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A new index for predicting malignant causes in patients with extrahepatic biliary obstruction: the hemoglobin, albumin, lymphocyte, and platelet (HALP) score

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Abstract. – OBJECTIVE: The study aimed to investigate whether the pre-procedural hemoglobin, albumin, lymphocyte, and platelet (HALP) scores can distinguish between benign and malignant causes of obstruction in patients who undergo endoscopic retrograde cholangiopancreatography (ERCP) for extrahepatic biliary obstruction (EBO).

PATIENTS AND METHODS: The HALP scores of the patients were calculated according to the values before ERCP. The patients were divided into two groups as malignant and benign according to their diagnosis after ERCP. The HALP scores, demographic characteristics, and some laboratory data of the groups were compared. The cut-off values of the HALP scores were found to detect malignant obstructive causes using the receiver operating characteristic (ROC) curve analysis.

RESULTS: A total of 295 patients had benign and 50 had malignant causes of obstruction among the total of 345 patients. The HALP score was found to be lower in the patient group with malignant biliary obstruction (p = 0.013). The ROC curve analysis was used to determine the diagnostic efficiency, and an area under the curve (AUC) of 0.610 was obtained (0.526-0.693, 95% CI) (p = 0.013). For the HALP score, the sensitivity was found to be 82.4% and the specificity was 30% when a cut-off value of <12.54 was used, and the sensitivity was 61.4% and specificity was 52% when the cut-off value was <21.25.

CONCLUSIONS: The study showed that a low HALP score can distinguish malignant causes in patients with EBO. We think that the HALP score, which is a low-cost index that can be easily calculated with simple tests, can be used in this patient population because it may allow early diagnosis of malignant causes in patients with EBO.

Key Words:
Extrahepatic biliary obstruction, HALP score, Malignancy.

Introduction

Biliary obstruction may occur with intrahepatic and extrahepatic etiologies[1]. Extrahepatic biliary obstruction (EBO) is defined as the condition in which bile is prevented from entering the duodenum because of lesions or obstructions at the common hepatic duct or choledochal level[2]. EBO may develop because of various benign and malignant causes. Benign causes are choledocholithiasis, choledochal cysts, Mirizzi Syndrome, primary sclerosing cholangitis (PSC), benign bile duct strictures, ampullary adenomas, and some parasites. The malignant diseases that cause EBO are cholangiocarcinoma, pancreatic head cancer, and ampullary carcinoma[1,3]. Endoscopic retrograde cholangiopancreatography (ERCP) is a biliary and pancreatic duct imaging method. The image of the biliary tract with contrast obtained during the ERCP procedure is usually sufficient for diagnosis and treatment[4].

Some previous studies[5,6] reported that the systemic inflammatory response is associated with tumor characteristics (e.g., proliferation, invasion, and metastasis), and also plays an important role in the formation and growth of the tumor[5]. Increasing evidence supports that nutrition also plays a role in the initiation and progression of various cancers in addition to inflammation[6]. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a novel index showing systemic inflammation and nutritional status[7]. The HALP score is calculated by using the formula hemoglobin × albumin × lymphocyte count/platelet count[8]. Some recent studies[9] show that the HALP score can be used as a novel prognostic marker for some malignant diseases.

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The accuracy of diagnostic modalities for distinguishing malignantand benign reasons of EBO is still limited. Cheap and easily measurable laboratory parameters for predicting malignant EBO are lacking. In the present study, the purpose was to investigate whether the pre-procedural HALP score can distinguish between benign and malignant causes in patients who undergo ERCP for EBO. It was also aimed to determine whether the HALP score can be used as a predictive parameter in predicting benign and malignant biliary obstructive etiologies and if so, to determine this predictive value. To the best of our knowledge, this is the first study in the literature evaluating whether the HALP score can distinguish between benign and malignant causes in patients with EBO.

Patients and Methods

The study population consisted of patients who were hospitalized with the diagnosis of EBO and underwent ERCP between February 2019 and February 2022. The patients were diagnosed with EBO as a result of clinical characteristics, bilirubin values, hepatobiliary ultrasonography imaging (USI) results, abdominal magnetic resonance (MR), and magnetic resonance cholangiopancreatography (MRCP) examination results. All laboratory tests, radiological examinations, pathology reports, and medical histories of the patients were searched by using the hospital's electronic database. The demographic characteristics of the patients, hemoglobin, albumin, lymphocyte, thrombocyte, white blood cell (WBC) count and total bilirubin values were recorded. The patients were divided into 2 groups according to the post-procedural benign and malignant causes of EBO. The diagnosis of malignancies was made according to imaging methods, ERCP procedure, and tissue biopsy results. The first group consisted of EBO cases that developed because of benign reasons and the second group consisted of EBO cases with malignant causes. The two groups were compared in terms of the HALP scores, total bilirubin values, WBC counts, and demographic characteristics (i.e., age and gender). The HALP score was calculated by the formula of hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L) / platelet count (/L) according to the HALP values of the patients before the ERCP procedure[8].

