DOI 10.20398/jscr.v13i1.29546

PREOPERATIVE HALP SCORE AS A PREDICTOR OF SURVIVAL IN LOCALLY ADVANCED COLON CANCER

ESCORE PRÉ-OPERATÓRIO HALP COMO PREDITOR DE SOBREVIVÊNCIA EM CÂNCER DE CÓLON LOCALMENTE AVANÇADO

Andreia Amado, Joana Pimenta, Tatiana Queirós, Mariana Leite, Amélia Tavares, João Cardoso, Lurdes Gandra, Manuel Oliveira

Study performed at Department of General Surgery, Centro Hospitalar Vila Nova de Gaia/Espinho, EPE.
Financial support: None.
Conflicts of interest: None.
Address for correspondence: Department of General Surgery, Centro Hospitalar Vila Nova de Gaia/Espinho, EPE.
E-mail: andreiapiresbranco@hotmail.com.
Submitted: jul 15; accepted after revision, sep 27, 2022.

ABSTRACT

Objective: Lower preoperative hemoglobin (H), albumin (A), lymphocyte (L) and platelet (P) score (HALP) has been identified as a predictive factor in LACC to categorize patients with higher risk of poor outcome. Therefore, it is important to identify biomarkers available in clinical practice that can predict survival and patient's prognosis. Our aim is to evaluate preoperative HALP score and its prognostic value. **Methods**: Our retrospective study included patients with LACC submitted to oncologic resection between January 2015 to December 2019 in our institution. LACC included stages II and III adenocarcinoma. HALP score was calculated as H (g/L) x A (g/L) x L (/L) / P (/L). A cutoff value was determined by ROC curve analysis and patients were divided accordingly into two groups (low and high HALP) to compare cancer-specific survival, through Kaplan-Meyer curve. **Results**: In our study, 127 patients were included. The mean age was 70,7 ± 11,9 years and 67 (52,8%) were male. Stage II incorporated 65 patients (51,2%) and stage III 62 (48,8%). The median follow-up time was 37 months. The HALP cutoff value estimated was 22,5. Age $\geq$ 65 years, right-sided tumor, surgical reintervention and cancer-specific survival were associated with a lower HALP scores (p=0,002; p=0,004; p=0,008 and p=0.001, respectively). **Conclusion**: Nutritional and systemic inflammation status are extremely important in colon cancer prognosis. Serum biomarkers, such as HALP score could easily identify patients with a higher risk of poor outcome. Thus, this prognostic index may be useful as a clinical predictor of survival for LACC patients.

Keywords: colon cancer; locally advanced colon cancer; biomarkers; preoperative score; HALP.

RESUMO

Objetivo: O escore pré-operatório mais baixo de hemoglobina (H), albumina (A), linfócitos (L) e plaquetas (P) (HALP) foi identificado como um fator preditivo no LACC para categorizar pacientes com maior risco de desfecho ruim. Portanto, é importante identificar biomarcadores disponíveis na prática clínica que possam predizer a sobrevida e o prognóstico do paciente. Nosso objetivo é avaliar o escore HALP pré-operatório e seu valor prognóstico. **Métodos**: Nosso estudo retrospectivo incluiu pacientes com LACC submetidos à ressecção oncológica entre janeiro de 2015 a dezembro de 2019 em nossa instituição. O LACC incluiu adenocarcinoma de estágios II e III. A pontuação HALP foi calculada como H (g/L) x A (g/L) x L (/L) / P (/L). Um valor de corte foi determinado pela análise da curva ROC e os pacientes foram divididos de acordo em dois grupos (HALP baixo e alto) para comparar a sobrevida específica do câncer, por meio da curva de Kaplan-Meyer. **Resultados**: Em nosso estudo foram incluídos 127 pacientes. A média de idade foi de 70,7 ± 11,9 anos e 67 (52,8%) eram do sexo masculino. O estágio II incorporou 65 pacientes (51,2%) e o estágio III 62 (48,8%). O tempo médio de seguimento foi de 37 meses. O valor de corte de HALP estimado foi de 22,5. Idade $\geq$ 65 anos, tumor do lado direito, reintervenção cirúrgica e sobrevida específica do câncer foram associados a menores escores de HALP (p=0,002; p=0,004; p=0,008 ep=0,001, respectivamente). **Conclusão**: O estado nutricional e inflamatório sistêmico são extremamente importantes no prognóstico do câncer de cólon. Biomarcadores séricos, como o escore HALP, podem identificar facilmente pacientes com maior risco de desfecho ruim. Assim, esse índice prognóstico pode ser útil como preditor clínico de sobrevida para pacientes com LACC.

