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Can HALP (Hemoglobin, albumin, lymphocyte, and platelet) score distinguish malignant and benign causes of extrahepatic cholestasis in patients with extrahepatic bile duct obstruction?

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ABSTRACT

OBJECTIVE: Cholestatic diseases are common and classified as benign or malignant based on their etiology. HALP is a unique nutritional immune marker that combines indicators of nutritional status, including hemoglobin and albumin, with immune function markers like lymphocyte and platelet counts. We investigated the HALP score's ability to differentiate between benign and malignant causes in extrahepatic cholestasis patients.

METHODS: This research was designed as cross-sectional and retrospective. Between 1 January 2020–1 January 2022, patients diagnosed with extrahepatic cholestasis were included. The diagnoses were confirmed using non-invasive imaging methods, ERCP (endoscopic retrograde cholangiopancreatography), and tissue biopsy results. Based on the type of extrahepatic biliary obstruction, either benign or malignant, the patients were divided into two groups. The HALP score was calculated by multiplying the patient's albumin (g/L), hemoglobin (g/L), and lymphocyte count (/L) and dividing by the platelet count (/L).

RESULTS: In 121 of 216 patients, extrahepatic cholestasis was caused by benign factors, mostly choledocholithiasis, while malignant causes, predominantly pancreatic head cancer, were responsible for extrahepatic cholestasis in 95 patients. The malignant cholestasis group had significantly higher bilirubin levels ($p<0.001$), lower hemoglobin levels ($p=0.005$), lower albumin levels ($p<0.001$), higher lymphocyte counts ($p<0.001$), and higher platelet levels ($p=0.001$) compared to the benign cholestasis group. There was no considerable difference in the HALP score between the two groups, as indicated by a p-value of 0.741.

CONCLUSION: The HALP score could not distinguish between benign and malignant causes of extrahepatic cholestasis.

Keywords: Albumin; extrahepatic cholestasis; HALP score; hemoglobin; lymphocytes; platelets.

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Cholestatic diseases affect bile flow and can be categorized as intrahepatic or extrahepatic. They can also be classified as benign or malignant based on their etiology and are associated with significant morbidity and mortality [1]. Benign extrahepatic cholestasis may result from choledocholithiasis and benign biliary strictures, whereas periampullary tumors predominantly lead to malignant biliary obstruction [2].

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Nutritional status and systemic inflammation have significant roles in the onset and progression of various cancers [3–5]. In this regard, it has been established that several indicators, including serum albumin, hemoglobin, lymphocytes, neutrophils, and platelets, which are readily measurable in clinical practice, are associated with different types of cancer and prognoses [4, 6]. It has been argued that using the HALP score, a composite index that combines hemoglobin, albumin, lymphocyte, and platelet levels, may offer a more accurate prognosis for patients with different types of cancer [6–9]. Moreover, the HALP score has been used to discriminate between benign and malignant cancers [10]. It has also been shown to help distinguish between benign and malignant in acute mechanical colonic obstructions [11] and colonic neoplasms [12]. However, just one study has evaluated the HALP score's ability to differentiate benign obstructive cholestasis from malignancy [13]. Therefore, we investigated the HALP score's ability to distinguish between benign and malignant causes in extrahepatic cholestasis patients.

Highlight key points

- The only study evaluating the ability of the HALP score to distinguish benign obstructive cholestasis from malignancy; the HALP score was significantly lower in the malignant extrahepatic cholestasis group.
- The HALP score components differed significantly between benign and malignant causes of extrahepatic cholestasis.
- The calculated HALP score was similar between benign and malignant causes of extrahepatic cholestasis.

Table 1. Etiologies of extrahepatic cholestasis of patients

	%		%
Benign group (n=121)	56	Choledocholithiasis n=118	54.6
		Benign stenoses	1.4
Malign group (n=95)	44	Pancreatic head cancer	19.4
		Klatskin tumor	5.1
		Distal cholangiocarcinoma	12.5
		Ampullary tumor	6.9