The patients who were over the age of 18 who underwent ERCP after detecting EBO and those whose study data could be accessed were included in the study. The patients with any active infection, known solid or hematological malignancy, chronic liver disease, chronic renal failure, nephrotic syndrome, patients receiving immunosuppressive or steroid therapy, and those with chronic inflammatory or autoimmune diseases and pregnant women were not included in the study. Also, patients who underwent ERCP for pancreatic duct cannulation, hydatid cyst, surgical complications, and stent removal or replacement were excluded from the analyses.

Statistical Analysis

Statistical analysis was performed with the SPSS Software (Statistical Package for the Social Sciences, version 15.0, SSPS Inc., Chicago, IL, USA). The descriptive statistics of the study groups were determined and the data were evaluated for normal distribution using the Kolmogorov-Smirnov test and visual parameters (histogram, variation coefficient, skewness, kurtosis, etc.). Quantitative variables with and without normal distribution were expressed as the mean±standard deviation (SD) and median (interquartile range) values, respectively. Student *t*-test and Mann-Whitney U Test were used for comparisons, according to the distribution status. The Chi-square test was used to analyze categorical data, and categorical variables were expressed with numbers and percentage values. The cut-off values of the HALP score for the detection of malignant EBO were calculated using receiver operating characteristic (ROC) curve analysis and $p < 0.05$ was considered statistically significant.

Results

All ERCP procedures, which were performed between July 2020 and May 2022, were retrospectively evaluated. ERCP procedures that were performed for pancreatic duct cannulation were not included in analyses. Patients whose procedure was performed for cyst hydatid, surgical complications, and stent retrieval or change were not included in the analysis. After the exclusion, 345 patients whose data were available for analysis were included in the study.

A total of 295 patients had benign reasons for cholestasis, whereas 50 patients had a malignant disease as the reason for cholestasis. The malignant group consisted of 27 patients with pancreas carcinoma, 10 patients with hilar cholangiocar-

cinoma (Klatskin tumor), 8 patients with distal cholangiocarcinoma, and 5 patients with ampullary tumor. The majority of the benign group consisted of patients with choledocholithiasis (270 patients). There were 23 benign stenoses (6 proximal, 3 middle, 14 distal stenoses) and 2 Mirizzi Syndrome in the benign group (Table I). Some laboratory and demographic parameters are summarized in Table II among benign and malignant groups. The HALP score was statistically and significantly lower in the malignant cholestasis group ($p = 0.013$).

The gender, age, hemoglobin, and total bilirubin values of the patients with malignant and benign EBO were found to be significantly different. Old age and male gender were more dominant in the malignant group. Also, the total bilirubin values of the malignant group were higher and these were consistent with the results of previous studies[10,11].

To determine the diagnostic efficiency, the receiver operating characteristic (ROC) curve analysis was performed (Figure 1). An area under the curve (AUC) value of 0.610 [0.526-0.693 and 95% confidence interval (CI)] ($p = 0.013$) were achieved. The HALP score was 12.54 and the cut-off value had a sensitivity of 82.4% with a specificity of 30%. When a cut-off value of 21.25 was chosen, the sensitivity was 61.4% with a specificity of 52%.

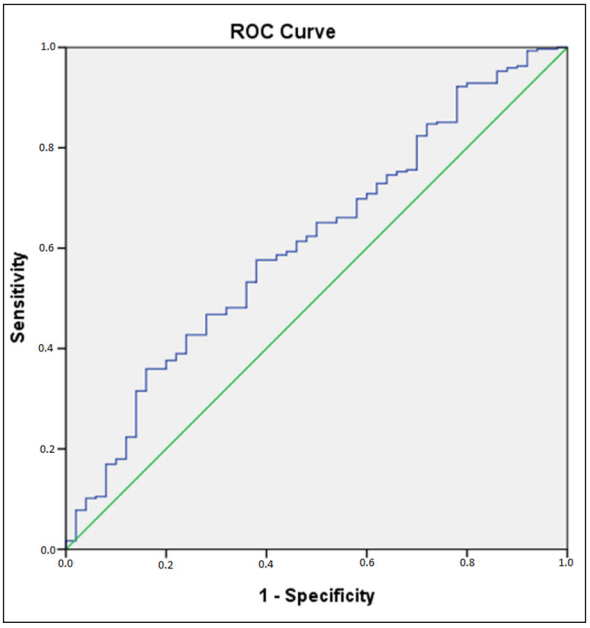

Figure 1. ROC curve analysis of HALP score for predicting malignant extrahepatic biliary obstruction.