Descritores: câncer de cólon; câncer de cólon localmente avançado; biomarcadores; escore pré-operatório; HALP.

INTRODUCTION

Nearly half of the patients with colon cancer present with locally advanced cancer (LACC) at diagnosis[1]. Nutritional and immune patient status are strongly connected with tumorigenesis and progression of cancer[2]. Serum biomarkers available in clinical practice can reveal information about patients' status and help recognize who is at higher risk of worst prognosis[3]. Anemia and hypoalbuminemia are indicators of decreased nutritional grade and have been acknowledged as risk factors for poor prognosis in gastrointestinal malignancies[4,5]. Lymphocytes function is based on the regulation of inflammation cytokines; thus, lymphopenia causes deregulation of inflammation response and enabling cancer progression[2,5]. A low immune status is also caused by an increased platelet reaction as it decreases cells' protection and promotes tumor proliferation[3]. It is essential to identify parameters that can predict postoperative complications and survival in order to stratify risk, predict patient's prognosis and define

the best therapeutic approach. A low preoperative hemoglobin (H), albumin (A), lymphocyte (L) and platelet (P) score (HALP) has been identified as a predictive factor in LACC to categorize patients with a higher risk of poor outcome. Our aim is to evaluate preoperative HALP score and access its prognostic value in LACC.

METHODS

We conducted a retrospective unicentric-based cohort that included patients with LACC submitted to oncologic resection between January 2015 to December 2019 in our institution. Patients > 18 years with stage II and III colon adenocarcinoma met our inclusion criteria. Clinical files were consulted and several parameters were evaluated, namely age, gender, personal background (family history of colon cancer) and tumor localization. Preoperative serum parameters (H, A, L, P) were collected. Pathological features of the surgical specimen (number of lymph nodes retrieved, lymphatic, vascular and perineural invasion, differentiation grade) were also documented. We also recorded data regarding neoadjuvant chemotherapy, if applicable, time of surgery, postoperative complications, local and distal recurrence and time of death (cancer-related or not). The exclusion criteria were: lack of follow-up (4); missing serum albumin levels (7); synchronous tumors (5) and patients that underwent emergency surgery (5) (Figure 1).

