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ORIGINAL ARTICLE

# The Prognostic Significance of ACLR and HALP Scores in Hepatocellular Carcinoma Patients Treated with Sorafenib

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## ABSTRACT

**Background:** Sorafenib is the standard treatment for patients with hepatocellular carcinoma (HCC) with advanced stage disease. An accurate prediction model is important to ascertain the prognosis of HCC patients treated with sorafenib. This study aimed to predict the outcome of HCC patients treated with sorafenib using ACLR and HALP scores.**Methods:** This Observational Retrospective Cohort Study was conducted on 110 Patients with HCC patients from January 2015 to December 2022 at Medical Oncology Department, Faculty of Medicine, Zagazig University**. Results:** HALP and ACLR score were significantly associated with treatment outcome among HCC patients treated with sorafenib. HALP was a predictor for treatment outcome among HCC patients treated with sorafenib at cut off point of 42.9 with sensitivity of 75.7% and specificity of 86.3%. ACLR was a predictor for treatment outcome among HCC patients treated with sorafenib at cut off point of 75.6 with sensitivity of 78.4% and specificity of 82.2%. High HALP score indicates better prognosis with a cut off of 42.9. Low ACLR indicates better prognosis with a cut of 75.6. **Conclusion:** Both HALP and ACLR scores can be used as valid prognostic scores for independently predicting the overall prognosis in HCC patients treated with Sorafenib. Having a low HALP score indicates worse prognosis, while, our results showed that the cut off for ACLR 75.6 .. but high and low score didn't show any significance in predicting the PFS or OS but they show significant sensitivity and specificity.
**Keywords:** hepatocellular carcinoma, sorafenib, prognostic significance.

## INTRODUCTION

Hepatocellular carcinoma (HCC) represents the sixth most common cancer worldwide [1]**.** In Egypt, it is the fourth most common occurring cancer and the most common cause of cancer-related mortality [2]**.** Its prognosis remains poor despite all efforts exerted in diagnosis and management due to its high metastatic rate and tumor recurrence [3]**.** Therefore, there has been an urgent need to develop more prognostic modalities assisting in predicting the overall prognosis.

It is settled that inflammatory response and nutrition status play a huge role in cancer occurrence, development, and prognosis especially in HCC[4]**.** Based on this, many prognostic scores have been evolved such as neutrophil-to-lymphocyte ratio, prognostic nutritional index, and aminotransferase-to-platelet index [5]**.**

Those modalities depend on only two elements and its prognostic value is not satisfactory. So, we incorporated many markers to achieve more valid predictive scores. HALP score consists of hemoglobin level, albumin level, lymphocyte count and platelet count [6]. On the other hand, ACLR score stands for aspartate transaminases, C-reactive protein, and lymphocyte count [7].

ACLR score is calculated as follows: AST (U/L) * CRP (mg/L) / Lymphocyte count (10^9/L). However, HALP score is calculated as follows: Hemoglobin (g/L) * Lymphocyte count (10^9/L) * Albumin (g/L) / Platelet (10^9/ L) **(6).**

## AIM OF WORK

This study aimed to predict the outcome of HCC patients treated with sorafenib using ACLR and HALP scores.

## METHODS

This Observational Retrospective Cohort Study was conducted on 110 Patients with HCC patients from January 2015 to December 2022 at Medical Oncology Department, Faculty of Medicine Zagazig University.

**Inclusion criteria:** Age ≥18 years. Radiological and/or pathological proven HCC.PS 0-1. Child Pugh score A.

**Exclusion criteria:** Combined with other malignant tumors; Recurrent liver cancer; Metastatic liver disease.

**The following data was collected from the patient's files.**

**History:** Personal data, Initial laboratory results, Child-Paugh score, Date of progression or recurrent disease and Date of last follow up

**Procedures**

**Calculation of cut off point for HALP and ACLR scores:**

**- Optimal cut-point value:** The optimal cut-point value is the value whose sensitivity and specificity are the closest to the value of the area under the receiver operating curve (ROC) curve and the absolute value of the difference between the sensitivity and specificity values is minimum**[8].**

**Outcome Measurements and Follow-up:** HALP score is calculated using the following equation: HB (g/L) *Albumin (g/L) *Lymphocyte (10^9/L)/ platelets (10^9/L), and ACLR score is calculated using the following formula: AST (U/L) * CRP (mg/L) / Lymphocyte count (*10^9/ L).