Discussion

Clinicians face various difficulties in accessing imaging methods to detect etiological factors causing EBO and distinguishing whether these etiological factors are malignant or benign. Patients are treated with different treatment modalities in different specialties according to the cause of EBO. For this reason, having reliable predictive biomarkers will provide important benefits such as predicting patients for whom an early diagnosis is important, such as malignancies, and directing patients to the right specialties without wasting time.

The study aimed to investigate whether the HALP score can be an index that can be used to predict benign and malignant causes in patients who undergo ERCP for EBO. It was found that the HALP score can distinguish whether the pathological condition causing EBO is benign or malignant and that the HALP score can be used as an easily accessible, easily calculated, and inexpensive index to predict malignant etiologies in patients with EBO.

Previous studies[1] show that inflammation and nutrition play important roles in the initiation and progression of various cancers. Lymphocytes and platelets, which are essential components of the systemic inflammatory response, are associated with persistent inflammation of the tumor microenvironment[12,13]. Although anemia and thrombosis may exacerbate inflammation, lymphocytes reduce it[14]. Hypoalbuminemia may develop in conditions such as malnutrition, systemic inflammation, hypercatabolism, and increased cytokine secretion. Serum albumin, which is a negative acute phase marker, can be used to evaluate nutritional status. Malnutrition is common in cancer patients and the etiology of cancer-related malnutrition is multifactorial[15]. Many studies[16,17] report that hypoalbuminemia is associated with poor survival outcomes in different types of cancer. Recent studies[18-20] also show that certain blood markers, such as the ratio of neutrophils to lymphocytes (NLR), the ratio of platelets to lymphocytes (PLR), and the ratio of lymphocytes to monocytes (LMR) all represent inflammatory changes in the tumor microenvironment. Also, the prognostic nutritional index (PNI) is calculated by combining the circulating albumin concentration with the lymphocyte count. For this reason, it was accepted as an index reflecting nutritional and inflammatory status[21].

Table I. Distribution of benign and malignant causes of extrahepatic biliary obstruction.

Causes of extrahepatic biliary obstruction			n	%
Benign group (n=295)	Choledocholithiasis		270	91.52
	Benign stenoses	Proximal	6	2.03
		Middle	3	1.01
		Distal	14	4.74
		Mirizzi Syndrome	2	0.67
Malignant group (n=50)	Pancreas carcinoma		27	54.00
	Hilar cholangiocarcinoma (Klatskin tumor)		10	20.00
	Distal cholangiocarcinoma		8	16.00
	Ampullary tumor		5	10.00

The percent values are expressed within the study groups.

The HALP score, which is a combination of hemoglobin, albumin, lymphocyte, and platelet parameters, is a novel index accepted as a marker of systemic inflammation and nutritional status[22]. The HALP score has generally been used to predict prognosis and survival rates in cancer patients in most studies[8,23-26] conducted so far. It was shown that low HALP scores are associated with poor prognosis in various cancers (with varying cut-off points depending on cancer types), including bladder, stomach, esophageal, colorectal, and prostate cancers. The present study, on the other hand, showed that the HALP score is an index that can distinguish malignant or benign pathology causing obstruction in patients with EBO. Demonstrating the ability of the HALP score to distinguish malignant etiologies is an important difference between the present study and others of the literature. To the best of our knowledge, the present study is the first to demonstrate that the HALP score can be used to predict malignant etiologies in patients with EBO. In a recent study, Akbas et al[27] investigated whether the preoperative HALP score could distinguish between malignant and benign causes in patients operated on for acute mechanical intestinal obstruction (AMIO). As a result of their study, it was shown that the HALP score is an independent prognostic factor in determining malignancy in patients with AMIO. They also concluded that the HALP score may be a useful parameter for the clinician in distinguishing AMIO because of malignant and benign origins. The result of the present paper parallels and supports the result of this study. To the best of our knowledge, aside from these two studies[27], there is no other study reporting that the HALP score, which is an index of inflammation and nutritional status, can be used for the etiological differentiation of diseases. The results of these two studies showed an important and different aspect of the HALP score that must be investigated whether it can be an index that can be used to predict malignant and benign causes in different diseases.

