Received: 24-09-2022 | **Accepted:** 17-10-2022
DOI: 10.54005/geneltip.1179659

ORIGINAL ARTICLE

Halp Score: A Simple and Easily Accessible Index for Predicting Prognosis in Colorectal Cancer Patients

Kolorektal Kanser Hastalarında Prognozu Tahmin Edebilen Basit ve Kolay Erişilebilir Bir İndeks

[1]Zeynep Gülsüm Güç

[1]Department of Medical Oncology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey

Correspondence

Zeynep Gülsüm Güç, Department of Medical Oncology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey

E-Mail : zeynepgsevgen@hotmail.com

How to cite ?

Güç Z. Halp Score: A Simple And Easily Accessible Index For Predicting Prognosis In Colorectal Cancer Patients. Genel Tıp Dergisi. 2022; 32(5): 577-582

ABSTRACT

Objective: Colorectal cancer is the fourth most common malignant tumor in the world, and survival times are seen to increase together with the increase in the options for targeted therapies, local ablative applications, and supportive care. The Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) score is used as a prognostic factor in different types of cancers. The aim of this study was to analyze the prognostic value of the HALP score in patients diagnosed with de novo metastatic colorectal cancer (mCRC).
Methods: De novo mCRC patients who were followed-up in the period from January 2017 to December 2021, were retrospectively evaluated. The optimal cut-off point for the HALP score was calculated with the Receiver Operating Characteristic (ROC) curve analysis. Predictive factors for overall survival (OS) were assessed with univariate analysis. Survival times were assessed with the Kaplan-Meier analysis.
Results: A total of 213 patients were included in the study. Univariate analysis showed that patients with low Body Mass Index (BMI), high Eastern Cooperative Oncology Group (ECOG) Performance Status score, and tumors located in the right colon, and RAS mutant patients, and those with a low HALP score were associated with worse survival rates. Namely, the overall survival time of patients with a HALP score >16.74 was found as 91 months, while the overall survival time of patients with a HALP score ≤16.74 was found as 16 months (p<0.001).
Conclusion: Our study showed the HALP score to be a simple, cost-effective, and useful marker that can predict OS in mCRC patients.

Keywords: hemoglobin-albumin-lymphocyte-platelet (HALP) score, metastatic, colorectal cancer, prognostic

ÖZ

Amaç: Kolorektal kanser (KRK), dünyada en sık karşılaşılan malign tümörlerden dördüncüsü olup, artan hedefleyici tedavi seçenekleri, lokal ablatif uygulamalar ve destek bakımdaki artış ile sağkalım sürelerinin de uzadığı görülmektedir. Hemoglobin, albümin, lenfosit ve trombosit (HALP) skoru, farklı kanserler türlerinde prognostik bir faktör olarak kullanılmaktadır. Bu çalışmanın amacı, de novo metastatik kolorektal kanser (KRK) tanılı hastalarda HALP skorunun prognostik değerini analiz etmektir.
Yöntemler: Ocak 2017-Aralık 2021 tarihleri arasında de novo metastatik KRK tanısıyla takip edilen hastalar retrospektif olarak değerlendirildi. HALP skoru için optimal kesme noktası, ROC (receiver operating characteristic) eğrisi analizi ile belirlendi. Genel sağkalım için öngördürücü faktörler, tek değişkenli analiz ile değerlendirildi. Sağkalımı değerlendirmek için Kaplan-Meier analizi yapıldı.
Bulgular: Toplam 213 hasta çalışmaya dahil edildi. Tek değişkenli analiz, düşük Vücut Kitle İndeksi'nin (VKİ), yüksek Eastern Cooperative Oncology Group (ECOG) Performans Statüsü skorunun, sağ kolon yerleşimli tümörlerin, RAS mutant hastaların ve düşük HALP skorunun daha kötü sağkalım oranları ile ilişkili olduğunu gösterdi. Özellikle HALP skoru >16.74 olan hastaların genel sağkalım süresi 91 ayken, HALP skoru ≤16.74 olan hastaların genel sağkalım süresi 16 ay bulundu. (p<0.001)
Sonuç: Sonuç olarak HALP skoru metastatik KRK hastalarında sağkalımı predikte eden basit, maliyeti düşük ve kullanışlı bir belirteçlerdir.

