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Hemoglobin Albumin Lymphocyte Platelet Score and Prognostic Nutritional Index are Markers of Malignancy in Patients with Elevated Serum Bilirubin Levels

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Abstract

Aim: To explore diagnostic role of prognostic nutritional index (PNI) and hemoglobin-albumin-lymphocyte-platelet (HALP) score in patients with hyperbilirubinemia.

Methods: Patients with hyperbilirubinemia divided into malignant and benign groups according to the etiology. PNI and HALP score values of the groups were compared.

Results: Median PNI of the malignant group (38.2 (20.2- 62.3)) was significantly lower than that of the benign group (42 (24.6-78.6)), (p=0.01). HALP scores of the malignant and benign groups were 18.5 (2.1-95.8) and 24.9 (2.9-255), (p=0.03). Considering HALP score, PNI, age, serum triglyceride, HDL-cholesterol, LDL-cholesterol, fibrinogen, GGT, fasting glucose, folic acid, ferritin, total bilirubin and CRP, HALP score remain an independent predictor of malignancy (p=0.004, OR: 0.94, 95%CI: 0.91-0.98). Similarly, PNI was an independent risk factor for malignancy (a unit increase in PNI reduced the malignancy risk by 1% (p=0.003, OR: 0.99, 95%CI: 0.988-0.999)).

Conclusion: Findings of the present study indicate that both HALP and PNI serve as independent predictors of malignancy, even after adjustment for age, lipid profile, and systemic inflammatory and metabolic markers. Higher PNI and HALP levels were associated with a lower risk of malignancy, highlighting the importance of inflammatory and nutritional status during malignant process.

Keywords

Hemoglobin-albumin-lymphocyte-platelet score, Prognostic nutritional index, Malignancy, Hyperbilirubinemia

Article History

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1. Introduction

Hyperbilirubinemia refers to an abnormal elevation of bilirubin levels in the blood, a condition frequently observed in both neonatal and adult populations. Bilirubin is generated from the breakdown of heme in senescent red blood cells and must be taken up by the liver, conjugated, and excreted via the bile; dysfunction at any step of this pathway, such as impaired conjugation, reduced hepatic uptake, or obstructed excretion, can lead to its accumulation [1,2]. In adults, elevated bilirubin is often a biomarker of underlying hepatobiliary disease or systemic illness. For example, in patients with acute-on-chronic liver failure, higher levels of total or conjugated bilirubin have been independently associated with short-term mortality [3]. In critically ill septic patients, dynamic changes in bilirubin, especially total bilirubin exceeding certain thresholds, have been linked to worse long-term survival [4].

Beyond its role as a marker of disease, more recent research has highlighted physiological roles of bilirubin, including potent antioxidant, anti-inflammatory, and immunomodulatory effects [1]. These studies suggest that, under controlled conditions, bilirubin may have protective functions, a paradigm shift away from viewing it solely as a toxic byproduct. On the contrary, emerging evidence from epidemiological and genetic studies suggests a complex relationship between bilirubin metabolism and cancer risk, with both protective and potentially promotive effects depending on cancer type and context. Bilirubin, long considered a waste product of heme metabolism, is increasingly recognized for its anti-inflammatory and antioxidant properties, and these biochemical roles may influence carcinogenesis [5]. Several large cohort studies report inverse associations between circulating bilirubin levels and the risk of certain cancers. For instance, data from the UK Biobank (about 440000 participants) show that higher prediagnostic total bilirubin is linked with reduced risk of esophageal adenocarcinoma [6]. Similarly, in a Swedish population-based cohort, elevated total bilirubin was associated with lower pulmonary malignancy incidence [7]. Moreover, in a prospective study of low-income African American and European American individuals, higher bilirubin levels measured years before diagnosis correlated with a decreased risk of lung cancer, especially among former/never smokers [8]. On the other hand, the epidemiological picture is not uniformly protective. Research on colorectal cancer provided a nuanced view. A nested case–control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort found sex-specific associations; higher unconjugated bilirubin was positively correlated with CRC risk in males, while inversely correlated in females [9]. Genetic (Mendelian randomization) analyses further support this complexity: genetically raised bilirubin (via bilirubin-related SNPs) was linked to a modest increase in CRC risk in men [9]. Such findings are mirrored in another epidemiological study (KORA) that detected a positive trend in men and an inverse trend in women, though confidence intervals were wide [10]. These data suggest the association between malignancy and hyperbilirubinemia.