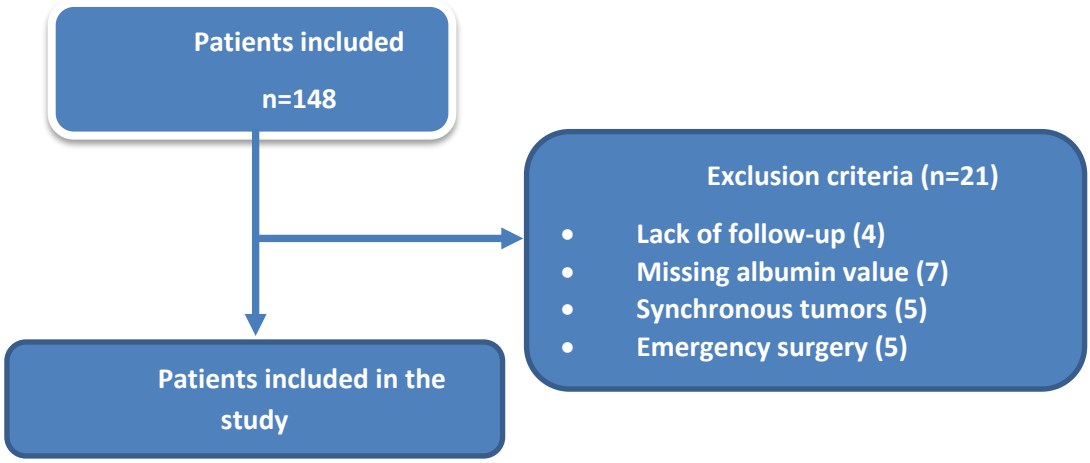

Figure 1: Flow diagram of included and excluded patients in the study

Our study was carried out according to the Ethics Committee of our hospital, which did not require informed consent, since clinical data were collected anonymously.

Statistical analysis

Statistical analysis was performed using SPPS (Statistical Package for Social Sciences), version 24. Statistical significance was defined as $p<0,05$. Categorical variables were expressed in frequencies (n) or percentages (%); continuous variables in mean and standard deviation or median with 95% interval of confidence. HALP score was calculated as H (g/L) x A (g/L) x L (/L) / P (/L). Qui-square test and independent t-test

were used for univariate analysis. Independent prognostic factors were estimated with multivariate analysis (binary regression) with hazard ratios (HR). A cutoff value was determined by Receiver Operating Characteristic (ROC) curve analysis and patients were divided accordingly into two groups (low and high HALP), to compare demographic, clinical characteristics, as well as overall survival and cancer-specific survival, through Kaplan-Meyer curves and log-rank test. The risk of poor outcome associated to low HALP score was assessed by multivariate Cox regression model

RESULTS

Among the 127 patients included in this study, the mean age was 70,7 ± 11,9 years old and 67 (52,8%) were male. The mean hospital-stay was 11,5 ± 9,8 days. Regarding, TNM stage, 65 patients were stage II (51,2%) and 62 (48,8%) stage III. The median follow-up time was 37 months and the median preoperative HALP score was 33,8. Fourteen patients (11,0%) presented postoperative complications (Clavien-Dindo III-IV) and 8 (6,3%) underwent surgical reinterventions. There were 30 (23,6%) cancer-related deaths (Table 1).

Table 1 – Variables included in the study and respective demographic, clinical and analytical features (defined as mean ± standard deviation and median 95% confidence interval) – univariate analysis.

Characteristics	n=127 patients n (%)
Age (mean, in years)	70,7 ± 11,9
Gender (male)	67 (52,8%)
First-degree relative cancer history	17 (13,4%)
Tumor location	
Right	75 (59,1%)
Left	52 (40,9%)
Differentiation grade	
Well/moderate (G1/2)	123 (96,8%)
Poor (G3)	4 (3,15%)
Positive invasion	
Vascular	71 (55,9%)
Lymphatic	88 (69,3%)
Perineural	53 (41,7%)
TNM stage	
II	65 (51,2%)
III	62 (48,8%)
Surgical reintervention	8 (6,3%)
Recurrence	30 (23,6%)
Cancer-specific survival	97 (76,4%)

To investigate an optimal value of HALP score that combined the highest sensitivity and specificity to best predict poor prognosis in LACC patients, we determined

a cutoff value for overall survival through ROC curve analysis. Approaching HALP score as a categorical variable, a statistically significant cutoff value (22,5) was discovered [AUC 0,63 (0,52-0,74); p=0,03] (Figure 2), dividing our sample into two groups (low and high HALP) accordingly