**Primary End Point:** Assessment of the correlation between HALP and ACLR scores and PFS.

**Secondary End Point:** Assessment of the correlation between HALP and ACLR scores and OS.

Response criteria was evaluated through the response evaluation criteria in solid tumors (RECIST1.1):

-Complete response (CR): disappearance of all target lesions.

-Partial response (PR): at least decrease a 30% in the sum of target lesions.

-Progressive disease (PD): at least 20% increase in the sum of the target lesions.

-Stable disease (SD): neither sufficient shrinkage to qualify to PR nor sufficient increase to qualify to PD.

**Ethical Consideration:** Study protocol was approved by Institutional Research Board (IRB) of Zagazig University Institution. Confidentially and personal privacy were respected in all levels of the study, collected data were not used for any other purposes.

## STATISTICAL ANALYSIS

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. Absolute frequencies were used to define categorical variables, and the chi-square test was used to compare them. The chi-square for trend test was performed to examine the relationship between the two sets of ordinal data. Means and standard deviations were used to characterize quantitative variables. One-way analysis of variance was used to compare quantitative data from more than two groups. Spearman rank correlation coefficients (for non-normally distributed data) were used to evaluate the degree and direction of correlation between two continuous variables. Mann-whitnney test was used to compare between two groups non- normally distributed variables. The optimal cutoff value for a quantitative parameter utilized in the diagnosis of a health issue was determined using a ROC curve.

-Overall Survival (OS) defined as the length of time from either the date of diagnose or the start of treatment to the date of death or last follow up.

-Progression Free survival (PFS) was defined as the length of time during and after the treatment to the date of disease progression or recurrence.

-P-value < 0.05 was considered statistically significant p-value ≥ 0.05 was considered statistically insignificant.

## RESULTS

Table (1) showed that the current study included total 110 patients and showed that mean age of the patients was 54.13 ± 12.73 years with mean BMI of 28.41 ± 3.12 kg/m$^2$, meanwhile 65.4% of the patients were males. The prevalent comorbidity was HCV and liver cirrhosis (92.7%) then smoking (32.7%). Most of the patients were PS I (60%) and all of the patients were Child-Pugh A (100%). Mean duration of Sorafenib treatment was 4.18 ± 1.49 months. There were 69.1% of the patients suffering from toxicity effect of Sorafenib treatment. Table (2) showed that the current study showed that there is a significant increase in hemoglobin and lymphocyte count pretreatment to follow up. Meanwhile, that there is a significant decrease in albumin in pretreatment compared to follow up. However, there is a slight change regarding ACLR score and HALP score without statistical significance. Table (3) showed that there is no significant difference in post treatment ACLR score in responding or progressive HCC patients, p>0.12. While there was a significant higher HALP score in responding disease, compared to progressive disease, p<0.009. Table (4) showed that HALP and ACLR scores were statistically significant associated with treatment outcome among HCC patients treated with sorafenib. Table (5) showed that HALP achieved significant level as a predictor for treatment outcome among HCC patients treated with sorafenib at cut off point of 42.9 with sensitivity of 75.7% and specificity of 86.3% ACLR achieved significant level as a predictor for treatment outcome among HCC patients treated with sorafenib at cut off point of 75.6 with sensitivity of 78.4% and specificity of 82.2%.