Recent studies reported the diagnostic and prognostic values of hemoglobin-albumin-lymphocyte-platelet (HALP) score and prognostic nutritional index (PNI) in various chronic and inflammatory conditions. PNI was recommended as a prognostic predictor in numerous disorders. For example, reduced PNI was reported by Karagoz et al, in 2025 [11]. Moreover, PNI has been linked to the inflammatory burden in type 2 diabetes mellitus, which is characterized by chronic low grade inflammation [12]. Similarly, reduced HALP score has been reported in diabetic kidney disease [13], and cancer [14].

In present study, we aimed to compare characteristics, laboratory data and PNI and HALP scores of the patients evaluated for hyperbilirubinemia.

2. Methods

Ethical approval was granted from Abant Izzet Baysal University Ethics Committee (approval date: 7 October, 2025; approval number: 2025/406) for present retrospective, observational work. The patients with total bilirubin levels above 3 md/dl whom presented to the Gastroenterology Clinic of Abant Izzet Baysal University Hospital between January 2022 and May 2025 were enrolled to the study. Pregnant subjects, patients with end stage renal disease, active infection and individuals with recent trauma or surgery history were excluded. Patients' demographics, complaints, and final jaundice etiologies were recorded from database of the clinic and files of the patients. Blood samples were drawn in the morning after an overnight fast, in accordance with standard institutional protocols, to minimize short-term metabolic variability. Age, gender, laboratory data including erythrocyte sedimentation rate (ESR), prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, fasting plasma glucose, serum total protein, serum albumin, serum globulin, C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), amylase, lipase, total, conjugated and unconjugated bilirubin, serum creatinine, estimated glomerular filtration rate (eGFR), serum uric acid, triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), serum iron, total iron binding capacity (TIBC), ferritin, vitamin B12, folate, blood leukocyte count (WBC), hematocrit (Htc), platelet count (PLT), hemoglobin (Hb), lymphocyte count (lym), and neutrophil count (neu) were filtered and recorded. PNI was calculated with the following formula: 10 × serum albumin (g/dl) + 0.005. × total lymphocyte count (mm^3). HALP score was calculated with the following formula: [hemoglobin (g/L) × albumin (g/L) × total lymphocyte count (/L)]/platelets (/L). Cases were divided into two groups according to the

hyperbilirubinemia etiology as malignant or benign. Data of the patients, including PNI and HALP scores were compared between study groups.

Table 1. Characteristics and laboratory data of malignant and benign group.

		Malignant group	Benign group	p
Gender	Men (n, (%))	25 (29.5%)	92 (58%)	0.85
	Women (n, (%))	17 (39.5%)	67 (42%)	
		Median (min.-max.)		
Age (years)		67 (35-91)	62 (18-95)	0.03
ESR (mm/h)		39 (4-103)	36 (1-122)	0.16
CRP (mg/L)		31 (1-222)	57 (0.1-271)	0.016
Coagulation markers				
PT (sec)		13.5 (11-28)	13.9 (10-37)	0.53
aPTT (sec)		29 (19-70	27 (11-89)	0.59
INR		1.19 (0.98-2.52)	1.24 (0.87-3.6)	0.06
Fibrinogen (mg/dL)		412 (115-759)	466 (115-853)	0.007
Serum biochemistry				
Fasting glucose (mg/dL)		114 (70-334)	111 (53-513)	0.027
Total protein (g/dL)		6.1 (3.8-7.9)	6.3 (3.7-8.1)	0.1
Serum albumin (g/dL)		3.3 (1.5-5.1)	3.6 (2.2-5.7)	0.036
Serum globulin (g/dL)		2.8 (1.4-5)	2.8 (1.5-4.7)	0.53
Amylase (U/L)		64 (8-464)	59 (17-2444)	0.34
Lipase (U/L)		39 (5-438)	40 (5-1752)	0.56
Uric acid (mg/dL)		4.5 (1.4-10.5)	5 (1.8-13.4)	0.15
Serum creatinine (mg/dL)		0.8 (0.4-5.2)	0.79 (0.4-5.7)	0.5
eGFR (mL/min/1.73m^2)		92 (11-124)	92 (4-147)	0.44
Liver markers				
ALT (U/L)		115 (40-1122)	168 (6-1478)	0.49
AST (U/L)		123 (28-633)	115 (10-2826)	0.31
ALP (U/L)		508 (155-1854)	191 (49-1226)	<0.001
GGT (U/L)		579 (69-2664)	308 (16-3198)	<0.001
LDH (U/L)		282 (153-1240)	304 (171-1795)	0.92
Conjugated bilirubin (mg/dL)		6.2 (1.7-14)	3.4 (0.3-12.5)	<0.001
Unconjugated bilirubin (mg/dL)		2.5 (0.4-6.2)	2.5 (0.6-10.2)	0.001
Total bilirubin (mg/dL)		8.8 (3-20.2)	5 (3-20.1)	<0.001
Serum Lipids				
Triglyceride (mg/dL)		154 (63-318)	113 (26-474)	<0.001
Total cholesterol (mg/dL)		236 (89-657)	170 (53-738)	<0.001
HDL cholesterol (mg/dL)		34 (13-101)	38 (9-78)	<0.001
LDL cholesterol (mg/dL)		171 (56-574)	109 (23-618)	<0.001
Anemia markers				
Serum iron (mcg/dL)		61 (7-207)	59 (6-264)	0.94
Total iron binding capacity (mcg/dL)		238 (88-397)	262 (139-427)	0.007
Ferritin (mcg/L)		390 (47-866)	241 (1.5-1745)	<0.001
Vitamin B12 (ng/L)		574 (174-1965)	515 (102-3235)	0.02
Folate (mcg/L)		7.2 (3.2-14.9)	6.1 (1.3-17.1)	0.006
Hemogram Indices				
WBC (k/mm^3)		7.6 (4.5-17.2)	7.9 (2.2-32.9)	0.99
Neu (k/mm^3)		5.4 (2.4-15.8)	5.8 (1.4-30.8)	0.96
Lym (k/mm^3)		1.1 (0.3-2.9)	1.1 (0.1-9.1)	0.85
PLT (k/mm^3)		202 (62-631)	207 (22-508)	0.48
PNI (%)		38.2 (20.2- 62.3)	42 (24.6-78.6)	0.01
HALP score (%)		18.5 (2.1-95.8)	24.9 (2.9-255)	0.03
		Mean ± SD		
Hb (g/dL)		11.7 ± 2	12.5 ± 2.2	0.02
Htc (%)		34.1 ± 5.8	37.1 ± 5.9	0.004

