.69 ± 1.25 months follow-up, the 1-, 3-, and 5-year OS was 98.9%, 76.9%, and 55.3% for all patients, respectively (Figure 1).

Table 1 Clinical Features of All Patients

Features	N=273	Features	N=273
Gender (male/female)	238 (87.2%)/35 (12.8%)	Monocyte (*10^9/L)	0.46 (0.35–0.60)
Age	53.99 ± 10.74	Hemoglobin (g/L)	140.00 (127.50–151.50)
HBsAg[a] (+/-)	214 (78.4%)/59 (21.6%)	Platelet (*10^9/L)	164.00 (119.50–222.00)
Liver cirrhosis (yes/no)	139 (50.9%)/134 (49.1%)	ALT[e] (U/L)	25.00 (20.00–37.00)
Tumor number (1/≥2)	241 (88.3%)/32 (11.7%)	AST[f] (U/L)	27.00 (22.00–38.00)
Tumor diameter	4.70 (3.00–7.00)	Albumin (g/L)	41.251 ± 4.354
TNM[b] stage (I–II/III–IV)	212 (77.7%)/61 (22.3%)	TBil[g] (μmol/L)	13.00 (9.80–16.25)
Cell differentiation (poor/moderate/well)	122 (44.7%)/134 (49.1%)/17 (6.2%)	ALP[h] (U/L)	77.00 (60.50–101.00)
MVI[c] status (+/-)	71 (26.0%)/202 (74.0%)	γ-GT[i] (U/L)	49.00 (30.00–101.00)
WBC[d] (*10^9/L)	5.27 (4.31–6.77)	PT[j] (S)	13.80 (13.30–14.40)
Neutrophil (*10^9/L)	3.10 (2.39–4.14)	AFP[k] (ng/mL)	85.12 (5.50–1446.00)
Lymphocyte (*10^9/L)	1.48 (1.14–1.87)		

Notes: [a]Hepatitis B surface antigen; [b]Tumor node metastasis; [c]Microvascular invasion; [d]White blood cell; [e]Alanine aminotransferase; [f]Aspartate aminotransferase; [g]Total bilirubin; [h]Alkaline phosphatase; [i]γ-glutamyl transpeptidase; [j]Prothrombin time; [k]Alpha-fetoprotein.

Optimal Cutoff Values of PT, GPR, Fib-4, ALT/AST, HALP Score, and AFP

The optimal cutoff values of PT, GPR, Fib-4, ALT/AST, and HALP scores were 14.35, 0.205, 2.824, 0.568, and 54.132, respectively (Figure 2). According to the definition of AFP level in our hospital, AFP >7.00 ng/mL is defined as AFP rising, that is, AFP positive; and AFP≤7.00 ng/mL is defined as AFP normal, that is, AFP negative.

Association Between HALP Score and Clinical Characteristics

There were 134 patients with high HALP scores and 139 patients with low HALP scores. The chi-square test was used to verify the relationship between preoperative HALP score and clinical features. Low HALP scores were found to be related to the high TNM stage (P=0.001, Table 2).

Prognostic Factors for Overall Survival

Factors included gender, microvascular invasion, ALT/AST, Fib-4, GPR, HALP score and treatment protocol associated with OS after surgical resection in univariate analysis. In multivariate analysis, we found that gender (HR=0.426, 95% CI=0.217–0.833), microvascular invasion (MVI) (HR=0.652, 95% CI=0.447–0.950), ALT/AST (HR=1.845, 95%

