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Assessment of Prognostic scores for sorafenib-treated among hepatocellular carcinoma cases

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Abstract:Background: Hepatocellular carcinoma (HCC) represents the sixth and the fourth most common cancer worldwide and Egypt, respectively. Inflammatory response and nutrition status play a huge role in cancer occurrence. Based on this, many prognostic scores have been evolved such as neutrophil-to-lymphocyte ratio, prognostic nutritional index, and aminotransferase-to-platelet index. HALP and ACLR scores are of those recently developed prognostic score. 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%. And, 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%.

Keywords:*HCC, HALP score, ACLR score*

Introduction

Hepatocellular carcinoma (HCC) is a type of primary liver malignancy. The majority (90%) of primary liver cancer cases are attributed to HCC **(L1ovet et al., 2021).** HCC represent the fourth common cancer in Egypt **(Akinyemiju et al., 2015).** Egypt ranks the third and 15th most populous country in Africa and worldwide, respectively **(El Zayadi et al., 2005)**. In Egypt, it is the most common cause of mortality- and morbidity-related cancer **(Rasheed et al., 2020).**

HCV, HBV, alcoholic liver disease, and non-alcoholic liver steatohepatitis/non-alcoholic fatty liver disease are the etiological factors for the development of HCC **(Grgurevic et al., 2021).** Chronic hepatitis caused by HCV and HBV infections is an important risk factor for HCC and in regions with high prevalence of these infections, HBV/HCV co-infection can occur, further increasing risk of HCC development **(Petruzziello, 2018).**

NAFLD refers to a spectrum of liver conditions ranging from steatosis to its more aggressive manifestation NASH. It is the most common liver disorder with a global prevalence of ~25%. Twenty percent of patients

with early NAFLD or steatosis progress to NASH-cirrhosis, from which 2.6% undergo further progression to HCC **(Maurice &Manousou, 2018).**

Alcohol-related liver disease (ALD) accounts for about 30% of HCC cases, including HCC occurrences where other risk factors, like obesity, diabetes, hepatitis infections might co-exist with ALD **(Ganne-Carrié& Nahon, 2019).**

Cirrhotic-related HCC patients may present with symptoms of decompensated liver failure, including worsening jaundice, pruritus, hepatic encephalopathy, ascites, and palpable mass in the upper abdomen, fever, malaise, weight loss, early satiety, abdominal distension, and cachexia. Abdominal pain is the commonest presentation for HCC **(Harding et al., 2018).**

Liver function tests including bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin may be elevated on the initial evaluation. This may indicate the severity of the disease. Other abnormal laboratory findings noted in patients with decreased synthetic liver function or reserve include an elevated international normalized ratio (INR), prothrombin time (PT), thrombocytopenia, anemia, hypernatremia, or hypoglycemia **(Lee et al., 2023).**

Alpha feto-protein (AFP) and other tumor serum marker such des-gamma-carboxy prothrombin (DCP), dumbbell former-4 protein DBF-4 dependent kinase1 (DDk1), and Midkine (MDK) can be used to help in diagnose **(Lu Q et al., 2020).**

Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are being used to diagnose cases with HCC. Contrast-enhanced ultrasound (CEUS) has specificity greater than 97% and sensitivity and sensitivity of 90% in diagnosing lesions previously demonstrated on the non-contrast US as HCC **(Claudon et al., 2013).** Tri-phasic CT scan criteria to diagnose HCC include hyper-enhancement in the arterial phase and rapid washout during the portal venous phase relative to the liver background **(Pai, 2020).**

Hyper-intense images on T1 are mostly well-differentiated tumors and appear as iso-intense on T2 images. Poorly or moderately differentiated tumors appear as iso-intense on T1 images and hyper-intense on T2 images. Contrast MRI has a sensitivity of 77%-90% and a specificity of 84-97% **(Choi et al., 2014).**

Liver biopsy is not routinely done for HCC as the procedure is associated with the risk of tumor seeding and bleeding, and false negative on failure to obtain tissue from the appropriate site. But, it might be necessary in HCC developed in a non-cirrhotic patient, in non- high risk patient for HCC, patient who has elevated CA19-9 and if imaging studies are inconclusive for being compatible with HCC **(Heimbach JK et al .,2018).**

Many scoring system were invented to predict prognosis in HCC patients. Child-Pugh scoring system (also known as the Child-Pugh-Turcotte score) was designed to predict mortality in cirrhosis patients. It consisted of prothrombin time, bilirubin level, albumin level, presence of ascites and hepatic encephalopathy. People divided into: Child A - good hepatic function, Child B - moderately impaired hepatic function, and Child C - advanced hepatic dysfunction **(Tsoris A et al., 2024).**