Anahtar Kelimeler: hemoglobin-albümin-lenfosit-trombosit (HALP) skoru, metastatik, kolorektal kanser, prognostik

Introduction

Colorectal cancer (CRC) is the third leading cause of death from cancer worldwide, with about 1.9 million new cases identified in 2020. (1,2) About 20% of the patients present with metastasis at the time of initial diagnosis, and 30 to 40% additionally develop metachronous metastasis after primary tumor resection. A 5-year survival time can be achieved at a rate of 40% with multimodal systemic treatment combinations. (3)

In recent years, there has been an increasing focus on identifying the molecular changes that are critical to the oncogenic phenotype of colorectal cancer and on therapies that target these molecular changes. Still, however, a great majority of the patients are treated with cytotoxic chemotherapy due to their molecular/pathological characteristics or the lack of access to treatment. Availability of prognostic and predictive indexes that allow physicians to make the most suitable treatment decision in these patients are of vital importance.

Current studies show that the systemic inflammatory response is associated with tumor characteristics such as proliferation, invasion, metastasis, and that inflammation has an important role in tumor formation

and growth. (4,5) Blood cells affect tumor cells through adaptive immune response by secreting different cytokines that help various inflammatory processes. (6) The neutrophil-to-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), the lymphocyte-monocyte ratio (LMR), and inflammatory indexes such as the prognostic nutritional index have been used to predict prognosis in different cancer types. (7,8)

It is known that a combination of these parameters can predict the patient's prognosis better than a single index. To that end, the HALP score—an index which is calculated based on hemoglobin, albumin, lymphocyte, and platelet levels—has been recently defined. The HALP score assesses both the immune system and the nutritional status of the patient. The score has been reported to be a good prognostic marker in various types of cancers, including gastrointestinal, lung, and genitourinary cancers. (9,10,11) These parameters can be calculated simply based on the laboratory parameters of patients used in everyday practice. In this study, we aimed to determine the relationship between the HALP score examined before treatment and prognosis in metastatic colorectal cancer (mCRC) patients.

Material and Methods

Data Collection and Follow-Up

The institutional and national research committees' ethical standards, as well as the 1964 Declaration of Helsinki and its later revisions or comparable ethical standards were followed in the study. The method and procedure for the study were approved by the Ethics Committee of the University. The study included 213 patients diagnosed with de novo mCRC and treated and/or followed-up by our medical oncology clinic from January 2017 to December 2021. Patients who had severe comorbidities, were receiving anti-inflammatory treatment, had active infection or inadequate organ function were excluded, as these might affect inflammatory parameters. Patients' age, weight, height, body mass index (BMI), comorbidities, Eastern Cooperative Oncology Group (ECOG) status, and demographic data were recorded. Lymphocyte and platelet counts, and serum albumin levels were recorded from the laboratory parameters examined one week before the first course of chemotherapy.

HALP scores were calculated using the laboratory data obtained. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score was calculated according to the following formula: hemoglobin (g/L)×albumin (g/L)×lymphocytes (/L)/platelets (/L).

Statistical Analyses

The Statistical Package for Social Sciences for Windows 20.0 (BM SPSS, IBM Corp., Armonk, NY, USA) was used for analysis. OS was defined as the time from diagnosis to death or the last visit. Descriptive statistics summarized frequencies and percentages for categorical, mean, and standard deviation for continuous variables. Categorical variables were compared with the Independent Samples T-test and categorical parameters with the $\chi 2$ test. The power of the HALP score was analyzed using the ROC curve analysis. A significant cut-off point was observed, and sensitivity, specificity, and positive and negative predictive values were detected. Survival analyses of prognostic indexes, and clinical and pathological features were calculated using the Kaplan-Meier method (log-rank test). Parameters that appeared significant in univariate analysis for survival and did not show multicollinearity were included in the Cox multivariate regression analysis. The 95% confidence interval (CI) was used to indicate the relationship between survival time and each independent factor. Statistical significance level was $p<0.05$.

Results

Of the 213 patients included in the study, 182 patients were <75 years and 31 were ≥75 years of age with a mean of 61±12.91 years. 58.7% (125) of the patients were male. The most common histopathological type was adenocarcinoma with a rate of 90.6% (193 patients), followed by mucinous adenocarcinoma 8% (17 patients). 61% of the tumors were moderately differentiated. While all patients were de novo metastatic, the most common site of metastasis was the liver (52.6%). The mean follow-up time of the patients was 31 (2-126) months. 77% (164 patients) had died by the end of the follow-up period. The main characteristics of the patients are shown in Table 1.