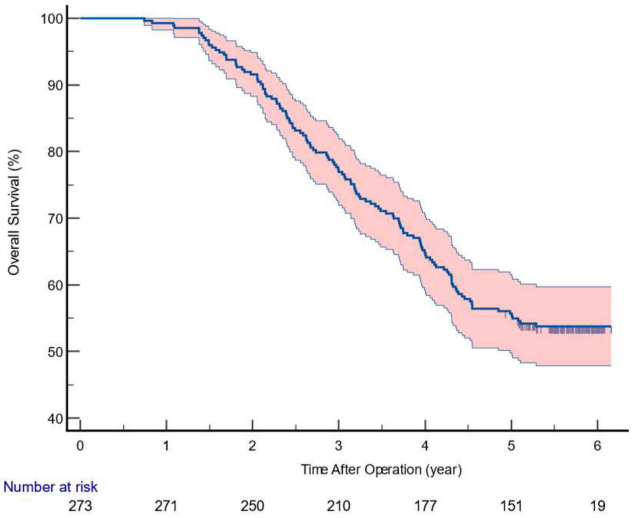
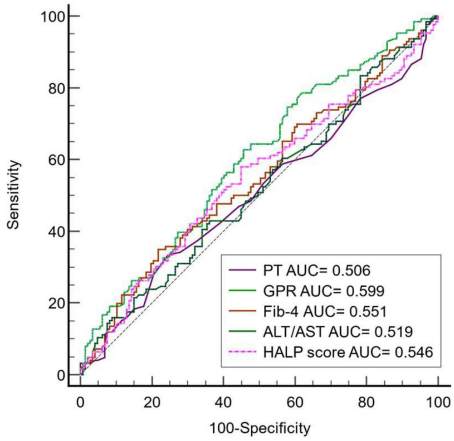


Figure 1 Overall survival curves of all patients after surgical resection.



PT: prothrombin time; GPR: γ-glutamyl transpeptidase to platelet ratio; Fib-4: fibrosis-4 score; ALT/AST: alanine aminotransferase/aspartate aminotransferase; HALP: hemoglobin, albumin, lymphocyte, and platelet.

Figure 2 The ROC curves of PT, GPR, Fib-4, ALT/AST and HALP score.

CI=1.093–3.114), HALP score (HR=1.708, 95% CI=1.192–2.448), and treatment protocol (HR=1.882, 95% CI=1.321–2.681) were significant independent risk factors of OS (Table 3, all $P < 0.05$).

Independent Risk Factors for Overall Survival Rates

The 1-, 3-, and 5-year OS was 98.7%, 76.1%, and 52.5% for male patients; and 100%, 82.9%, and 74.3% for female patients, respectively (Figure 3a). The 1-, 3-, and 5-year OS was 100%, 73.2%, and 43.7% for patients with microvascular invasion positive; and 98.5%, 78.2%, and 59.4% for patients with microvascular invasion negative, respectively (Figure 3b). The 1-, 3-, and 5-year OS was 98.7%, 78.7%, and 57.5% for patients with high ALT/AST; and 100%, 63.6%,

Table 2 Relationship Between HALP Score and Clinical Features in Patients

Features	HALP[e]		
	High (n=134)	Low (n=139)	P value
Gender			P=0.250
Male	120 (89.6%)	118 (84.9%)	
Female	14 (10.4%)	21 (15.1%)	
Age (years)			P=0.130
<60	87 (64.9%)	102 (73.4%)	
≥60	47 (35.1%)	37 (26.6%)	
HBsAg[a]			P=0.548
Positive	103 (76.9%)	111 (79.9%)	
Negative	31 (23.1%)	28 (20.1%)	
Liver cirrhosis			P=0.101
Yes	75 (56.0%)	64 (46.0%)	
No	59 (44.0%)	75 (54.0%)	
Cell differentiation			P=0.770
Poor	57 (42.5%)	65 (46.8%)	
Moderate	68 (50.7%)	66 (47.5%)	
Well	9 (6.7%)	8 (5.8%)	

(*Continued*)

Table 2 (Continued).

Features	HALP[e]		
	High (n=134)	Low (n=139)	P value
Microvascular invasive			P=0.583
Positive	37 (27.6%)	34 (24.5%)	
Negative	97 (72.4%)	105 (75.5%)	
Tumor number			P=0.076
=1	123 (91.8%)	118 (84.9%)	
≥2	11 (8.2%)	21 (15.1%)	
TNM[b] stage			P=0.001
I–II	115 (85.8%)	97 (69.8%)	
III–IV	19 (14.2%)	42 (30.2%)	
AFP[c]			P=0. 092
>7.00 ng/mL	92 (68.7%)	108 (77. 7%)	
≤7.00 ng/mL	42 (31.3%)	31 (22. 3%)	
PT[d]			P=0.789
≥14.35s	37 (27.6%)	41 (29.5%)	
<14.35s	97 (72.4%)	98 (70.5%)	
Treatment protocol			P=0.727
Surgery only	78 (58.2%)	78 (56.1%)	
Combined treatment	56 (41.8%)	61 (43.9%)	

