Section A -Research paper

Prognostic scores for sorafenib-treated hepatocellular carcinoma patients

Amrallah A. Mohamed [1], Marwa Abo Shabana [2] Yara Naser Mohamed [3] and Adel Bakry[4]
[1] Professor of Medical Oncology, Faculty of Medicine, Zagazig University
[2] Assistant Professor of Clinical Pathology, Faculty of Medicine, Zagazig University
[3] Resident of Medical Oncology, Faculty of Medicine, Zagazig University
[4] Lecturer of Medical Oncology, Faculty of Medicine, Zagazig University
Corresponding author: Yara Naser Mohamed
Email: yaraarlo95@gmail.com **Mobile: 01227894549**

Article History: Received: 21.06.2023 **Revised:**04.07.2023 **Accepted:** 16.07.2023

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.

Doi:10.53555/ecb/2023.12.1198

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 now 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 in gastric 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 curative 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).**

Micro RNAs (miRNAs)achieved a key role in gastrointestinal cancers. In particular, up/down-regulation of several miRNAs has been reported to be able to impair the TKI response, which affects the expression of genes involved in several pathways. For example, miRNA-21 could enhance resistance to sorafenib in vitro through the PTEN/Akt pathway by inhibiting autophagy. MicroRNA-122 obtained sorafenib resistance to HCC cell lines through the RAS/RAF/ERK pathway **(Nedaeinia et al., 2017)**.

Moreover, in an animal HCC model, elevated miR-122 levels were associated with a stem-like phenotype in HCC associated with resistance to sorafenib. So far, an anti-miRNA122 transfection increased cell viability in sorafenib-treated HCC cells, which restored sorafenib activity HCCs. The predictive role of circulating miRNAs has also been investigated. The miRNA181a-5p levels resulted in the unique independent factor for sorefenib-treated patients achieving a DCR in 53 patients (HR 0.139, 95% CI 0.011–0.658, p = 0.0092) **(Turato et al., 2019).**

Sorafenib upregulated MiRNA423-5p both in vitro and in vivo and its increase from baseline to evaluation at six months correlated with the response. In fact, 75%

of patients with a miR423-5p level increase achieved disease control. In addition, MiR-126-3p was down-regulated after sorafenib treatment in HCC cells lines. So far, Faranda et al. determined the expression levels of miR-126-3p in HCC tissues and plasma. This miRNA was down-regulated in HCC tissues compared to levels of peritumoral tissues (HCC average = 3.91 ± 0.48 vs. RQPT average = 5.84 ± 0.51, p-value = 0.0074). Moreover, circulating miR-126-3p expression levels were significantly higher in HCC patients when compared to control subjects (26.7 vs. 26.6 mean expression levels, p-value = 0.0002). In vitro data and in vivo determination led authors to hypothesize that a reduction of this miRNA could be predictive of a response to sorafenib **(Faranda et al., 2019)**.

The predictive role of miRNA has been evaluated in HCC tissue in clinical studies. In particular, high levels of miRNA-224 in HCC samples were correlated with an increase of PFS (HR = 0.28, 95% CI: 0.09–0.92, p = 0.029) and OS (HR = 0.0.24, 95% CI: 0.07–0.79, p = 0.012) in patients treated with sorafenib. In another study, patients with high levels of miR-425-3p in HCC tissue treated with sorafenib achieved a better PFS (HR = 0.5, 95% CI: 0.3–0.9, p = 0.007) and TTP (HR = 0.4, 95% CI: 0.2–0.7, p = 0.0008) **(Yoon et al., 2017)**.

Conclusions

In conclusion, our study concluded that both scores are valid for independently predicting the overall prognosis in HCC patients treated with Sorafenib. With having a low HALP score indicates worse prognosis. And, having a high ACLR score indicates poor prognosis.

References:

Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. JAMA Oncol. 2017; 3:1683–91.

Bruix, J., Qin, S., Merle, P., Granito, A., Huang, Y. H., Bodoky, G., et al. (2017). Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 389(10064), 56-66.

Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. (2019). Transplantation versus liver resection in patients with hepatocellular carcinoma. Translational Gastroenterology and Hepatology, 4(May).

Choi, J. Y., Lee, J. M., & Sirlin, C. B. (2014). CT and MR imaging diagnosis and staging of hepatocellular carcinoma. Part II. Extracellular agents, hepatobiliary agents, and ancillary imaging features. Radiology, 273(1), 30–50.

Claudon, M., Dietrich, C. F., Choi, B. I., Cosgrove, D. O., Kudo, M., Nolsøe, C. P., et al. (2013). World Federation for Ultrasound in Medicine; European Federation of Societies for Ultrasound. Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver-update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultrasound Med Biol, 39(2), 187-210.

El Zayadi A-R, Badran HM, EMF B, Attia Mel- D, Shawky S, Mohamed MK, et al. Hepatocellular carcinoma in Egypt: a single center study over a decade. World J. Gastroenterol. 2005; 11:5193–8.

Farag CM, Antar R, Akosman S, Ng M, Whalen MJ. What is hemoglobin, albumin, lymphocyte, platelet (HALP)

score? A comprehensive literature review of HALP's prognostic ability in different cancer types. Oncotarget. 2023 Feb 25; 14:153-172.