Figure (1) showed that median progression free survival per years for HALP >42.9 HCC patients is 11 months compared to 5 months for HALP ≤42.9Patients. There was longer significant progression free survival per years regarding HALP >42.9 score compared to patients HALP ≤42.9score patients, p=0.001. Figure (2) showed that median progression free survival per years for ACLR <75.6 HCC patients is 9 months compared to 6 months for ACLR ≥75.6 Patients. There was no significant difference of progression free survival per years regarding ALCR score, p=0.133. Figure (3) showed that median overall survival per months for HALP >42.9 HCC patients is 12.8 months compare to 9.5 months for HALP ≤42.9 Patients. There was longer significant overall survival per months regarding HALP >42.9 score compared to patients with HALP ≤42.9 score patients, p=0.022. Figure (4) showed that median overall survival per months for ACLR <75.6 HCC patients is 11.9 months compare to 10.25 months for ACLR ≥75.6 Patients. There was no significant difference of overall survival per months regarding ALCR score, p=0.66.

**Table (1):** Clinical pathological feature among the studied patients

| | | **Patients (n=110)** | |
|---|---|---|---|
| Age (years) | Mean ± SD | 54.13 ± 12.73 | |
| BMI (kg/m$^2$) | Mean ± SD | 28.41 ± 3.12 | |
| | | n. | % |
| Gender | Female | 38 | 34.5% |
| | Male | 72 | 65.4% |
| Comorbidities | Hepatitis C virus | 102 | 92.7% |
| | Liver Cirrhosis | 102 | 92.7% |
| | Smoking | 36 | 32.7% |
| | Diabetes mellitus | 29 | 26.4% |
| | Hypertension | 24 | 21.8% |
| | Hepatitis B virus | 8 | 7.3% |
| PS | 0 | 44 | 40% |

| | | | |
|---|---|---|---|
| | I | 66 | 60% |
| Child Pugh | A | 110 | 100.0% |
| Duration of treatment (months) | Mean ± SD | 4.18 ± 1.49 | |
| Treatment dose | Full dose | 34 | 30.9% |
| | Dose adjustment (reduction) | 49 | 44.5% |
| Discontinuation of treatment | | 27 | 24.5% |
| toxicity of Sorafenib | Overall incidence | 76 | 69.1% |
| | Liver dysfunction | 30 | 27.3% |
| | Fatigue | 17 | 15.5% |
| | Hand-foot syndrome | 13 | 11.8% |
| | Diarrhea | 12 | 10.9% |
| | Bleeding | 4 | 3.6% |

**BMI:** Body Mass Index, **PS**: performance status

**Table (2):** Laboratory parameters among the studied patients.

| | **Patients** (n=110) | | **P** |
|---|---|---|---|
| | **Pre** | **Follow up** | |
| **Hemoglobin** (g/dL) Mean ± SD | 11.73 ± 1.7 | 12.2 ± 1.4 | **.002** |
| **PLT** ($x10^3$/L) Mean ± SD | 151.05 ± 71.03 | 147.95 ± 42.65 | .559 |
| **Lymphocyte count** Mean ± SD | 1.57 ± 0.813 | 1.72 ± 0.716 | **.028** |
| **AST** (U/L) Mean ± SD | 75.46 ± 34.74 | 79.72 ± 22.76 | **.043** |
| **Serum Albumin** (g/dL) Mean ± SD | 3.31 ± 0.55 | 3.1± 0.50 | **<0.001** |
| **CRP** (mg/L) Mean ± SD | 2.28 ± 1.52 | 2.04 ± 1.09 | .448 |
| **ACLR** Mean ± SD | 114.76 ± 76.31 | 106.57 ± 68.8 | .353 |
| **HALP** Mean ± SD | 46.24 ± 31.23 | 45.92 ± 22.43 | .975 |

**AST:** Aspartate Amino Transferees, **ACLR score:** AST, CRP, lymphocyte**, CRP:** C- reactive protein, **HALP score**: Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score, **PLT:** platelet

**Table (3):** Comparison between Responding disease, Progressive disease post treatment regarding ACLR score, HALP score

| | **Outcome** | | **U** | **P** |
|---|---|---|---|---|
| | **Responding disease n.52** | **Progressive disease n.58** | | |
| **ACLR score Median(range)** | 90.07(13.45-278.4) | 101.9(18.5-289.7) | 1.57 | 0.12 |
| **HALP score Median(range)** | 48.4(8.33-170) | 34.06(8.8-153.46) | 2.63 | 0.009* |

ACLR score: AST, CRP, lymphocyte, HALP score: Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score, U: Mann Whitnney $p>0.05$ no significant, *$p<0.05$ significant

**Table (4):** Multivariate regression analysis of factors associated with treatment outcome among HCC patients treated with sorafenib.