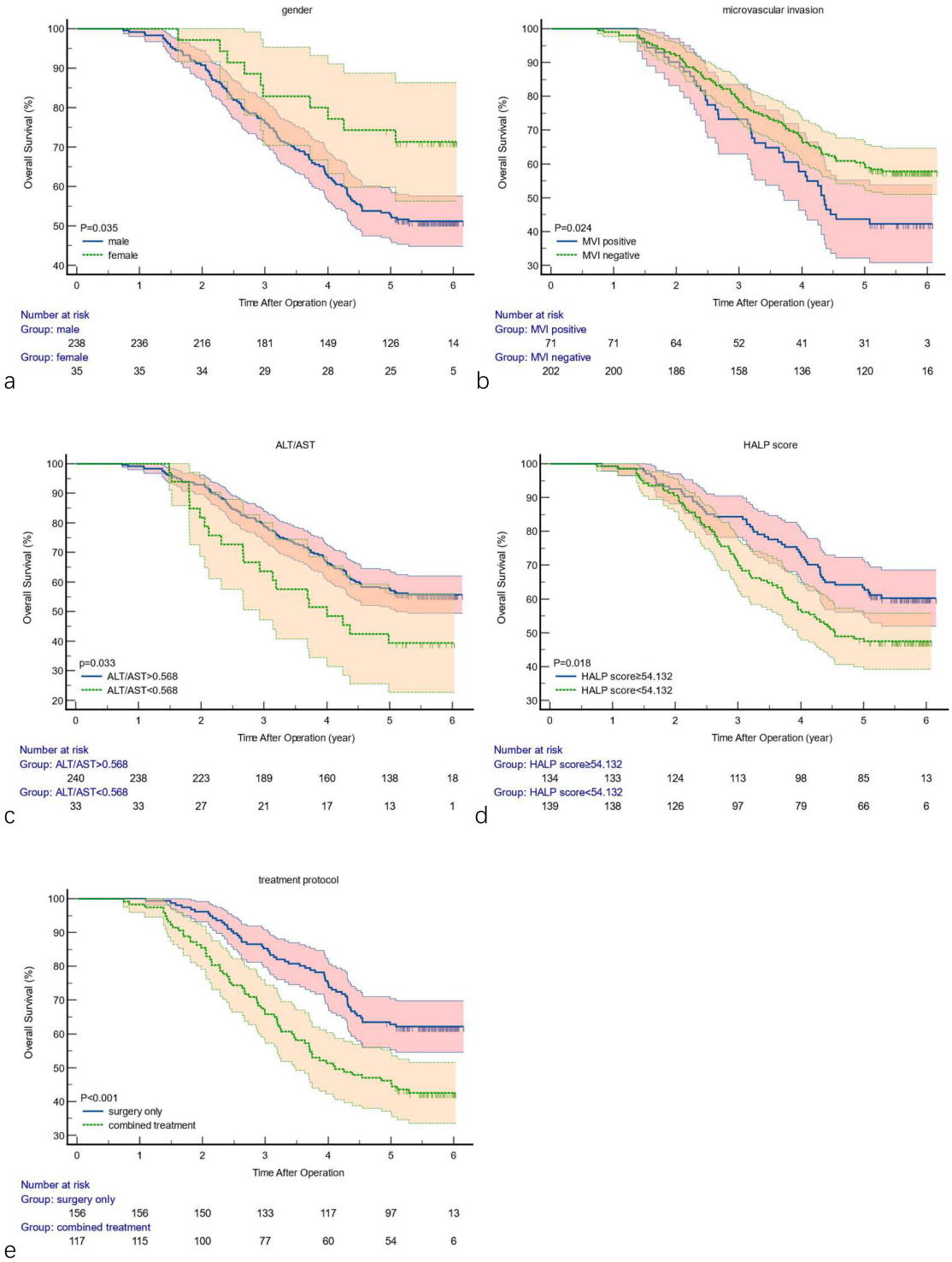
Notes: [a]Hepatitis B surface antigen; [b]Tumor node metastasis; [c]Alpha-fetoprotein; [d]Prothrombin time; [e]Hemoglobin, albumin, lymphocyte, and platelet.