Statistical software (SPSS 16.0 for Windows, IBM, Armonk, NY, USA) was used in statistical analyses. Homogeneity of the study variables was assessed by Kolmogorov-Smirnov test. The variables with normal distribution were

expressed as mean (SD) and compared with independent samples t test. Mann Whitney U test was used in comparison of the variables that not fit into normal distribution and those variables were expressed as median (min-max). Categorical variables were expressed as numbers and percentages and compared between groups by chi-square test. Correlation between study variables was conducted with Pearson's correlation analysis test. Receiver operative characteristics (ROC) curve analysis was conducted to find out sensitivity and specificity of HALP and PNI values in detecting malignancy. Binary logistic regression analysis was utilized to reveal whether PNI and HALP score were independent risk factor for cancer in patients with hyperbilirubinemia. Statistics were considered significant when p values were lower than 0.05.

3. Results

Total 201 subjects were enrolled. Of those, 42 were in malignant and 159 in benign group. Median age of the participants in malignant and benign groups were 67 (35-91) years and 62 (18-95) years, respectively (p=0.03). 25 (59.5%) of malignant group and 92 (58%) of the malignant group were men (p=0.85). Characteristics and laboratory findings of the study groups were summarized in table 1.

Median PNI of the malignant group (38.2 (20.2- 62.3)) was significantly lower than that of the benign group (42 (24.6-78.6)), (p=0.01). HALP scores of the malignant and benign groups were 18.5 (2.1-95.8) and 24.9 (2.9-255), (p=0.03).

There were significant correlations between PNI and HDL cholesterol (r=0.25, p<0.001), Hb (r=0.39, p<0.001), Htc (r=0.42, p<0.001) and unconjugated bilirubin (r=0.22, p=0.002). Moreover, PNI was inversely correlated with age (r=-0.25, p<0.001), conjugated bilirubin (r=-0.25, p<0.001), total bilirubin (r=-0.25, p<0.001), and ferritin (r=-0.25, p<0.001). There were significant positive correlations between HALP score and PNI (r=0.58, p<0.001), unconjugated bilirubin (r=0.23, p=0.001), Hb (r=0.35, p<0.001) and Htc (r=0.32, p<0.001). In addition, HALP score was inversely correlated with age (r=-0.26, p<0.001), fibrinogen (r=-0.31, p<0.001) and conjugated bilirubin (r=-0.20, p<0.001).