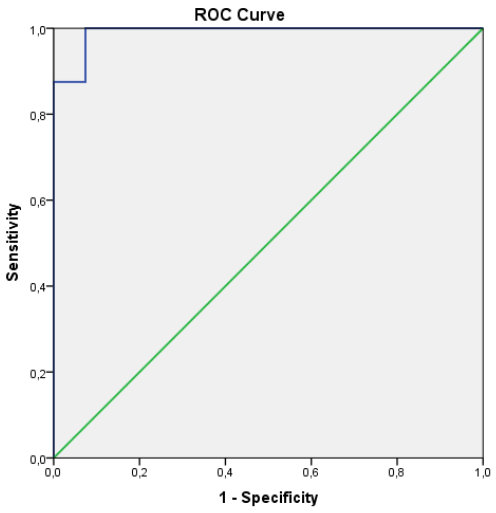

Figure 1. ROC curve for HALP score

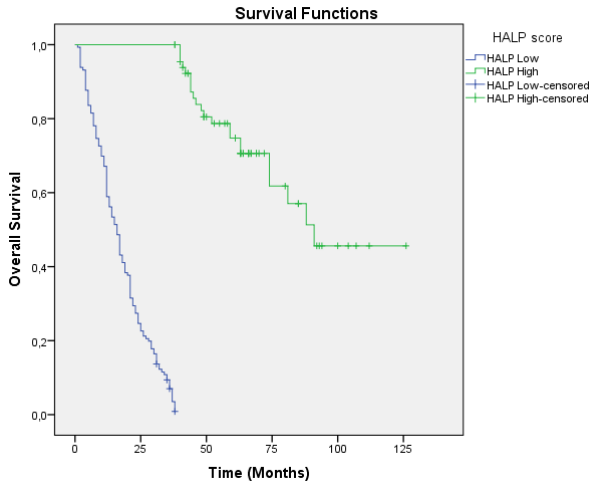

Figure 2. Kaplan-Meier curves for OS in patients with mCRC according to HALP score

Table 1. Clinical and pathological features of patients

Parameters	Number of patients (%)
Age	
<75	182 (85.4%)
≥75	31 (14.6%)
Gender	
Female	88 (41.3%)
Male	125 (58.7%)
Histology	
Adenocarcinoma	193 (90.6%)
Mucinous adenocarcinoma	17 (8%)
Neuroendocrine carcinoma	3 (1.4%)
Differentiation	
Well differentiated	78 (36.6%)
Moderately differentiated	130 (61%)
Poorly differentiated	5 (2.3%)
BMI (kg/m2)	
BMI <24	86 (40.4%)
BMI ≥24	127 (59.6%)
ECOG	
ECOG 0-1	168 (78.9%)
ECOG 2-3	45 (21.1%)
Localization	
Left colon	90 (42.3%)
Right colon	123 (57.7%)
RAS Type	
Wild	110 (51.6%)
Mutant	103 (48.4%)
Localization of Metastasis	
Liver	112 (52.6%)
Lung	47 (22.1%)
Peritoneum	29 (13.6%)
Bone	1 (0.5%)
Other	24 (11.2%)

BMI: Body Mass Index, ECOG: Eastern Cooperative Oncology Group, RAS: Rat Sarcoma Gene

The median HALP score of the patients was 17.49 (Range: 1.98-47.3). ROC analysis was done to determine the most appropriate cut-off point for the HALP score. The ROC curve showed the optimal cut-off point to be 16.74 (AUC=0.991; 95% CI 0.97-1.0, p<0.001) (Figure 1). Based on this cut-off point, patients were grouped as those with a low HALP score and those with a high HALP score.

Table 2. The relationship between basic clinicopathological characteristics and HALP scores

Parameters	HALP score		
	High (n)	Low (n)	*p*
Age			
<75	60	122	
≥75	7	24	0.174
Gender			
Female	34	54	
Male	33	92	0.41
Histology			
Adenocarcinoma			
Mucinous	62	131	
adenocarcinoma	5	12	
Neuroendocrine	0	3	0.484
carcinoma			
Differentiation			
Well differentiated	28	50	
Moderately	38	92	
differentiated	1	4	0.518
Poorly differentiated			
BMI (kg/m2)			
BMI <24	17	69	
BMI ≥24	50	77	**0.002**
ECOG			
ECOG 0-1	59	109	
ECOG 2-3	8	37	**0.018**
Localization			
Left colon	63	27	
Right colon	4	119	**<0.001**
RAS Type			
Wild	42	67	
Mutant	24	77	**0.015**
Localization of Metastasis			
Liver	30	82	
Lung	22	25	
Peritoneum	10	19	
Bone	0	1	
Other	5	19	0.283