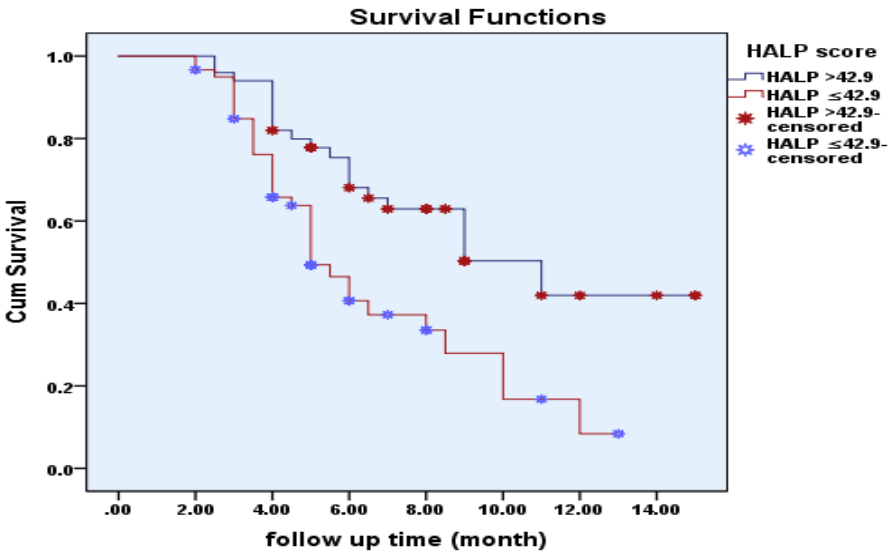
| | B | S.E. | Sig. | OR | 95% C.I. | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Age per years** | .129 | .083 | .118 | 1.138 | .968 | 1.338 |
| **Male gender** | 2.731 | 1.868 | .144 | 15.354 | .395 | 9.235 |
| **Duration of treatment** | 2.359 | 2.039 | .247 | .095 | .002 | 5.141 |
| **HALP score** | 3.461 | 1.118 | **.039** | 1.391 | .028 | 2.277 |
| **ACLR** | 1.501 | .632 | **.042** | 1.650 | .478 | 5.695 |

**ACLR score:** AST, CRP, lymphocyte**, HALP score**: Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score.

**Table (5):** Performance of HALP and ACLR Scores in prognosis of Hepatocellular Carcinoma Patients Treated with Sorafenib.

| Variables | AUC | Std. Error | Sig. | 95% Confidence Interval | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| **HALP** | .672 | .053 | .003 | .567 - .781 | 75.7% | 86.3% |
| **ACLR** | .632 | .055 | .017 | .524 - .740 | 78.4% | 82.2% |