The most used scoring system and the one who has the greatest impact on treatments decisions is the BCLC classification which consists of 4 different stages [A: early, B: intermediate, C: advanced, D: terminal] with different prognosis, according to the liver function, the extent of the tumor and its consequences **(Wang JH et al., 2008).**

The score mainly depends on Performance status (PS), liver function which can be assessed by using child score, and nodule size and number **(Reig et al., 2022).**

HCC is a disease with different modalities of treatment. Surgical resection comes in the first place, followed by liver transplantation. Ablative techniques come next, including ethanol (percutaneous ethanol injection), microwave (MWA) or radiofrequency (RFA), catheter-directed trans-arterial chemoembolization (TACE) or radio embolization (TARE). Lastly, the external beam radiation therapy in the form of stereotactic body radiation therapy or proton beam therapy, systemic targeted small molecule tyrosine kinase inhibitors (TKIs), check-point inhibitor immunotherapy.

Surgery for HCC includes tumor resection or liver transplantation. Liver transplantation is the best choice. However, this is not possible in all cases. Milan criteria were developed to diagnose the patient's suitability to be a candidate for liver transplantation **(Chieh Kow, 2019).**

Using thermal ablation for hepatic focal lesions has many advantages, such as the ability to repeating the maneuver, low morbidity and very few complications. MWA ablation provides better results in areas with high blood flow, or near vessels, because it is not affected by the heat sink effect **(M et al., 2014).**

TACE is the treatment of choice for patients with intermediate stage HCC, according to BCLC. It is also the standard treatment in non-resectable HCC. It is considered to be a palliative treatment, with positive impacts on survival and quality of life **(Galle et al., 2018).**

Guidelines recommend TARE as the standard line of treatment for BCLC-B, Radio embolization with Yttrium-90 microspheres is used as catheter-based treatment for HCC. It can be performed safely in patients with portal vein thrombosis, due to its low embolic effect. TARE has the advantages of short hospital stay, prolonged time until progression, and long progression free survival period **(Padia et al., 2017).**

Treatment for advanced HCC is based on systemic therapy relying on TKIs, anti-angiogenesis agents, and immunotherapy. Before the development of sorafenib, no drug was available that could provide this improved the OS in such patients **(Galle et al., 2018).**

Sorafenib is an oral multi-kinase inhibitor with anti-proliferative and anti-angiogenic properties. The median OS with sorafenib was significantly longer at 10.7 m compared to 7.9 m with placebo. With sorafenib, 1-year survival rates were 44%, while with placebo, they were 33% **(Llovet JM et al., 2008).**

Lenvatinib is an oral TKI of fibroblast growth factor receptor (FGFR), VEGFR, and PDGFR-α, rearranged during transfection, and KIT. It has been accepted as a first-line therapy for unresectable HCC **(Javan et al., 2020).**

Regorafenib is a potent oral inhibitor of VEGFR, PDGFR, and FGFR, and was approved as a second line treatment for patients who show disease progression **(Bruix et al., 2017).**

Immunotherapy introduce a new spectrum in treating HCC. The combination of atezolizumab and bevacizumab has been shown to improve OS relative to sorafenib, granting a food and drug administration (FDA) approval of this regimen. This regimen improved OS by 67.2% at 12 m vs. sorafenib which improved OS by 54.6%. Moreover, Atezolizumab-bevacizumab combination had an objective response rate (ORR) of 27.3%, and sorafenib had an ORR of 11.9% **(Cheng AL et al., 2022).**

Combination between atezolizumab and cabozatinib had achieved median PFS 6.8 m vs. 4.2 m in the sorafenib arm, while in the combination treatment group, the median OS was 15.4 m, compared to 15.5 m in the sorafenib group as was shown in the phase 3 study (COSMIC-312) **(Kelley et al., 2022).**

Ipilimumab which is anti-cytotoxic T-lymphocyte- associated protein 4(CTLA-4) was approved in combination with nivolumab as a second-line therapy for HCC patients **(Yau T et al., 2020).**

Immune-nutritional status is an important consideration for patients with cancer as cancer patients have increased metabolic demands and are at risk for a chronic catabolic state/cachexia. Also, caloric deficits from the anorexia induced by systemic oncologic treatments (i.e., chemotherapy) **(Christian Mark et al., 2023).**

One of these scores is the HALP score which is calculated as follow :

-HB (g/L) *Albumin (g/L) *Lymphocyte (10^9/L)/ platelets (10^9/L) **(Farag et al., 2023).**

The HALP score was used in predicting the prognosis ingastric cancer utilizing the score in predicting lymph node metastasis, with HALP score ≤35.3 were over four times at risk of having lymph node metastasis **(Wang X et al., 2021).**