BMI: Body Mass Index, ECOG: Eastern Cooperative Oncology Group, RAS: Rat Sarcoma Gene

Univariate analysis showed that low BMI, high ECOG score, tumors located in the right colon, RAS mutant patients, and low HALP score were associated with

worse survival rates (Table 3). Particularly, the overall survival time of patients with a HALP score >16.74 was found as 91 months, while the overall survival time of patients with a HALP score ≤16.74 was found as 16 months (p<0.001) (Figure 2).

Table 3. Univariate analysis of prognostic factors for OS

Parameters	Univariate Analysis of OS		
	Number of patients (%)	Median OS in Months (95% CI)	p
Age			
<75	182 (85.4%)	25 (19.82-30.17)	0.110
≥75	31 (14.6%)	16 (8.75-23.24)	
Gender			
Female	88 (41.3%)	25 (14.91-35.08)	0.187
Male	125 (58.7%)	23 (19.08-26.91)	
BMI (kg/m2)			
BMI <24	86 (40.4%)	17 (13.50-20.49)	**<0.001**
BMI ≥24	127 (59.6%)	32 (21.97-42.02)	
ECOG			
ECOG 0-1	168 (78.9%)	28 (21.32-34.67)	**<0.001**
ECOG 2-3	45 (21.1%)	19 (11.37-26.62)	
Localization			
Left colon	90 (42.3%)	74 (47.30-100.69)	**<0.001**
Right colon	123 (57.7%)	14 (12.02-15.97)	
RAS Type			
Wild	110 (51.6%)	31 (22.99-39.00)	**0.002**
Mutant	103 (48.4%)	18 (14.89-21.10)	
HALP score			
High	67 (31.5%)	91 (15.56-19.03)	**<0.001**
Low	146 (68.5%)	16 (13.50-18.49)	

BMI: Body Mass Index, ECOG: Eastern Cooperative Oncology Group, RAS: Rat Sarcoma Gene

When the relationship between the HALP scores and the clinicopathological characteristics of patients were evaluated, ECOG performance score, BMI, localization of the tumor (right/left colon), and RAS mutation status were found to be associated with the HALP score (p<0.005) (Table 2).

Discussion

This study investigated the relationship between the HALP score examined before the first cycle of chemotherapy and overall survival in patients with de novo mCRC. We assessed simple prognostic markers such as complete blood count parameters and serum albumin levels that are obtained from basic laboratory measurements done as part of the routine evaluation process for every patient. Review of the literature showed our study to be the first to demonstrate that low HALP scores (≤16.74), similar to important prognostic factors such as RAS mutation and tumor location, could be used as a biomarker predicting survival in mCRC patients.

While in the recent past, until about ten or fifteen years ago, survival times of about one year could be achieved in mCRC patients, today this period can exceed three years thanks to the availability of targeted therapies and the effective local therapies. (12,13) However, when the studies were examined in detail, despite all the favorable factors, some mCRC patients were seen to have lower survival times, and research on the prognostic factors and markers that affect overall survival continued.

It is widely accepted that inflammatory response and nutritional status are associated with prognosis in cancer patients. Serum albumin is one of the most commonly used indicators showing the nutritional status of patients and has been used to assess progression and prognosis in different types of cancers. Low albumin levels are associated with poorer survival in cancer patients. (14,15) Lymphocytes are critical in the host's anticancer defense. Lymphocytes, which can release cytokines such as interferon-γ and tumor necrosis factor-alpha (TNF-α), can improve the prognosis by causing apoptosis, suppressing cancer cell proliferation, invasion, and migration. (16,17) As a result, lymphocytopenia can contribute to tumor growth. Anemia is a commonly observed result in various cancers, including CRC. (18) That hemoglobin levels are directly related to survival and tumor development in cancer patients have been shown in several studies. (19,20,21) Platelet stimulation is linked to metastasis, and platelets can also protect cancer cells from immune attack. (22)

The HALP score is the integration of four hematological parameters—hemoglobin, lymphocytes, platelets, and albumin levels—and basing on the data obtained in our study, we can say that the HALP score is a comprehensive index that measures the nutritional status and immune health of patients. It has been shown to have prognostic effect in gastric cancer (23), squamous cell carcinoma of the esophagus (24), colorectal cancer (25), renal cell carcinoma (26), bladder cancer (10) and small cell lung cancer. (27) However, the prognostic significance of the HALP score in mCRC patients has not been previously studied in the literature. Our results confirmed that the HALP score is an independent prognostic factor in de novo mCRC patients, and that improvements in the HALP score could, in turn, significantly improve overall survival in CRC patients.