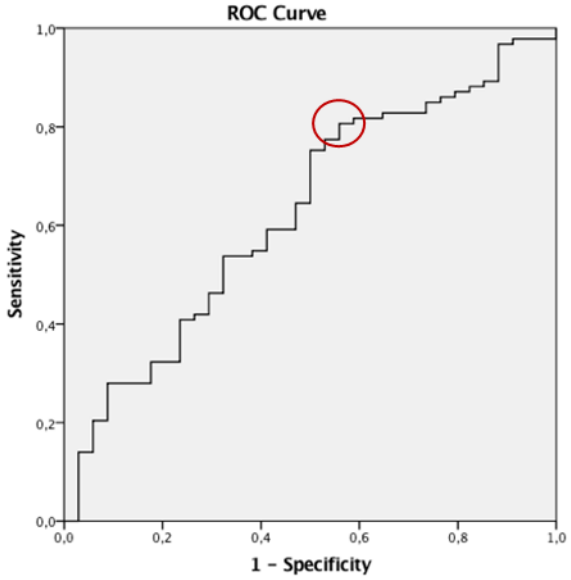

Figure 2: ROC curve for cancer-specific survival. Cutoff value determined and shown by the red circle (22,5) p=0.03

Comparing the two groups, based on the cutoff HALP score value, we then classified low HALP score as < 22,5 and high HALP score as ≥ 22.5. HALP < 22.5 were found in 37 patients (29,1%) and 90 (70,9%) had an HALP ≥ 22.5. We compared the clinical variables between the two groups and we revealed that age ≥ 65 years, right-sided tumor, surgical reintervention and cancer-specific survival were associated with a lower HALP score (p=0,002; p=0,004; p=0,008 and p=0.001, respectively). The remaining variables did not demonstrate a significant difference between the two groups (p>0,05). After conducting a multivariate analysis through binary regression model, we found that age ≥ 65 years (HR: 5,1; 95% CI 1,4-18,4; p=0,024); right-sided tumor (HR: 3,8; 95% CI 1,5-9,6; p=0,004), surgical reintervention (HR 8,4; 95% CI 1,3 -54,5; p=0,011) and a low HALP score (HR 3,4; 95% CI 1,4-8,0; p=0,005) to be independent prognostic factors for poor outcome in LACC patients. (Table 2)

Table 2: Characteristics of clinical variables in patients with low and high HALP score – univariate and multivariate analysis. Values are shown as frequencies (n) and percentages (%).

Characteristics	Low HALP **(< 22,5)** n=37 (%)	High HALP **(≥ 22,5)** n=90 (%)	p value[1]	p value[2]
Age ≥ 65 years	34 (91,9%)	59 (65,5%)	**0,002**	**0,024**
Gender (male)	18 (48,6%)	49 (54,4%)	0,34	-
Smoking history	5 (13,5%)	19 (21,1%)	0,45	-
Alcohol-drinking history	5 (13,5%)	17 (18,9%)	0,33	-
First-degree relative cancer history	5 (13,5%)	12 (13,3%)	0,59	-
Tumor location				
Right	30 (81,1%)	45 (50,0%)	**0,001**	**0,004**
Left	7 (18,9%)	45 (50,0%)	1 (reference)	-
Differentiation grade				
Well/moderate (G1/2)	37 (100%)	86 (95,6%)	1 (reference)	-
Poor (G3)	0 (0%)	4 (4,4%)	0,28	-
Positive invasion				
Vascular	20 (54,1%)	51 (56,7%)	0,84	-
Lymphatic	26 (70,3%)	62 (68,9%)	0,53	-
Perineural	17 (45,9%)	36 (40,0%)	0,34	-
TNM stage (III)				
II	16 (43,3%)	49 (54,5%)	1 (reference)	-
III	21 (56,7%)	41 (45,5%)	0,34	-
Surgical reintervention	6 (16,2%)	2 (2,2%)	**0,008**	**0,011**
Recurrence	8 (21,6%)	22 (24,4%)	0,62	-
Cancer-specific survival	22 (59,5%)	75 (83,3%)	**0,001**	**0,006**

1-p value univariate. 2 – p value multivariate

Lower levels of HALP were associated with a lower cancer-specific survival comparing to higher HALP score group (59,5% vs 83,3%; log-rank p<0.001) represented through Kaplan-Meyer survival curve (Figure 3). To evaluate the score and how it could increase the risk of cancer-related death, we performed a Cox regression analysis. We discovered that low HALP score group presented with 3.15 times (95% CI 1,54-6,45; p=0,002) increased risk of cancer-related death than patients with higher HALP scores.