In ROC analysis, the sensitivity and specificity of HALP score (when lower than 19.4) in detecting malignant cases were 65% and 55%, respectively (AUC: 0.61, p=0.03, 95%CI: 0.51-0.71). Moreover, the sensitivity and specificity of PNI value (when lower than 39.2) in detecting malignancy in the study cohort were 64% and 55%, respectively (AUC: 0.63, p=0.01, 95%CI: 0.53-0.73). Figure 1 shows the ROC curves of HALP score and PNI in detecting malignancy.

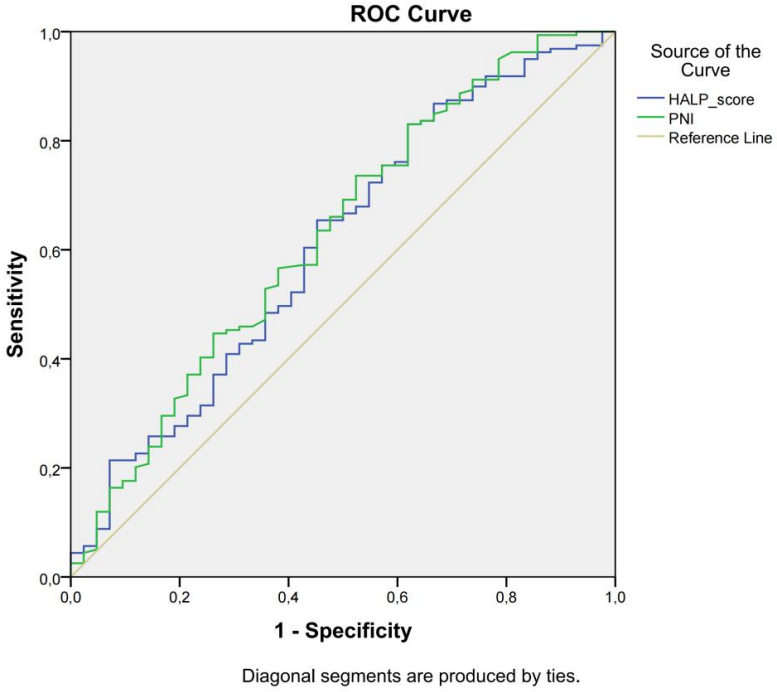

Figure 1. ROC curves of PNI and HALP score in diagnosis of malignant cases.

Footnote of figure 1:

For HALP score; AUC: 0.61, p=0.03, 95% CI: 0.51-0.71.

For PNI; AUC: 0.63, p=0.01, 95%CI: 0.53-0.73.

In binary logistic regression analysis, considering HALP score, PNI, age, serum triglyceride, fibrinogen, fasting glucose, and CRP, HALP score remain an independent predictor of malignancy (p=0.004, OR: 0.94, 95%CI: 0.91-0.98). Similarly, PNI was an independent risk factor for malignancy with a unit increase in PNI reduced the cancer odds by 1% (p=0.003, OR: 0.99, 95%CI: 0.988-0.999). Results of regression analysis were presented in table 2.

Table 2. Results of binary logistic regression analysis.

	HALP	PNI
P	0.004	0.003
OR	0.94	0.99
95% CI	0.91-0.98	0.988-0.999

Multivariate model included HALP score, PNI, age, serum triglyceride, fibrinogen, fasting glucose, and CRP.

4. Discussion

This study showed that PNI and HALPs cores were significantly reduced in malignant cases presented with hyperbilirubinemia, compared to those with benign hyperbilirubinemia cases. We also demonstrated significant correlations between PNI and HDL, hemoglobin, hematocrit, and unconjugated bilirubin; inversely with age, conjugated/total bilirubin and ferritin levels. Furthermore, study results revealed that HALP score was correlated positively with PNI, unconjugated bilirubin, Hb and Htc while inversely correlated with age, fibrinogen and conjugated bilirubin. Diagnostic performance was modest for both HALP score and PNI. Finally, in multivariable logistic regression including many labs and demographics, PNI and HALP score remained independent predictors of malignancy.

PNI is a well-recognized prognostic/nutritional predictor in many cancers. Meta-analyses and multiple tumor-specific studies report that lower pre-treatment PNI is associated with worse outcomes (OS/DFS) across gastrointestinal and other cancers [15,16]. Our finding that malignant cases have a lower PNI is consistent with that literature (PNI reflects albumin + lymphocyte-related immune/nutritional status).