Various prognostic models based on different hematological parameters have been proposed for CRC patients. (28) There are studies that include preoperative carcinoembryonic antigen (CEA) levels and examine (29) the Glasgow prognostic score in high-risk stage II or stage III CRC patients to predict prognosis after resection of pulmonary metastases in CRC patients. (30) However, as stated earlier, the HALP score is both simple and cost-effective marker as it is calculated using the complete blood count parameters and albumin levels that are used in the assessment of every patient.

Based on the retrospective data of studies on colon cancer, the localization of a primary tumor has been shown to be factor affecting survival and chemotherapy response. In a recently published meta-analysis, survival was found to be significantly shorter in metastatic colon cancer patients when the tumor was localized on the right side rather than on the left side. (Overall survival [HRright=2.03 (95% CI: 1.69-2.42) and HRleft=1.38 (95% CI: 1.17-1.63)], respectively). (31) In our study, primary tumors in the right colon were found to be associated with worse prognosis.

The Rat Sarcoma (K-RAS) gene, CRC, functions as a proto-oncogene in the tumor suppressor pathway, which is one of the genetic pathways in its development. It is also a membrane protein capable of binding GTP, which is involved in the transmission of extracellular mitogenic signals. (32) RAS gene mutations are found at different incidences in different cancer types. This mutation is encountered mostly in pancreatic cancers (90%), followed by colon cancers (50%), lung adenocarcinomas (30%) and thyroid tumors (50%), and in myeloid leukemia (30%). (33) The prognostic significance of the mutation status has been demonstrated, alongside the changes in treatment targets according to the RAS mutation in CRC. (34,35,36) Similar to the literature, in our study, we observed that patients with wild-type RAS had better prognosis.

Whilst being the first to demonstrate the HALP score as an independent predictive factor for overall survival in de novo mCRC patients, our study has some major limitations. This is a retrospective study conducted in a single center. The BRAF mutation statuses of the patients have not been included in the analysis. A prospective multi-center study is needed to more clearly assess how these scores should be used in the follow-up and for the survival benefit of patients.

To conclude, the HALP score is a reliable, simple, easily accessible, and inexpensive biomarker that can be used to predict the prognosis of advanced colorectal cancer patients. Our results suggest that prognostic models based on the HALP score are a useful tool that can be used to predict survival in mCRC patients.

Funding: No funding to declare.

Conflicts of interest/Competing interests: The author declare that she has no conflict of interest.

Availability of data and material: The author confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Ethics approval: The study was approved by the Institutional Review Board at Izmir Katip Celebi University

Consent to participate: All patients provided written informed consent to participate in the study.

Consent for publication: Patients signed informed consent regarding publishing their data.

References

1.Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.

2.Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.

3.Jones RP, Kokudo N, Folprecht G, et al. Colorectal Liver Metastases: A Critical Review of State of the Art. Liver Cancer. 2016;6(1):66-71.

4.McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care. 2009;12(3):223-226.

5.Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30(7):1073-1081.

6.Varga G, Foell D. Anti-inflammatory monocytes-interplay of innate and adaptive immunity. Mol Cell Pediatr. 2018;5(1):5.

7.Hong YF, Chen ZH, Wei L, et al. Identification of the prognostic value of lymphocyte-to-monocyte ratio in patients with HBV-associated advanced hepatocellular carcinoma. Oncol Lett 2017;14:2089-96.

8.Magdy M, Hussein T, Ezzat A, Gaballah A. Pre-treatment Peripheral Neutrophil-Lymphocyte Ratio as a Prognostic Marker in Gastric Cancer. J Gastrointest Cancer. 2019;50(4):763-768.

9.Jiang H, Li H, Li A, et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. Oncotarget. 2016;7(44):72076-72083.

10.Peng D, Zhang CJ, Gong YQ, et al. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. Sci Rep. 2018;8(1):794.

11.Güç ZG, Alacacıoğlu A, Kalender ME, et al. HALP score and GNRI: Simple and easily accessible indexes for predicting prognosis in advanced stage NSCLC patients. The Izmir oncology group (IZOG) study. Front Nutr. 2022;9:905292.