ACLR score consist of three components which directly affect the tumor progression and outcomes of HCC patients. The combination of AST, C-reactive protein (CRP), and lymphocyte counts simultaneously reflects liver function damage, systemic inflammation, and immune response of patients with HCC. All three processes could affect the outcomes of patients with HCC after urative resection. It calculated as follows:

Having a high ACLR score more than 80 is associated with poor prognosis and significantly shorter OS than patient with low 80. Moreover, high ACLR level is associated with high risk of recurrence **(Xu X et al., 2022).**

Sorafenib is an orally available, small molecule, multi-specific tyrosine kinase inhibitor with activity against VEGF receptors -1, -2 and -3 as well as against the receptor for PDGF and several RAF kinases. Inhibition of these kinases decreases angiogenesis, which plays an important role in the growth and spread of several forms of solid tumors (**O'Connor et al., 2018).**

Sorafenib received approval for use in the United States in 2005 for therapy of advanced renal cell carcinoma (RCC), and indications were subsequently expanded to HCC in 2007 and refractory thyroid cancer in 2014. Sorafenib is available in tablets of 200 mg. The typical dose is 400 mg twice daily, continued until there is tumor progression or unacceptable toxicity (**Pitoia& Jerkovich, 2016).**

Results

Table (1): Clinical pathological feature among the studied patient

		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%
Discontinue of treatment		27	24.5%
Sorafenib toxicity	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

This table shows 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. Most prevalent comorbidity was HCV and liver cirrhosis (92.7%) followed by 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. 69.1% of the patients suffered from toxicity effect of Sorafenib treatment.

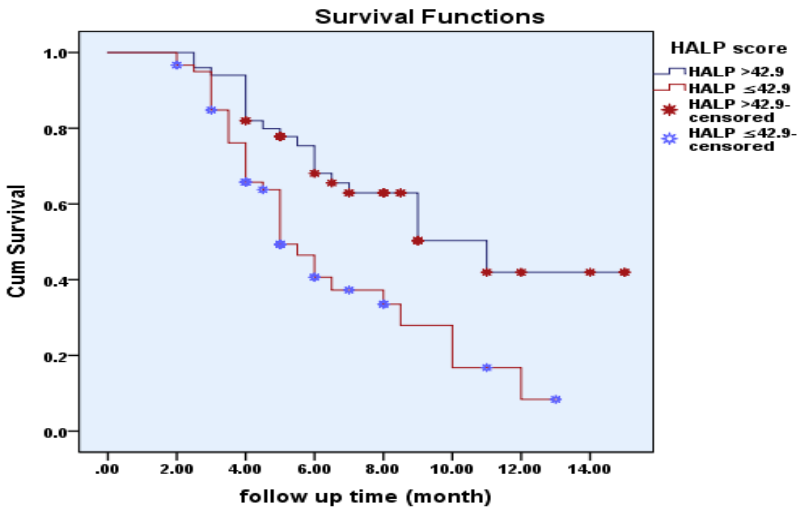


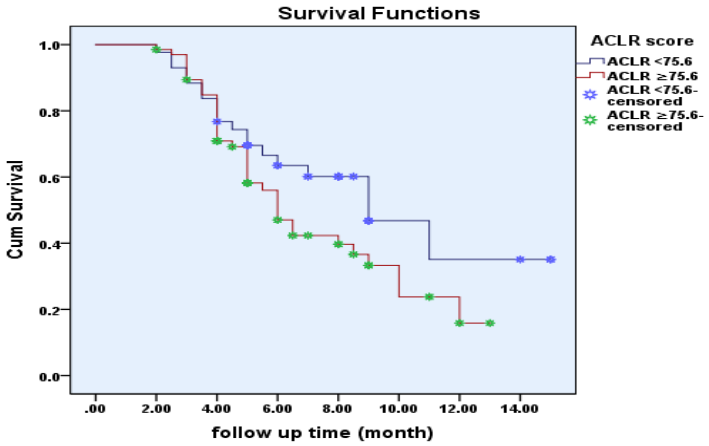
Figure (1): Kaplan-Meier method chart of progression free survival according to HALP score among HCC patients

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
HALP ≤42.9(60)	5 (4.13-5.87)	37(61.7 %)	(S)

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

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

Median progression free survival per years for HALP cutoff >42.9 HCC patients is 11 months compared to 5 months for HALP cutoff ≤42.9Patients. There was longer significant progression free survival per years regarding HALP cutoff >42.9 score compared to patients HALP cutoff ≤42.9score patients, p=0.001.



Figure(2): Kaplan-Meier method chart of progression free survival regarding ACLR score in 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
ACLR ≥75.6 (n.67)	6(5.02-6.98)	39(58.2%)	(NS)

ACLR score: AST, CRP, lymphocyte

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

Median progression free survival per years for ACLR cutoff <75.6 HCC patients is 9 months compared to 6 months for ACLR cutoff ≥75.6 Patients. There was no significant difference of progression free survival per years regarding ALCR score, p=0.133.