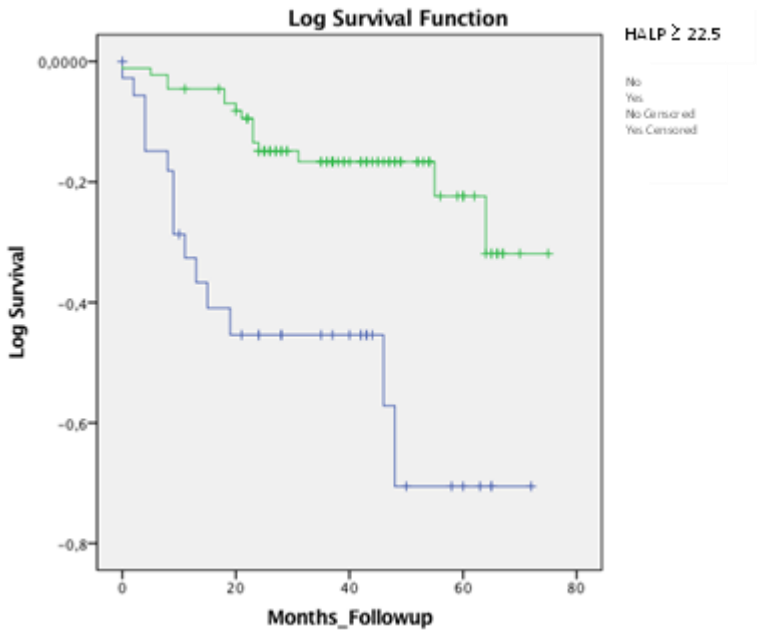

Figure 2: Cancer-specific survival (p=0.001) comparing low and high HALP scores

DISCUSSION

Immunological and nutritional status are established to have a prognostic significance in the natural history of cancer and are known to play an important role regarding its progression[2]. Lower hemoglobin, albumin and lymphocyte levels are related with a higher risk of adverse outcomes, postoperative complications and poor prognosis in cancer patients due to changes in tumor behavior[3,5,6]. Furthermore, increased levels of platelets seem to lower the protection against tumor cytotoxicity leading to a dysfunctional systemic inflammatory response and, consequently, to rapid tumor growth and proliferation[3,4]. Current literature uncovers a few studies demonstrating how the combination of these four analytical parameters can predict patient's clinical prognosis in a variety of malignancies, including colon cancer, revealing to be a good prognostic index in patients with LACC[7-10].

Over the years, several biomarkers have been evaluated as prognostic factors in colon cancer[3,11,12]. We aimed to investigate how can HALP score predict the risk of postoperative surgical events, disease recurrence and how these levels can be associated with cancer-specific survival. Predicting prognosis is challenging and this score based on analytical parameters is a simple, accessible tool that can identify patients with a higher risk of worse outcome[3]. This is the main highlight of our analysis as there are few studies linking HALP score in colon cancer behavior[8,10]. Two recent published studies showing HALP score association with colon cancer outcome, demonstrated a higher risk of poor prognosis towards lower HALP scores[8,10]. Jiang et al also determined an optimal cutoff value[2,5,6], similar to our study and revealed a statistically significant correlation between lower HALP scores and overall survival[8].