HALP score has growing evidence as a prognostic marker (not primarily a diagnostic test). Several recent studies and systematic reviews show low HALP associates with poorer survival, worse response or progression across gastric, colorectal, pancreatic, biliary and lung cancers [17]. Most HALP score work so far focused on prognosis/stratification, and reported cut-offs vary substantially between cohorts and cancer types. That matches with our finding that malignant cases had lower HALP, however, the literature cautions against applying a universal HALP diagnostic cut-off.

Diagnostic discrimination of HALP score and PNI (AUC: 0.61-0.63) is modest and expected. Published studies generally show HALP score and PNI are prognostic rather than highly accurate diagnostic biomarkers for distinguishing benign vs malignant disease. AUCs in the low-to-moderate range are common when nutritional/inflammatory scores are tested for diagnosis rather than prognosis [15,17]. These indices capture host status (nutrition/inflammation) which overlaps between benign inflammatory conditions and cancer. The AUCs of HALP score and PNI in our work show modest discriminatory power and therefore are more useful as part of a composite model than alone.

The correlation of HALP score and PNI with bilirubin, HDL-cholesterol and hematologic indices have literature support but are complex. The inverse and non-linear relationships between serum bilirubin and various cancer risks and outcomes have been reported. Mild increases in bilirubin can be protective (antioxidant) for some cancers while associations differ by cancer type and bilirubin fraction (direct vs indirect) [5,18]. That fits with our mixed correlations (unconjugated bilirubin positively correlated with PNI/HALP; conjugated/total bilirubin inversely correlated).

HDL has been linked in some studies to cancer prognosis and risk (direction varies by cancer type). The positive correlation of PNI with HDL is plausible (better nutrition and metabolic reserve cause higher HDL), but causal direction is unclear [19]. Similarly, we showed reduced HDL cholesterol levels in malignant patients compared to the benign cases.

PNI and HALP score integrate nutrition, anemia and systemic inflammation and immune competence. Lower values in malignant patients plausibly reflect cancer-associated cachexia, anemia of chronic disease, and systemic inflammation. Those mechanisms are well described in the literature [15,17]. Cancer is associated with chronic, low grade inflammation. Conditions characterized with chronic inflammation usually cause a reduction in total lymphocyte count [13]. This reduction may trigger decrement in PNI value in malignant cases in the present report. Albumin is a negative marker of inflammation ad it reduces in inflammatory states [20]. On the other hand, malignancy is sometimes associated with increased platelet values [21]. Reduced albumin and lymphocyte and increased platelet count may cause a reduction in HALP score in malignant cases with hyperbilirubinemia in the present study.

In our multivariable model, both HALP and PNI remained independent predictors of malignancy after adjustment for age, lipids, inflammatory markers and metabolic variables. Each one-unit increase in HALP was associated with a small reduction in odds of malignancy, and each one-unit increase in PNI decreased malignancy odds by 3%. These findings are concordant with an expanding body of literature that conceptualized HALP and PNI as composite indices reflecting the intersection of nutritional status, anemia, lymphocyte-mediated immune competence and systemic inflammation; pathophysiologic domains known to be altered in cancer [22]. The prognostic and risk-stratifying value of PNI is well documented in meta-analyses and tumor-specific series, where lower PNI is consistently associated with worse survival and adverse clinical outcomes [23].

Similarly, HALP score, which combines hemoglobin, albumin, lymphocyte and platelet measurements, has been repeatedly reported as a robust prognostic marker across multiple malignancies (including gastric, colorectal, biliary and lung cancers), with low HALP linked to poorer response to therapy, advanced stage, and shorter survival in several cohorts [24]. These studies support the biological plausibility of our finding that higher HALP (better integrated hematologic/nutritional status) is associated with lower odds of malignancy [25]. We reported reduced HALP score in patients with malignancy compare to those with benign etiology of hyperbilirubinemia, which is in line with current literature knowledge.

Two points deserve emphasis when interpreting the magnitude and clinical meaning of our regression coefficients. First, the per-unit ORs are small because HALP and PNI are continuous scores with broad ranges; therefore, clinically meaningful effects are better appreciated over larger, clinically plausible changes (for example, a 10-point change in PNI or HALP would produce a substantially larger change in odds than a single unit). Second, although both indices remained statistically significant in adjusted models, their discrimination as single diagnostic tests is limited and they are most useful as adjuncts for risk-stratification or prognosis rather than as stand-alone diagnostic classifiers [26].