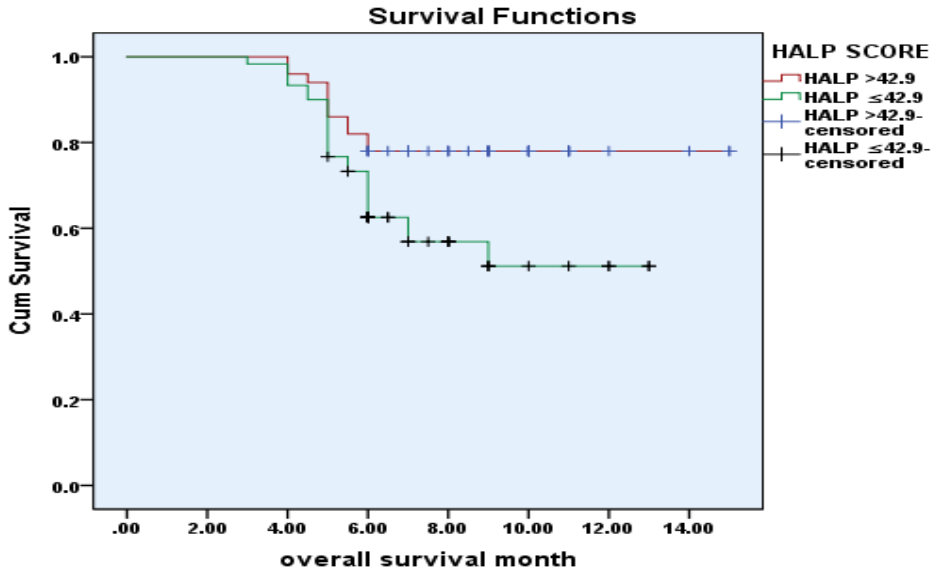


Figure (3): Kaplan-Meier method chart of overall survival according to HALP score among HCC patients.

Prognostic HALP score	Median (95% CI) overall survival per months	Number (%) of deaths	*P - value
HALP >42.9(50)	12.8(11.66-13.96)	11(22.0%)	0.022 (S)
HALP ≤42.9(60)	9.5 (8.40-10.52)	25(41.7 %)	

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

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

Median overall survival per months for HALP cutoff >42.9 HCC patients is 12.8 months compared to 9.5 months for HALP cutoff ≤42.9 Patients. There was longer significant overall survival per months regarding HALP cutoff >42.9 score compared to patients HALP cutoff ≤42.9 score patients, p=0.022.

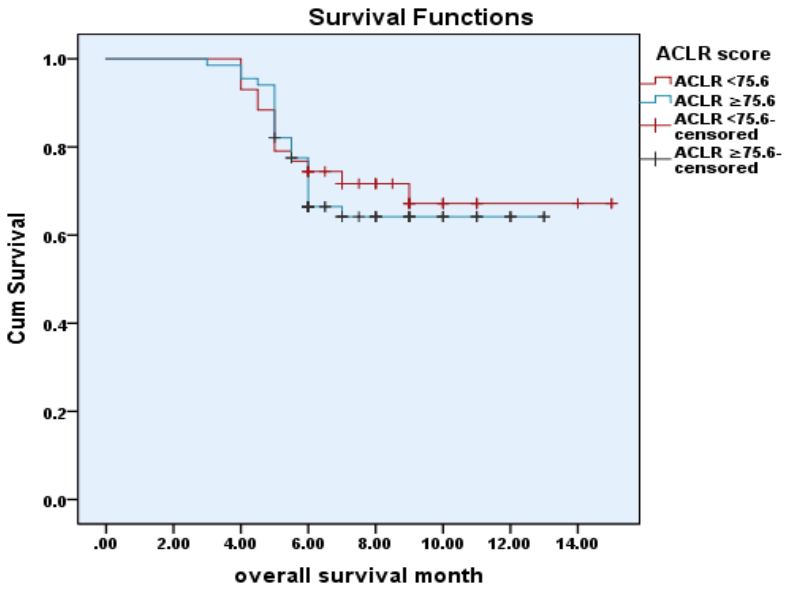


Figure (4): Kaplan-Meier method chart of overall survival according to ACLR score among HCC patients

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

Median overall survival per months for ACLR cutoff <75.6 HCC patients is 11.9 months compared to 10.25 months for ACLR cutoff ≥75.6 Patients. There was no significant difference of overall survival per months regarding ALCR score, p=0.66.

Conclusion:

our study concluded that HALP score 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, having a high ACLR or low score did not show any significance in predicting the overall prognosis

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