**HALP score**: Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score, **ACLR score:** AST, CRP, lymphocyte

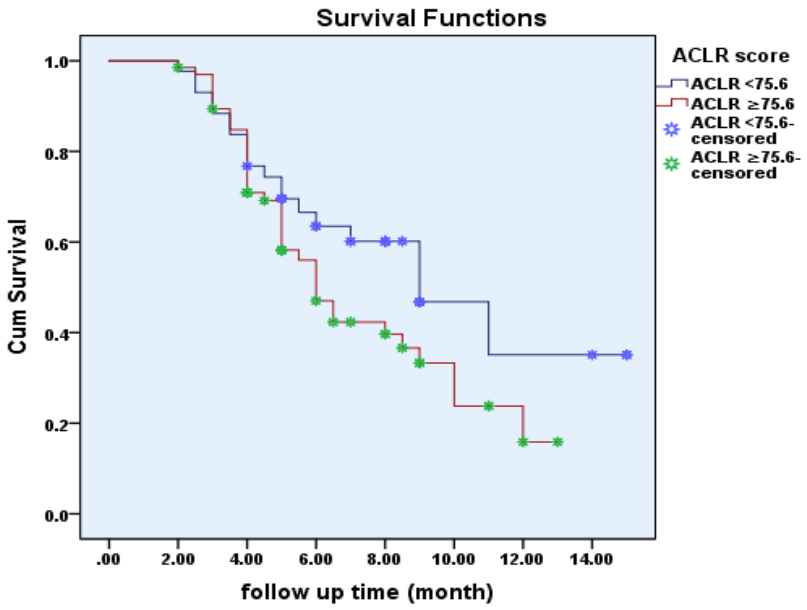



| Prognostic HALP score | Median (95% CI) progression free survival per months | Number (%) of progression | *P - value |
|---|---|---|---|
| **HALP >42.9(50)** | 11(7.05-14.95) | 21(42.0%) | 0.001 (S) |
| **HALP ≤42.9(60)** | 5 (4.13-5.87) | 37(61.7 %) | |

HALP score: Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score

95%CI: 95 confidence interval, *Log Rank test, (S) p<0.05: significant

**Figure (1):** Kaplan-Meier method chart of progression free survival according to HALP score among HCC patients

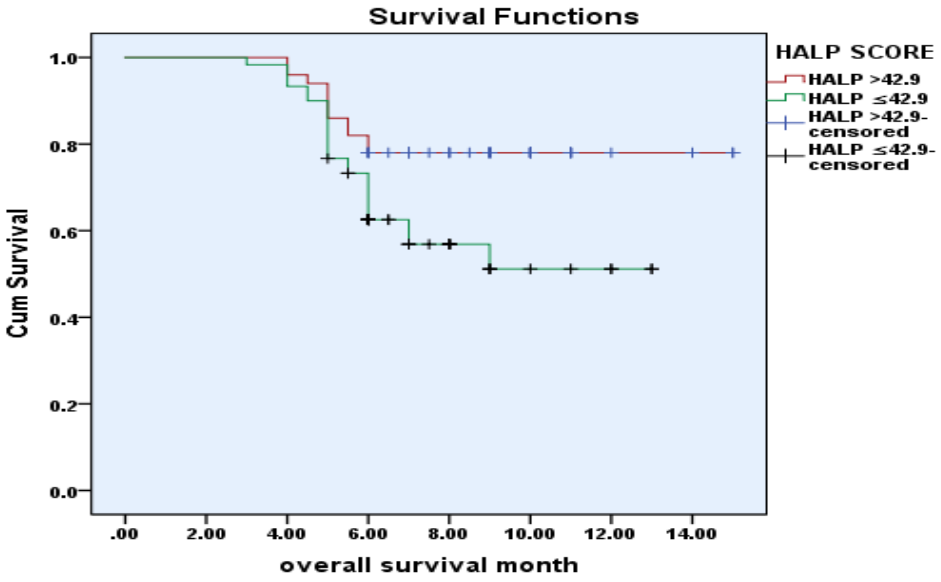



| Prognostic ACLR score | Median (95% CI) progression free survival per months | Number (%) of progression | P - value |
|---|---|---|---|
| **ACLR <75.6 (n.43)** | 9(5.76-12.24) | 19(44.2%) | 0.122 (NS) |
| **ACLR ≥75.6 (n.67)** | 6(5.02-6.98) | 39(58.2%) | |