Accurate differential diagnosis is the most important step before further treatment in patients with obstructive jaundice. Biliary obstructions may occur because of benign causes such

Table II. Demographic and laboratory parameters among patients with benign and malignant extrahepatic biliary obstruction.

		Benign group	Malignant group	*p*
Gender	Female	175	21	0.030
	Male	120	29	
Age		71 (57-80)	76 (71-81)	0.003
WBC count (/μL)		7,940 (6,260-11,400)	8,110 (6,080-11,830)	0.381
Total bilirubin (mg/dL)		2.09 (0.84-4.01)	8.84 (5.55-13.37)	<0.001
HALP score		26.95 (15.32-45.33)	20.61 (11.44-31.89)	0.013

WBC: White blood cell; HALP: Hemoglobin, albumin, lymphocyte, and platelet.

as choledocholithiasis, post-cholecystectomy, chronic pancreatitis, primary sclerosing cholangitis, IgG4-associated sclerosing cholangitis, choledochal cysts, Mirizzi Syndrome, recurrent pyogenic cholangitis, ischemic cholangiopathy, various infections, vasculitis, traumas, extraluminal pressures, or malignant causes such as cholangiocarcinoma, cancer of the pancreas head and ampullary region carcinomas[28]. Patients with malignant biliary obstruction usually present with symptoms of anorexia, weight loss, and painless jaundice. However, these symptoms can also be seen in patients with benign biliary obstruction[29]. For this reason, it is very difficult to distinguish the etiology of patients with biliary obstruction based on clinical characteristics alone. In the evaluation of patients with biliary obstruction, various laboratory tests, noninvasive radiological imaging methods, invasive methods, and tissue biopsy examinations (if necessary) are used together with clinical characteristics. Noninvasive radiological imaging methods are abdominal USI, contrast-enhanced computed tomography (CT), MR, and MRCP. ERCP, Percutaneous transhepatic cholangiography (PTC), and endoscopic ultrasonography (EUS) are invasive methods. Some of the invasive methods may offer additional imaging data as well as tissue sampling and treatment in the same session[30].

The treatment approaches for biliary obstructions, which can occur because of various etiological reasons, also differ considerably. Early detection of patients with malignant etiology is very important for successful treatment, especially for those requiring surgical intervention or initiating cancer chemotherapy. The malignancies that cause biliary obstruction have a very aggressive progression (e.g., the 5-year survival rate of patients with pancreas carcinoma is only 2-9%), and early diagnosis and treatment are very important in this respect[31]. However, despite the existence of many diagnostic methods and developments in new endoscopic techniques, it is still not easy to distinguish benign and malignant causes of biliary obstruction. Noninvasive radiological methods such as CT, MR, and MRCP are expensive, not available in every center, and their accuracy does not reach 100%[32]. In a previous study that was conducted by Zhong et al[33], the sensitivity, specificity, and accuracy of MRCP in distinguishing malignant and benign causes of pancreato-biliary obstruction were found to be 64.7%, 81.2%, and 74.4%, respectively, and that of ERCP/PTC was 77.8%, 86.4%, and 82.5%, respectively. Endoscopic tissue collection techniques (e.g., biopsies, scrubs, and fine needle aspiration) can provide a definitive tissue diagnosis. However, serious complications such as bleeding, perforation, pancreatitis, and cholangitis may develop because of these invasive endoscopic examinations[34]. In patients with biliary obstruction, making the distinction between benign and malignant causes accurately or increasing the predictability with easily accessible and noninvasive methods will protect patients from the risk of complications that may develop because of unnecessary invasive methods. In the present study, it was shown that the HALP score, which is a non-invasive, easily accessible, and easily calculated index, can distinguish between benign and malignant causes in patients with EBO with a statistical significance. We found that a cut-off value of 21.25 can be used for this distinction. According to this result, we think that the HALP score will provide important benefits such as guiding clinicians in determining which patients with EBO require invasive methods, and also protecting patients from the risks of complications that may develop because of unnecessary invasive methods.