According to our study, the cutoff value estimated was 22,5 and we could divide our population into two groups (low and high HALP) with a statistically significant value (p=0,03). Moreover, regarding the clinical characteristics of our sample, and comparing between the two groups, lower HALP scores revealed a significant association with age ≥ 65 years and right-sided tumor. As for postoperative events, although postoperative complications including Clavien-Dindo III-IV did not show differences, surgical reintervention presented with a significant higher rate in low HALP score group versus high HALP scores (16,2% vs 2,2%). Anatomopathological features included in the study such as vascular, lymphatic and perineural invasion or differentiation grade were similar comparing groups, which was not concordant in other studies[8,10]. Furthermore, our results did not disclose a significant difference in disease recurrence. Nevertheless, according to our analysis, cancer-specific survival was found to be statically lower with lower HALP scores in comparison to the high HALP score group (p=0.001), which is consistent with published literature[7-9]. Moreover, after conducting a multivariate analysis, we divulged that age ≥ 65 years, right-sided tumor, surgical reintervention and lower HALP scores were independent prognostic factors in LACC and can be used to stratify patients' risk of poor outcome. To enrich our analysis, we discovered that a HALP score < 22,5 presented with an increase of 3.15 times regarding risk of cancer-related death in our population. This value appears to be slightly lower than that estimated in Jiang et al article that discloses a 3.87-fold higher risk of cancer-related death with lower HALP scores8. Our results suggest an accurate identification of two distinct prognostic groups based on HALP score model that could help clinical guidance in LACC patients.

This study presents with a limited bias of selection/exclusion. Our pool of patients was consecutively selected and the exclusion criteria were carefully chosen to minimize bias. Analytical parameters were evaluated objectively using pre-determined reference values in general population. In a more critical view, we point out some limitations in our study. Firstly, a retrospective and single-institutional analysis may create a selection bias and secondly, it was limited to locally advanced cancer since stage I and IV were not included due to bias in low-risk tumors (stage I) and distant metastatic disease (stage IV).

From these observations, our study validates a prognostic prototype accessible, low-cost that could helpful in identifying patients with a higher risk of poor outcome, stratifying risk and defining the best therapeutic approach in LACC.

CONCLUSION

From the retrospective analysis of this study, we can conclude that lower HALP score levels are associated with an increased risk of poor prognosis in LACC. Analytical parameters are simple and readily available in clinical practice and give key information regarding nutritional and systemic inflammation status that are extremely important in colon cancer prognosis. Therefore, serum biomarkers, such as HALP score could

successfully identify patients with a higher risk of poor outcome. Thus, this promising prognostic index may be useful as a clinical predictor of survival for LACC patients.

REFERENCES

1. Siegel RL., et al., Cancer statistics, 2021. CA: a cancer journal for clinicians, 2021; 71(1):7-33.
2. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010; 6(1):149-63.
3. Rossi S, et al. Are markers of systemic inflammation good prognostic indicators in colorectal cancer? Cl Colorect Cancer. 2017;16(4): 264-74.
4. Colotta F, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis, 2009; 30(7): 1073-81.
5. McMillan .C. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opinion Cli Nutr Metab Care. 2009; 12(3): 223-6.
6. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010; 9(1):1-16.
7. Peng D, et al. Prognostic significance of the combination of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients with renal cell carcinoma after nephrectomy. BMC Urol. 2018; 18(1): 1-8.
8. Jiang H, et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. Oncotarget. 2016; 7(44):2076.
9. Topal U, et al. Combination of Preoperative Haemoglobin and Albumin Levels and Lymphocyte and Platelet Counts (HALP) in Patients with Oesophageal Cancer. J Evol Med Dental Sci. 2021; 10(4):173-79.
10. Yalav O, et al. Prognostic significance of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients undergoing curative resection for colorectal cancer. Ann ital Chir. 2021; 92:283-92.
11. Aoyama T, et al. Comparison of clinic pathological characters and survival between right-and left-side colon cancer. Ann Cancer Res Ther. 2016; 24(2): 62-63.
12. Kasahara K, et al. Preoperative lymphocyte-to-monocyte ratio in the prognostication of advanced resectable colon cancer: A retrospective observational study. Indian J Surg Oncol. 2021; 12(3):498-506.