**ACLR score:** AST, CRP, lymphocyte

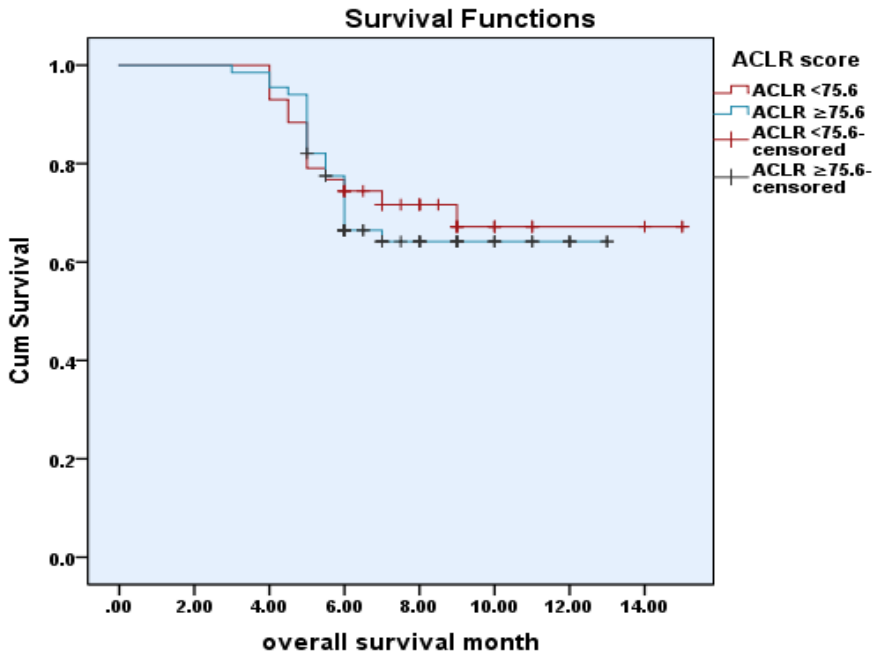
**95%CI: 95 confidence interval, Log Rank test, (NS) p>0.05: no significant**

**Figure (2):** Kaplan-Meier method chart of progression free survival according to ACLR score among HCC patients



HALP score: Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score
95%CI: 95 confidence interval, *Log Rank test, (S) p<0.05: significant

**Figure (3):** Kaplan-Meier method chart of overall survival according to HALP score among HCC patients




| Prognostic ACLR score | Median (95% CI) overall survival per months | Number (%) of deaths | P - value |
|---|---|---|---|
| **ACLR <75.6 (n.43)** | 11.9(10.48-13.31) | 13(30.2%) | 0.66 (NS) |
| **ACLR ≥75.6 (n.67)** | 10.25(9.33-11.16) | 23(34.3%) | |

ACLR score: AST, CRP, lymphocyte

95%CI: 95 confidence interval, Log Rank test, (NS) p>0.05: no significant

**(4):** Kaplan-Meier method chart of overall survival according to ACLR score among HCC patients. **Figure**

## DISCUSSION

HCC is one of the most common cancers throughout the world. Because of the high recurrence rate and high metastasis rate, its treatment and management are still a big challenge. Yet there are many ways to treat HCC [9].

Many inflammatory markers based on hematology have been proven to be prognostic factors of HCC. As we all know, nutritional status plays a critical role in the occurrence, development, and prognosis of many diseases, and HCC is no exception [9].

HALP score consisting of hemoglobin content, albumin level, lymphocyte count, and platelet count can comprehensively evaluate the inflammatory response and nutritional status. However, many researchers have shown that the HALP score is an effective predictive factor of the overall prognosis of various tumors, such as pancreatic cancer, gastrointestinal stromal tumor, esophageal

cancer, etc. [9].

This Observational Retrospective Cohort Study was conducted on 110 Patients with HCC patients from January 2015 to December 2022 at Medical Oncology Department, Faculty of Medicine Zagazig University to predict the outcome of HCC patients treated with sorafenib using ACLR and HALP scores.

Our study shows that mean age of the patients was 54.13 ± 12.73 years with mean body mass index (BMI) of 28.41 ± 3.12 kg/m2, meanwhile 65.4% of the patients were males. Most prevalent comorbidity was HCV and liver cirrhosis (92.7%) then smoking (32.7%). Most of the patients were PS I (60%) and all of them were Child-Pugh A (100%). Mean duration of Sorafenib treatment was 4.18 ± 1.49 months. There were 69.1% of the patients suffering from toxicity effect of Sorafenib treatment.

**Zhou et al. [6]** results showed that male gender forms (87.2%) of the total selected patients, which was consistent with the previous studies done by **Peng et al. [10].** Both **De Toni et al. [11]** and **Hajiev et al. [12]** results demonstrated that mean age was 67.1±10.6. **Sweed et al. [13]** results demonstrated that HCV and consequently, liver cirrhosis, represented 90.6% of the total selected patients.