MATERIALS AND METHODS

This research was designed as retrospective and cross-sectional. Between 1 January 2020 and 1 January 2022, patients older than 18 diagnosed with extrahepatic cholestasis in the gastroenterology clinic were enrolled in the study. Based on the type of extrahepatic biliary obstruction, either benign or malignant, the patients were divided into two groups. The diagnoses were confirmed using non-invasive imaging methods, endoscopic retrograde cholangiopancreatography (ERCP), and tissue biopsy results. Patients with intrahepatic cholestatic disease, malignancy other than the periampullary tumor, chronic liver disease, chronic kidney failure, cerebrovascular disease, chronic heart failure, palliative care patients, pregnant women, those who smoke and alcohol and those with insufficient file information were excluded from the study. Initial laboratory parameters at diagnosis were recorded. The HALP score was calculated by multiplying the patient's albumin (g/L), hemoglobin (g/L), and lymphocyte count (/L) and dividing by the platelet count (/L).

The Zonguldak Bulent Ecevit University Non-Interventional Clinical Research Ethics Committee approved this study (date: 21.09.2022, number: 2022/16).

The statistical analysis was conducted with SPSS 22.0 software. Shapiro-Wilk and Kolmogorov-Smirnov tests were performed on the data to verify that it was normally distributed. For normally distributed data, the Student t-test was employed, and for non-normally distributed data, the Mann-Whitney U test was used. To compare differences among categorical variables, the Chi-square test was performed. A significance level of 0.05 was utilized as the threshold to determine statistical significance.

RESULTS

In 121 out of 216 patients, the cause of extrahepatic cholestasis was benign, primarily due to choledocholithiasis. Malignant causes, mainly pancreatic head cancer, were found to cause extrahepatic cholestasis in 95 patients (Table 1).

There was no noticeable distinction in gender or comorbidity among both groups, but the patient group with malignant extrahepatic cholestasis was older ($p<0.001$). The group diagnosed with malignant cholestasis had a significantly higher bilirubin level ($p<0.001$). In this group, the hemoglobin level was notably lower ($p=0.005$), the albumin level was significantly lower ($p<0.001$), the lymphocyte count was significantly higher ($p<0.001$), and the platelet level was considerably higher ($p=0.001$). There was no considerable difference in the HALP score between the two groups, as indicated by a p-value of 0.741 (Table 2).

TABLE 2. Demographic and laboratory parameters of patients with benign and malignant extrahepatic cholestasis

	Benign group	Malign group	p
Gender, (%)			0.451
Male (n=52)	43	37.9	
Female (n=69)	57	62.1	
Comorbidity, (%)			
DM	21.5	27.4	0.316
PD	8.3	9.5	0.755
CVD	4.1	3.2	0.705
CAD	6.6	11.6	0.201
Age, Mean±SD	65.4±18.2	71.6±13.6	<0.001
Hemoglobin (gr/dl), Mean±SD	12.3±1.6	11.3±1.9	**0.005**
Albumin (gr/dl), Median (IQR)	3.7 (3.2–4)	3.3 (2.7–3.7)	<**0.001**
Platelet count (10^3/ml), Median (IQR)	195 (143–271)	231 (183–298)	**0.001**
Lymphocyte count (mcl), Median (IQR)	1000 (600–1600)	1400 (1000–2600)	<**0.001**
Blood urea nitrogen (mg/dl), Median (IQR)	32 (22–45)	36 (26–50)	0.209
Creatinine (mg/dl), Median (IQR)	0.9 (0.7–1.2)	0.8 (0.7–1)	0.379
Alanine transaminase (U/L), Median (IQR)	145 (80–286)	118 (69–177)	0.046
Aspartate transaminase (U/L), Median (IQR)	107 (62–174)	101 (63–169)	0.824
Total bilirubin (mg/dL), Median (IQR)	5.43 (4.28–7.32)	9.32 (5.61–15.85)	<0.001
Direct bilirubin (mg/dL), Median (IQR)	4.57 (3.49–6.15)	7.28 (4.52–12.69)	<0.001
Gamma-glutamyltransferase (U/L), Median (IQR)	402 (237–637)	440 (229–789)	0.325
Alkaline phosphatase (U/L), Median (IQR)	285 (189–433)	404 (296–649)	<0.001
HALP score, Median (IQR)	23.49 (14.4–36.3)	25.42 (14.94–39.45)	0.741

SD: Standard deviation; IQR: Interquartile range; HALP: Hemoglobin, albumin, lymphocyte, and platelet; DM: Diabetes mellitus; PD: Pulmonary disease; CVD: Cerebrovascular disease; CAD: Coronary artery disease.