Clinical characteristics, laboratory tests, and noninvasive imaging tools make up the initial evaluation parameters of patients with EBO, followed by invasive advanced endoscopic techniques such as ERCP and EUS[35]. Accurate diagnosis of EBOs based on imaging alone is often difficult because there is a wide variety of benign and malignant causes. It is already known that the availability of reliable predictive biomarkers that will contribute to the early diagnosis of malignant diseases will contribute positively to the prognosis of cancer. In the literature was shown that some laboratory parameters can be guiding in differentiating biliary obstruction types.

Kurt et al[36] examined 120 patients who underwent ERCP with the clinical manifestation of intrahepatic and extrahepatic cholestasis and found that low-density lipoprotein cholesterol (LDL-C) and triglyceride were significantly higher and high-density lipoprotein cholesterol (HDL-C) levels were lower in the malignant group, concluding that serum lipid profile could be used as an auxiliary marker to identify malignant causes of obstructive jaundice. It was shown in a recent study[10] that the ratio of serum carbohydrate antigen 19-9 (CA19-9) to total bilirubin (more strongly), CA19-9, and total bilirubin can distinguish between benign and malignant causes in patients with obstructive jaundice. Also, it was shown

in another prospective study[37] that evaluated the diagnostic accuracy of laboratory parameters in distinguishing benign and malignant causes of hilar biliary obstruction that patients with serum total bilirubin level >8.4 mg/dL and CA19-9 level >100 U/mL were more likely to have a malignant etiology. The finding of higher total bilirubin in malignant patients is parallel with the result of the present study. Although in the literature was shown that some laboratory parameters can be useful in distinguishing benign and malignant causes of biliary obstruction, there are also studies reporting that they cannot make this distinction. In a cross-sectional study, Ince et al[38] concluded that serum and biliary carcinoembryonic antigen (CEA), CA 19-9, vascular endothelial growth factor receptor-3 (VEGFR-3), and total antioxidant capacity (TAC) tests could not be useful in differentiating malignant and benign biliary obstructions. In another study[32] conducted in 2018, it was determined that complete blood count parameters such as red blood cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), NLR, and PLR did not have significant roles in differentiating the etiologies of extrahepatic cholestasis. In the present study, it was shown that the HALP score can distinguish between benign and malignant causes in patients with EBO at a statistically significant level.

Having reliable predictive parameters that every clinician can easily make use of and calculate during the initial clinical evaluation of patients with obstructive jaundice may bring significant benefits, which include guiding clinicians working in primary healthcare services to direct patients to relevant units, provide early diagnosis and treatment for patients with malignant etiology, decide which patients need advanced and invasive examinations, and decrease medical costs because of unnecessary examinations. Also, we think that the results of the present study may guide other researchers to find reliable new biomarkers that can accurately distinguish benign and malignant causes.

The strength of the present study was that it was conducted with a sufficient number of patients. However, the study also had some limitations. The first limitation of this study was that it had a retrospective design. Also, some patients' data could not be included in the study, and the study was conducted based on the data from one single center. Larger, multicenter, and prospective studies are needed to confirm the findings of the present study.

Conclusions

The present study showed that low HALP scores can distinguish malignant causes in patients with EBO. With this characteristic, we think that the HALP scores will increase the diagnostic accuracy of noninvasive radiological examinations, enable the early detection of malignant causes and initiation of early treatment in patients with EBO, and make positive contributions to cancer prognosis. We believe that it will prevent unnecessary invasive procedures by guiding clinicians in deciding which patients should undergo such procedures, and protect patients from unnecessary radiation exposure and the risks of complications, which may develop in this regard. The HALP score, which is a low-cost index that can be easily calculated with simple tests, especially for clinicians working in centers that do not have advanced radiological imaging methods, can be a useful biomarker that can be used to predict malignant causes when evaluated together with demographic and clinical characteristics in patients with EBO. We recommend calculating the HALP score for patients with EBO who present with obstructive jaundice, performing rapid further investigations of patients with low HALP scores, and a more careful evaluation for malignancy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was approved by the Hitit University Non-Interventional Research Ethics Committee (No: 2022-09).

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Informed Consent

Not applicable.

Authors' Contributions

Eskin F: Project development, research design, manuscript reviewing, writing, editing and revising. Köseoğlu H: Research design, data collection, interpretation of data, writing, editi ng and revising. Düzenli T: Data collection, interpretation of data, editing and revising. Özden M: Research design, data collection, editing and revising. Bebek B: Research design, data collection, editing and revising. Kaya M: Data collection, manuscript reviewing, editing and revising. Sezikli M: Research design, data collection, interpretation of data, editing and revising. All authors approved the final version of the study. Data availability statement: The authors indicate that the data are available upon request.

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