Table 3 Univariate and Multivariate Analysis of Factors for OS

Variable	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Gender (male/female)	0.505 (0.265–0.964)	0.038	0.426 (0.217–0.833)	0.013
Age (<60 years/≥60 years)	0.871 (0.601–1.261)	0.464		
Liver cirrhosis (yes/no)	0.971 (0.684–1.377)	0.868		
TNM[a] stage (I–II/III–IV)	1.383 (0.929–2.057)	0.110		
Cell differentiation (poor/moderate-well)	1.136 (0.798–1.618)	0.480		
Microvascular invasion (positive/negative)	1.530 (1.054–2.222)	0.025	0.652 (0.447–0.950)	0.026
Tumor number (=1/≥2)	1.113 (0.659–1.881)	0.688		
HBsAg[b] (positive/negative)	0.956 (0.625–1.464)	0.837		
AFP[c] (≤7.00 ng/mL/>7.00 ng/mL)	0.953 (0.669–1.358)	0.791		
PT[d] (<14.35s/≥14.35s)	1.324 (0.914–1.918)	0.138		
ALT/AST[e] (<0.568/≥0.568)	1.673 (1.037–2.700)	0.035	1.845 (1.093–3.114)	0.022
Fib-4[f] (<2.824/≥2.824)	0.635 (0.440–0.916)	0.015	0.737 (0.488–1.112)	0.146
GPR[g] (<0.205/≥0.205)	0.584 (0.394–0.866)	0.007	0.673 (0.443–1.021)	0.063
HALP score[h] (<54.132/≥54.132)	1.527 (1.072–2.176)	0.019	1.708 (1.192–2.448)	0.004
Treatment protocol (surgery only/combined treatment)	1.913 (1.348–2.716)	<0.001	1.882 (1.321–2.681)	<0.001

Notes: [a]Tumor node metastasis; [b]Hepatitis B surface antigen; [c]Alpha-fetoprotein; [d]Prothrombin time; [e]Alanine aminotransferase/aspartate aminotransferase; [f]Fibrosis-4 score; [g]γ-glutamyl transpeptidase to platelet ratio; [h]Hemoglobin, albumin, lymphocyte, and platelet.

and 39.4% for patients with low ALT/AST, respectively (Figure 3c). The 1-, 3-, and 5-year OS was 99.3%, 84.3%, and 63.4% for patients with high HALP scores; and 98.6%, 69.8%, and 47.5% for patients with low HALP scores, respectively (Figure 3d). The 1-, 3-, and 5-year OS was 99.4%, 84.6%, and 62.8% for patients with surgery only; and 97.4%, 65.8%, and 45.3% for patients with combined treatment, respectively (Figure 3e).