12.Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005 [published correction appears in CA Cancer J Clin. 2005 Jul-Aug;55(4):259]. CA Cancer J Clin. 2005;55(1):10-30.

13.Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016; 66(4): 271-89.

14.Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010;9:69.

15.Oñate-Ocaña LF, Aiello-Crocifoglio V, Gallardo-Rincón D, et al. Serum albumin as a significant prognostic factor for patients with gastric carcinoma. Ann Surg Oncol. 2007;14(2):381-389.

16.Lim JA, Oh CS, Yoon TG, et al. The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. BMC Cancer. 2018;18(1):159.

17.Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-444.

18.Keeler BD, Mishra A, Stavrou CL, Beeby S, Simpson JA, Acheson AG. A cohort investigation of anaemia, treatment and the use of allogeneic blood transfusion in colorectal cancer surgery. Ann Med Surg (Lond). 2015;6:6-11.

19.Belcher DA, Ju JA, Baek JH, et al. The quaternary state of polymerized human hemoglobin regulates oxygenation of breast cancer solid tumors: A theoretical and experimental study. PLoS One. 2018;13(2):e0191275.

20.Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent

prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer. 2001;91(12):2214-2221.

21.Xia L, Hu G, Guzzo TJ. Prognostic Significance of Preoperative Anemia in Patients Undergoing Surgery for Renal Cell Carcinoma: A Meta-analysis. Anticancer Res. 2017;37(6):3175-3181.

22.Zhang GM, Zhu Y, Luo L, et al. Preoperative lymphocyte-monocyte and platelet-lymphocyte ratios as predictors of overall survival in patients with bladder cancer undergoing radical cystectomy. Tumour Biol 2015;36:8537-43.

23.Chen XL, Xue L, Wang W, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget. 2015;6(38):41370-41382.

24.Cong L, Hu L. The value of the combination of hemoglobin, albumin, lymphocyte and platelet in predicting platinum-based chemoradiotherapy response in male patients with esophageal squamous cell carcinoma. Int Immunopharmacol. 2017;46:75-79.

25.Jiang H, Li H, Li A, et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. Oncotarget. 2016;7(44):72076-72083.

26.Peng D, Zhang CJ, Tang Q, 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):20.

27.Shen XB, Zhang YX, Wang W, Pan YY. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score in Patients with Small Cell Lung Cancer Before First-Line Treatment with Etoposide and Progression-Free Survival. Med Sci Monit. 2019;25:5630-5639.

28.Kawai K, Sunami E, Yamaguchi H, et al. Nomograms for colorectal cancer: A systematic review. World J Gastroenterol. 2015;21(41):11877-11886.

29.Kanemitsu Y, Kato T, Hirai T, Yasui K. Preoperative probability model for predicting overall survival after resection of pulmonary metastases from colorectal cancer. Br J Surg. 2004;91(1):112-120.

30.Toiyama Y, Miki C, Inoue Y, Tanaka K, Mohri Y, Kusunoki M. Evaluation of an inflammation-based prognostic score for the identification of patients requiring postoperative adjuvant chemotherapy for stage II colorectal cancer. Exp Ther Med. 2011; 2:95-101.

31.Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol. 2017;28(8):1713-1729.

32.Zeng M, Kikuchi H, Pino MS, Chung DC. Hypoxia activates the K-ras proto-oncogene to stimulate angiogenesis and inhibit apoptosis in colon cancer cells. PLoS One. 2010;5(6):e10966. Published 2010 Jun 4.

33.Jiang Y, Mackley H, Cheng H, Ajani JA. Use of K-Ras as a predictive biomarker for selecting anti-EGF receptor/pathway treatment. Biomark Med. 2010;4(4):535-541.

34.Ribeiro KB, Ribeiro KB, Feres O, et al. Clinical-Pathological Correlation of KRAS Mutation Status in Metastatic Colorectal Adenocarcinoma. World J Oncol. 2013;4(4-5):179-187.

35.Morris VK, Lucas FAS, Overman MJ, et al. Clinicopathologic characteristics and gene expression analyses of non-KRAS 12/13, RAS-mutated metastatic colorectal cancer. Ann Oncol. 2014;25(10):2008-2014.

36.Kawazoe A, Shitara K, Fukuoka S, et al. A retrospective observational study of clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer. BMC Cancer. 2015;15:258.