Mechanistically, the literature shows that low albumin reflects systemic inflammation and altered hepatic protein synthesis, lymphopenia signals impaired adaptive immune surveillance, anemia mirrors chronic disease or marrow involvement, and thrombocytosis often reflects an acute-phase/tumor-driven inflammatory response. Together producing the signal that HALP and PNI capture. That these composite indices remained predictive even after adjusting for CRP, fibrinogen and ferritin in our model suggests they integrate overlapping but distinct aspects of host–tumor biology and may capture subclinical immuno-nutritional compromise not fully explained by single inflammatory biomarkers [24,27].

Consistent with the, we recommend treating HALP and PNI as low-cost, widely available adjunct markers to inform clinical suspicion and triage (for example, to prioritize further imaging or biomarker testing), while emphasizing the need for external validation. Future work should report effect sizes over clinically meaningful score intervals (such as per 5–10 point changes), evaluate disease-specific thresholds, and test whether models that combine HALP score and PNI with imaging or tumor markers materially improve diagnostic accuracy in prospective cohorts [23]. Li et al studied HALP score in patients with non-small cell lung cancer in a 7024 patients cohort in their meta-analysis and reported that patients with decreased HALP score had poor overall survival compared to the subjects with higher HALP score [28]. They also found that HALP score was correlated with age [28]. In another work, authors studied HALP score in subjects with metastatic renal cell cancer and found that HALP score was closely associated with the prognosis of the participants [29]. Similarly, Demir et al researched the prognostic capacity of HALP score in patients with pancreas cancer in 227 subjects and reported that overall survival of the subjects with low HALP score were significantly lower than the survival of the pancreas cancer patients with higher HALP score [30]. Jiang et al studied HALP score in breast cancer in a propensity score-matching study and revealed that HALP score could be an independent marker of overall and progression free survival of the patients with breast cancer [31]. The role of HALP score in prostate cancer and benign prostate hyperplasia has been also studied. In contrast, in an analysis of data of 155 patients with benign prostatic hyperplasia and 70 patients with prostate cancer, authors found no statistical difference in HALP scores of the patients with benign prostatic hyperplasia and prostate cancer [32]. In addition, authors studied the HALP scores of the women with early breast cancer and reported that HALP score was an independent prognostic predictor of the patients with early breast cancer [33]. Accordingly, Wang et al studied the HALP score of 626 women with endometrial cancer and suggested that HALP score was a useful marker of lymph node metastasis, disease recurrence and mortality [34]. In terms of PNI, it is also associated with cancer. A study on 776 breast cancer patients analyzed the role of PNI and numerous markers and reported that PNI had the highest predictive value in the prognosis of the patients [35]. In 2022, Ding et al compared the prognostic roles of systemic inflammatory index and PNI in patients with gastric cancer and reported that PNI score significantly predicted chemosensitivity of locally advanced gastric cancer patients after immunotherapy combined with chemotherapy [36]. The role of PNI in gastrointestinal cancers has been studied in a recent meta-analysis, which suggested PNI as a reliable predictor of survival in those patients [37]. Moreover, preoperative PNI has been introduced as an independent prognostic factor that influence overall survival in patients with colorectal cancer [38]. Another meta-analysis of 4250 subjects studied the prognostic role of PNI in lung cancer and revealed that low PNI values were associated with poor survival outcome measures in the study cohort [39]. Furthermore, a study from Japan showed that PNI of the patients with oral cancer was correlated with survival of the patients [40]. Finally, Tan et al conducted a meta-analysis to find out the prognostic role of PNI in patients with ovarian cancer and reported that PNI could be a promising predictor of prognosis in women with ovarian cancer [41]. Our findings were compatible with these literature data.

Our work has several limitations to mention. First, study design was retrospective, so we only revealed simple associations not causations. Results of a multicenter work would be more generalizable. Second, this work was designed in a single center. Third, the sample size was small. Yet, our results indicating decreased HALP score and PNI in malignant cases with hyperbilirubinemia is clinically important.

In conclusion, our findings indicate that both HALP and PNI serve as independent predictors of malignancy, even after adjustment for age, lipid profile, and systemic inflammatory and metabolic markers. Higher PNI and HALP levels were linked to a reduced risk of malignancy, emphasizing the importance of nutritional and immunologic status in the

malignant process. While these indices alone demonstrate modest diagnostic performance, their independent predictive value suggests that HALP and PNI may be useful adjunct biomarkers for malignancy risk stratification. Because they are cost-effective, simple, and available in routine clinical practice, these scores may help guide clinical decision-making and identify patients who warrant further diagnostic evaluation.

Conflict of Interest

There is none.

Data Availability Statement

Anonymized data is available upon reasonable request.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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