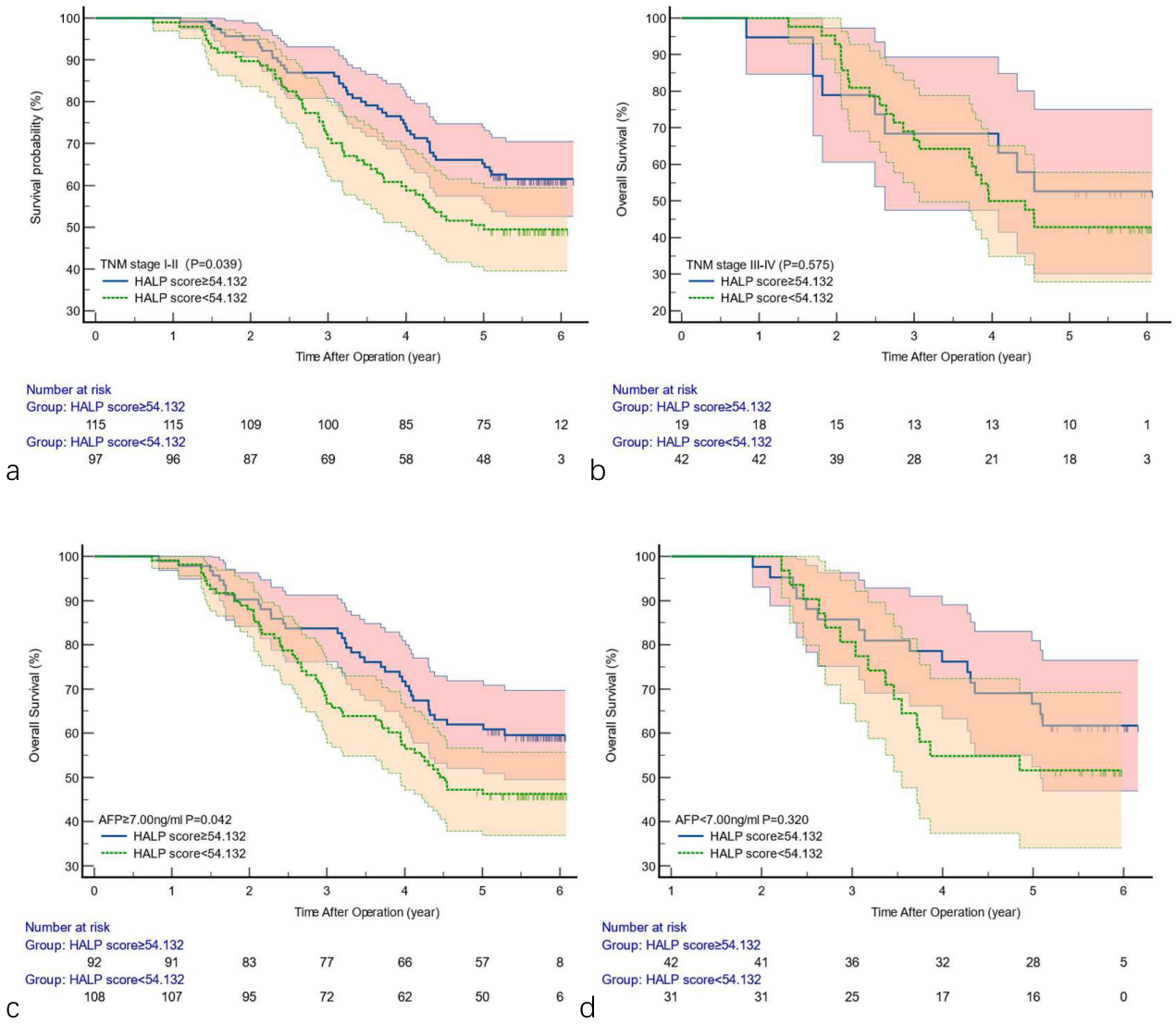
MVI: microvascular invasion; ALT/AST: alanine aminotransferase/aspartate aminotransferase; HALP: hemoglobin, albumin, lymphocyte, and platelet.

Figure 3 Overall survival curves of HCC patients after surgical resection based on gender (**a**), microvascular invasion (**b**), ALT/AST (**c**), HALP score (**d**) and treatment protocol (**e**).

Predictive Value of HALP Score in Subgroup

The above analysis shows the HALP score is associated with the TNM stage. So, patients with HCC were divided into different subgroups according to different TNM stages, and the effects of HALP score on OS were studied, respectively. In TNM I–II stage patients, compared with high HALP scores, low HALP scores have worse OS (P=0.039, Figure 4a). In TNM III–IV stage patients, there was no significant difference in OS with different HALP scores (P=0.575, Figure 4b).

AFP is one of the important markers to monitor the occurrence of HCC and tumor recurrence after hepatectomy. So according to the different levels of AFP, all patients in our study were divided into two subgroups, and the effects of HALP score on OS were studied, respectively. In AFP positive subgroup, compared with high HALP scores, low HALP scores have worse OS (P=0.042, Figure 4c). In AFP negative subgroup, there was no significant difference in OS with different HALP scores (P=0.320, Figure 4d).



TNM: tumor node metastasis; HALP: hemoglobin, albumin, lymphocyte, and platelet; AFP: alpha-fetoprotein.

Figure 4 Kaplan–Meier curves of OS according to different HALP scores in patients with TNM I–II stage (**a**), TNM III–IV stage (**b**), AFP positive (**c**), and AFP negative (**d**).