DISCUSSION

The "HALP" score has recently become a new predictive biomarker for various clinical outcomes in neoplasms [9]. The present study evaluated whether the HALP score can differentiate between benign and malignant causes in patients with extrahepatic cholestasis. Although the HALP score components differed significantly, the calculated HALP score was similar between the two groups. In the only recent study published on this subject, the HALP score was considerably lower in the malignant extrahepatic cholestasis group. However, in that study, the number of patients in the benign group was almost six times that of the malignant group [13]. The patient number in both groups was approximately equal in the present study. Another reason for the similarity in HALP scores between the two groups in our study may be attributed to the surprisingly elevated lymphocyte count that was used in the calculation of the HALP score for the malignant group. It may also be associated with prolonged cholestasis in the malignant cohort, which more accurately represents the cholangitis clinical presentation. HALP is a unique nutritional immune marker that combines indicators of nutritional status, including hemoglobin and albumin, with immune function markers like lymphocyte and platelet counts [9]. It has been demonstrated that platelets play critical roles in cancer progression and inflammation [14, 15]. As expected, we observed that the platelet count was higher in our malignant cholestasis group than in the benign group. Lymphocytes are crucial in controlling the immune system, which has several mechanisms to defend against cancer. A low lymphocyte count in cancer patients indicates a poor prognosis [16]. Surprisingly, our study found a higher lymphocyte count in malignant cholestatic patients, possibly due to a septic component such as cholangitis. Individuals in the malignant cholestatic category tended to experience more severe and prolonged cholestasis, potentially due to a higher incidence of biliary sepsis in this patient group.

The patient's dietary status and metabolic needs affect their albumin levels, which are linked to inflammation and high nutritional risk [17]. Albumin correlates negatively with C-reactive protein and leukocyte levels during inflammation while positively correlating with platelet count [18]. Anemia and hypoalbuminemia resulting from malnutrition in cancer patients accompany cancer cachexia [19]. Anemia is a prevalent condition impacting cancer patients and can manifest in several forms [20]. In the present study, hemoglobin and albumin levels were also lower in the malignant cholestasis group than in the benign group. However, the HALP score could not differentiate between benign and malignant causes of extrahepatic cholestasis.

Accurate differential diagnosis is the most crucial step in patients with obstructive jaundice before treatment [21]. The etiology of extrahepatic cholestasis can be determined by various methods, including noninvasive imaging approaches, ERCP, endoscopic ultrasonography (EUS)-guided biopsies, or percutaneous transhepatic cholangiography (PTC). Despite using various techniques, gastroenterologists may still face diagnostic confusion [2, 21]. Tumor markers, including CA 19-9, contribute to the diagnosis and monitoring of cancer. However, they often cause false positives due to a lack of cell specificity [22].

There is insufficient research on using blood tests to distinguish between benign and malignant extrahepatic cholestasis. In a study by Morsy et al. [23], it was found that complete blood count parameters, such as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and red blood cell distribution width (RDW), did not significantly differentiate the etiologies of extrahepatic cholestasis. However, Beyazit et al. [24] demonstrated the usefulness of RDW in distinguishing benign and malignant causes of biliary obstruction. Biochemical parameters such as serum lipid profiles were also used to differentiate malignant and benign cholestasis [25]. Ince et al. [26] found that tests for serum and biliary total antioxidant capacity (TAC), vascular endothelial growth factor receptor-3 (VEGFR-3), CA 19-9, and carcinoembryonic antigen (CEA) were not helpful in distinguishing benign from malignant biliary obstructions. The association between HALP parameters and benign and malignant cholestasis requires further investigation.

This research has limitations due to its retrospective methodology and being conducted in a single center.

Conclusion

The HALP score could not distinguish between benign and malignant causes of extrahepatic cholestasis.

Ethics Committee Approval: The Zonguldak Bulent Ecevit University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 21.09.2022, number: 2022/16).

Authorship Contributions: Concept – ZGS; Design – ZGS, ID; Supervision – ZGS; Materials – ID, UC; Data collection and/or processing – UC, FS; Analysis and/or interpretation – FS; Literature review – ZGS; Writing – ZGS; Critical review – ZGS.

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