**Choi et al. [14]** proved that Child score A patients represented 75.6% of the collected cases, while score B and C were 21.1% and 3.3%m respectively. In regard to PS, in **Köstek et al. [15]** and **Nishikawa et al.[16]** results we can realize the PS 0 represented 74.9% and PS I 25%. **Dou et al. [17]** found that median BMI was 24.8±3.4. Smoking directly affects the liver through (1) toxic, (2) immunological, and (3) oncogenic mechanisms and is associated with a poor prognosis.

Out of the110 selected patients, 47.3% of the selected patients showed responding disease, while the others showed progressive disease.

Our results showed that there was no significant difference in ACLR score in responding or progressive HCC patients, p> 0.12. While there was a significant higher HALP score in stable compared to progressive HCC patients, p< 0.009.

It is widely accepted that an inflammatory response and an overall nutritional status correlate with the survival rates for cancer patients. The presence of a tumor is detrimental due to its chronic resource-consumptive nature, and hemoglobin levels have also been reported to be significantly related to the survival and progression of tumors **(12).** Serum albumin is an indicator of nutritional status; many studies have reported that serum albumin levels were significantly correlated with the survival of cancer **[18]**. **Yang et al. [19]** reported that hemoglobin, albumin, and lymphocytes may be risk factors, where if levels are good, can highlight a good prognosis. However, high platelets may be harmful.

**Peng et al. [10]** reported that HALP might be an excellent prognostic index for OS for patients with bladder cancer after radical cystectomy, and low HALP predicted a decreased OS rate.

In the present study, we showed that HALP score and ACLR score were significantly associated with treatment outcome among HCC patients treated with sorafenib. HALP score were significantly associated with treatment outcome among HCC patients treated with sorafenib, as the HALP score increase; the progression is less likely to occur. Otherwise, there were no significant difference with treatment outcome among HCC patients treated with sorafenib and other parameters.

The current study showed that HALP achieved significant level as a predictor for treatment outcome among HCC patients treated with sorafenib at cut off point of 42.9 with sensitivity of 75.7% and specificity of 86.3%. ACLR achieved significant level as a predictor for treatment outcome among HCC patients treated with sorafenib at cut off point of 75.6 with sensitivity of 78.4% and specificity of 82.2%.

According to our study, HALP score achieved median progression free survival per months, Our study showed that the cutoff value for HALP score is >42.9 at 11 months compared to 5 months for HALP ≤42.9 Patients. There was longer significant progression free survival per months regarding HALP >42.9 score compared to patients HALP ≤42.9score

patients, p=0.001. While achieved median overall survival per months for HALP >42.9 12.8 months compared to 9.5 months for HALP ≤42.9 Patients. There was longer significant overall survival per months regarding HALP >42.9 score compared to patients HALP ≤42.9 score patients, p=0.022.

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.

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 **[20]**. Low hemoglobin level is an influential index in the poor overall prognosis of patients with cancer **[21]**. Albumin is produced by the liver, which not only reflects the inflammatory level of the body but also reflects the nutritional status of the body **[22]**. At the same time, studies have shown that low albumin level suggests that the overall prognosis of cancer patients is poor [18]. 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 **[4]**. Platelets almost participate in the whole process of tumor occurrence and development, including tumor formation, growth, and metastasis **[23]**. Many inflammatory markers related to platelets have been proven to be related to the overall prognosis of many cancer patients, including HCC **[24]**.

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, it is one of the measures to better judge the prognosis of patients to include the HALP score in the assessment scope.

**Conclusion:** Both HALP and ACLR scores can be used as valid prognostic scores for independently predicting the overall prognosis in HCC patients treated with Sorafenib. Having a low HALP score indicates worse prognosis, while, our results showed that the cut off for ACLR 75.6 .. but high and low score didn't show any significance in predicting the PFS or OS but they show significant sensitivity and specificity

**Recommendations:** Further prospective randomized studies should be done with large sample size including multicenter studies to validate our findings. To accurately assess long-term outcomes, studies should have a longer follow-up period.

**Conflict of Interest** :None

**Financial Disclosures**: None

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