Discussion

HALP score can not only comprehensively evaluate the inflammatory response and nutritional status of the body, but also be obtained in a simple, economical, and non-invasive way, which is an index worthy of clinical use. We have proved that the preoperative HALP score has a statistically significant correlation with the OS of HCC patients undergoing hepatectomy. Moreover, the preoperative HALP score is related to the tumor TNM stage. Subgroup analysis suggests a low HALP score is related to poor OS in TNM I–II stage patients. Because AFP cannot be ignored in HCC, we further analyzed the relationship between HALP scores and OS in different AFP subgroups. Similarly, in AFP positive subgroup, a low HALP score indicates poor OS. In patients with AFP negative and TNM III–IV stage, there is no statistical difference between HALP score and OS, which may be due to insufficient sample size. The results of the subgroup analysis showed that the HALP score was relatively stable as an independent prognostic factor of HCC patients with hepatectomy.

Our results also show gender, MVI status, and ALT/AST are independent influencing factors of OS in HCC patients. This is consistent with previous studies.[34] However, in our study, GPR is not an independent factor affecting the postoperative survival of patients with HCC. This is inconsistent with the research conclusions of other scholars.[35] It may be associated with the insufficient sample size of our study, the single area of our research object, and the different clinical variables included in different studies. For the controversial Fib-4 in previous studies, this study suggests that the level of Fib-4 has no obvious relationship with the patient's OS. In our study, the prognosis of patients who only receive surgical treatment is better than that of patients who receive comprehensive treatment. This does not mean that comprehensive treatment is an absolute predictive factor of a worse prognosis for patients with HCC. It is mainly because the patient has tumor recurrence during postoperative follow-up that comprehensive anti-tumor treatment will be carried out. This further proves the importance of early identification of patients with high risk and early intervention treatment to improve prognosis.

As we all know, hemoglobin, albumin, lymphocytes, and platelets are all closely associated with the occurrence and development of tumors. Hemoglobin is associated with the progress of tumors.[36] Low hemoglobin level is an influential index in the poor overall prognosis of patients with cancer.[37] Albumin is produced by the liver, which not only reflects the inflammatory level of the body[38] but also reflects the nutritional status of the body.[39] At the same time, studies have shown that low albumin level suggests that the overall prognosis of cancer patients is poor.[40,41] Lymphocytes and platelets belong to immune inflammatory cells. The lymphocyte is one of the important immune cells that kill tumor cells.[42] Lymphocyte count can reflect the immune ability and inflammatory state to some extent. Many studies have shown inflammatory markers composed of lymphocytes can predict the overall prognosis of tumor patients.[13,43] Platelets almost participate in the whole process of tumor occurrence and development, including tumor formation, growth, and metastasis.[44,45] Some scholars believe that platelets have the potential to diagnose tumors,[46] and monitor the progress of disease.[47] Many inflammatory markers related to platelets have been proven to be related to the overall prognosis of many cancer patients,[48–50] including HCC.

As mentioned above, at present, there are many treatments for hepatocellular carcinoma, but they still cannot raise the overall prognosis of HCC patients. Personalized management is a critical factor in improving the overall prognosis of patients with the advent of the era of precise treatment. However, there is no uniform standard for identifying high-risk patients with HCC at present. So, to identify high-risk patients with HCC in the clinic, in addition to pathological features, nutritional status, and inflammatory reactions are also important parts that should not be ignored. Our study's results show that the low HALP score of HCC patients is a symbol of poor prognosis. Therefore, in the early assessment of a patient's risk, it is one of the measures to better judge the prognosis of patients to include the HALP score in the assessment scope.

Our research has some limitations. Firstly, the clinical data were obtained from a single examination before curative resection, which is likely to cause numerical deviation. Secondly, this is a single-center study, and its conclusion is not as convincing as that of a multi-center study. Thirdly, this is a retrospective study, so the research conclusion needs further prospective study verification.

Conclusion

Our research proved the preoperative HALP score is an independent predictive factor of overall prognosis, and a low HALP score indicates a worse prognosis in HCC patients who underwent surgical resection.

Data Sharing Statement

The details of the data are available from the first author upon reasonable request.

Ethics Approval

This is an observational study. This study was approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Consent to Participate

Patient consent was waived, as approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

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Disclosure

The authors report no conflicts of interest in this work.

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