Faranda, T.; Grossi, I.; Manganelli, M.; Marchina, E.; Baiocchi, G.; Portolani, N.; et al. Differential expression profiling of long non-coding RNA GAS5 and miR-126-3p in human cancer cells in response to sorafenib. Sci. Rep. 2019, 9, 9118.

Galle, P. R., Forner, A., Llovet, J. M., Mazzaferro, V., Piscaglia, F., Raoul, J. L., et al. (2018). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology, 69(1), 182–236.

Ganne-Carrié, N., & Nahon, P. (2019). Hepatocellular carcinoma in the setting of alcohol-related liver disease. *Journal of Hepatology*, *70*(2), 284–293

Grgurevic, I., Bozin, T., Mikus, M., Kukla, M., & O'beirne, J. (2021). Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease: From Epidemiology to Diagnostic Approach. *Cancers*, *13*(22), 5844.

Harding, J. J., Abu-Zeinah, G., Chou, J. F., Owen, D. H., Ly, M., Lowery, M. A., et al. (2018). Frequency, Morbidity, and Mortality of Bone Metastases in Advanced Hepatocellular Carcinoma. Journal of the National Comprehensive Cancer Network: JNCCN, 16(1), 50–58.

Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018; 67:358–380.

Javan, H., Dayyani, F., & Abi-Jaoudeh, N. (2020). Therapy in Advanced Hepatocellular Carcinoma. Seminars in Interventional Radiology, 37(5), 466–474.

Kelley RK, Rimassa L, Cheng AL, Kaseb A, Qin S, Zhu AX, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2022; 23:995–1008.

Lee, A. S., Persoff, J., & Lange, S. M. (2023). Liver Function Tests. Mayo Clinic Medical Manual, 373–387.

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378–390.

Llovet, J.M.; Kelley, R.K.; Villanueva, A.; Singal, A.G.; Pikarsky, E.; Roayaie, S.; et al. Hepatocellular carcinoma. Nat. Rev. Dis. Primers 2021, 7, 6.

Lu Q, Li J, Cao H, Lv C, Wang X, Cao S. Comparison of diagnostic accuracy of Midkine and AFP for detecting hepatocellular carcinoma: a systematic review and meta-analysis. Biosci Rep. (2020) 40: BSR20192424.

Maurice, J., & Manousou, P. (2018). Non-alcoholic fatty liver disease. *Clinical Medicine*, *18*(3), 245.

Nedaeinia, R.; Manian, M.; Jazayeri, M.H.; Ranjbar, M.; Salehi, R.; Sharifi, M.; et al. Circulating exosomes and exosomal microRNAs as biomarkers in gastrointestinal cancer. Cancer Gene Ther. 2017, 24, 48–56.

Padia, S. A., Johnson, G. E., Horton, K. J., Ingraham, C. R., Kogut, M. J., Kwan, S., et al. (2017). Segmental Yttrium-90 Radioembolization versus Segmental Chemoembolization for Localized Hepatocellular Carcinoma: Results of a Single-Center, Retrospective, Propensity Score-Matched Study. Journal of Vascular and Interventional Radiology: JVIR, 28(6), 777-785.e1

Pai, M. (2020). Tuberculosis: the story after the Primer. Nature Reviews Disease Primers 2020 6:1, 6(1), 1–2.

Petruzziello, A. (2018). Epidemiology of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Related Hepatocellular Carcinoma. *The Open Virology Journal*, *12*(1), 26–32.

Rashed, Wafaa & Kandeil, Mohamed & Mahmoud, Mohamed & Ezzat, Sameera. (2020). Hepatocellular

Carcinoma (HCC) in Egypt: A comprehensive overview. Journal of the Egyptian National Cancer Institute. 32.

Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693.

Tsoris A, Marlar CA. Use of The Child Pugh Score in Liver Disease. 2023 Mar 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–.

Turato, C.; Fornari, F.; Pollutri, D.; Fassan, M.; Quarta, S.; Villano, G.; et al. MiR-122 Targets SerpinB3 and Is Involved in Sorafenib Resistance in Hepatocellular Carcinoma. J. Clin. Med. **2019**, 8, 171

Wang JH, Changchien CS, Hu TH, Lee CM, Kee KM, Lin CY, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma - Survival analysis of 3892 patients. Eur J Cancer. 2008; 44:1000–1006.

Wang X, He Q, Liang H, Liu J, Xu X, Jiang K, Zhang J. A novel robust nomogram based on preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) for predicting lymph node metastasis of gastric cancer. J Gastrointest Oncol. 2021; 12:2706–18.

Xu X, Huang A, Guo DZ, Wang YP, Zhang SY, Yan JY, et al. Integration of Inflammation-Immune Factors to Build Prognostic Model Predictive of Prognosis and Minimal Residual Disease for Hepatocellular Carcinoma. Front Oncol. 2022 Jun 8; 12:893268.

Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib: The CheckMate 040 Randomized Clinical Trial. JAMA Oncol. 2020;6: e204564.

Yoon, E.L.; Yeon, J.E.; Ko, E.; Lee, H.J.; Je, J.H.; Yoo, Y.J.; et al. An Explorative Analysis for the Role of Serum miR-10b-3p Levels in Predicting Response to Sorafenib in Patients with Advanced Hepatocellular Carcinoma. J. Korean Med. Sci. 2017, 32, 212–220.