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Prognostic Value of the Hemoglobin Albumin Lymphocyte Platelet Score in Extrapulmonary Neuroendocrine Carcinomas

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ABSTRACT

Aim: Extrapulmonary neuroendocrine carcinomas (EPNECs) are rare and aggressive malignancies characterized by poor prognosis. The hemoglobin, albumin, lymphocyte, platelet (HALP) score is an immunonutritional index that has shown prognostic value in various cancers. However, its significance in EPNECs remains unclear.

Methods: This retrospective study included 48 patients with metastatic EPNECs treated at a single institution between 2018 and 2023. Baseline HALP scores were calculated from laboratory values obtained before systemic treatment. Patients were categorized into low (≤19.54) and high (>19.54) HALP groups based on receiver operating characteristic curve analysis. Associations between HALP score and survival outcomes, overall survival (OS) and progression-free survival (PFS), were assessed using Kaplan-Meier and Cox regression methods.

Results: The median OS was 7.8 months. Although the HALP score was not a statistically significant predictor of OS (p=0.072), patients with low HALP scores demonstrated a numerical trend toward shorter survival. Elevated lactate dehydrogenase (LDH) levels and absence of chemotherapy were significantly associated with poorer OS. Chemotherapy was confirmed as an independent prognostic factor in multivariate analysis (p=0.001). No significant association was found between HALP scores and PFS.

Conclusion: While the HALP score did not show statistically significant prognostic impact in this cohort, the observed trends suggest potential clinical relevance. Further prospective studies are needed to validate its utility in EPNEC and to explore whether immunonutritional factors may inform treatment decisions.

Keywords: Extrapulmonary neuroendocrine carcinomas, HALP score, inflammatory markers, predictive biomarkers

Introduction

Neuroendocrine carcinomas are a group of poorly differentiated, biologically aggressive malignancies believed to originate from neuroendocrine cells located in endocrine glands, within glandular structures, or scattered among epithelial tissues. These tumors can arise in various anatomical locations, with the lungs being the most common site.

When these carcinomas develop outside the pulmonary system, they are referred to as extrapulmonary neuroendocrine carcinomas (EPNECs), most frequently found in the gastroenteropancreatic tract, followed by the urinary and gynecological systems [1,2]. In certain cases, the primary tumor remains undetected despite extensive diagnostic workup, and such cases are categorized as unknown primary tumors.

EPNECs are known for their aggressive clinical course, often marked by early and extensive metastasis. Although a minority of patients with localized disease may achieve durable remission through intensive multimodal therapy, recurrence rates remain high, and the overall prognosis is generally poor, with five-year survival reported to be below 15% [3]. The hemoglobin, albumin, lymphocyte, platelet (HALP) score is a composite biomarker derived from routine hematological and biochemical parameters, and has emerged as a prognostic indicator in various malignancies.

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Anemia in cancer can be driven by chronic inflammation or iron deficiency related to blood loss and malnutrition. Hypoalbuminemia, similarly, often reflects poor nutritional and inflammatory status and has been linked to worse outcomes in several cancer types [4,5]. These alterations are also commonly seen in cancer cachexia, a multifactorial syndrome characterized by progressive skeletal muscle loss [6].

Lymphocytes play a key role in anti-tumor immunity, and lymphopenia has been associated with worse survival in studies evaluating ratios such as the platelet-to-lymphocyte ratio and the neutrophil-to-lymphocyte ratio [7,8].

On the other hand, platelets contribute to tumor progression by promoting angiogenesis through VEGF release and by shielding tumor cells from immune surveillance. Thrombocytosis, a marker of systemic inflammation, has been shown to correlate with poor prognosis in many cancers [9,10].

First introduced by Chen et al. [11] in gastric cancer, the HALP score is calculated using the formula:

[hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L)] / platelet count (/L), and integrates immune and nutritional markers to reflect systemic host status. Since then, its prognostic utility has been explored in various malignancies.

While several studies have reported the prognostic value of the HALP score in small cell lung cancer (SCLC) patients receiving first-line etoposide-based chemotherapy, there remains a lack of evidence regarding its role in EPNECs. Therefore, this study aims to investigate the prognostic significance of the HALP score in this rare and heterogeneous tumor group.

Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (1st Medical Research Scientific and Ethics Review Board) (decision no: TABED 1-24-777, date: 04.12.2024).

This retrospective cohort study included 48 adult patients diagnosed with EPNEC at Ankara Bilkent City Hospital between March 2018 and October 2024. Eligibility criteria comprised age ≥18 years, histopathological confirmation of neuroendocrine carcinoma, and presence of metastatic disease at the time of diagnosis. Patients were excluded if they had incomplete medical records, non-metastatic disease, pulmonary-origin NEC, or were younger than 18 years. Data collected for analysis included demographic variables (age and sex), clinical characteristics (Eastern Cooperative Oncology Group [ECOG] performance status), pathological features (histological subtype: small cell, large cell, or mixed type), primary tumor site (colorectal, pancreatic, gastric, or unknown origin), Ki-67 proliferation index, and laboratory parameters : hemoglobin, albumin, lymphocyte count, and platelet count. Additional variables included lactate dehydrogenase (LDH) levels and systemic treatment status, specifically whether patients received chemotherapy.

The HALP score, reflecting the patient's immune and nutritional status, was calculated using the following formula:

HALP = Hemoglobin (g/L) × Albumin (g/L) × Lymphocyte count (/L) ÷ Platelet count (/L)

Values used for this calculation were obtained from blood tests performed prior to the initiation of chemotherapy to ensure assessment of baseline conditions.

To determine the optimal HALP threshold for prognostic classification, a receiver operating characteristic (ROC) curve analysis was conducted. The analysis identified 19.54 as the cut-off value (area under curve: 0.676, sensitivity: 75%, specificity: 58.3%, p=0.07). Based on this threshold, patients were categorized into two groups: low HALP (≤19.54) and high HALP (>19.54). Similarly, LDH levels were classified as ≤246 IU/L or >246 IU/L, based on the upper limit of normal (ULN) in our institution. The Ki-67 index was dichotomized at the median value (85%) into ≤85% and >85%.

Endpoints

The primary endpoints were overall survival (OS), defined as the time from diagnosis to death from any cause, and progression-free survival (PFS), defined as the time from diagnosis to disease progression or death from any cause.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Group comparisons were performed using the chi-square or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. The optimal HALP cut-off value was determined by ROC analysis. Kaplan-Meier survival analysis was used to estimate OS and PFS, and survival differences between groups were evaluated using the Log-Rank Test. Univariate and multivariate analyses were conducted using Cox proportional hazards regression to identify independent prognostic factors. Results were reported as hazard ratios with corresponding 95% confidence intervals, and statistical significance was defined as a two-tailed p value <0.05.

Results

Patient Characteristics

A total of 48 patients diagnosed with EPNECs were enrolled in this study. The median age was 60 years, ranging from 20 to 83. Males comprised the majority of the cohort (77.1%, n=37). Most patients (87.5%, n=42) had an ECOG performance status of 2 or below. Regarding histological subtypes, small cell NEC was the predominant form (81.3%, n=39), followed by mixed NEC types (14.6%, n=7) and large cell NEC (4.2%, n=2). The most common primary tumor sites were colorectal (20.8%, n=10), unknown sites (20.8%, n=10), gastric (14.6%, n=7), and pancreas (12.5%, n=6). LDH levels were elevated (>246 IU/L) in 64.6% (n=31) of patients (Table 1).

HALP Groups and Baseline Characteristics

Patients were divided into low HALP (≤19.54, n=24) and high HALP (>19.54, n=24) groups. Comparison of baseline features revealed that elevated LDH levels were significantly more common in the low HALP group (83.3%) compared to the high HALP group (45.8%) (p=0.006). No statistically significant differences were detected between the two groups concerning age, sex, ECOG status, histological subtype, or Ki-67 proliferation index (Table 2).

Overall Survival (OS)

The median OS for the entire cohort was 7.8 months (range 0.09-10.48 months). Univariate analysis identified elevated LDH levels (≥246 IU/L) as significantly associated with decreased OS (p=0.023). Although the HALP score demonstrated a trend toward predicting OS, this association did not reach statistical significance (p=0.072). These results should therefore be interpreted with caution. (Figure 1).

Patients who received chemotherapy had significantly better OS than those who did not (p<0.001). Multivariate analysis identified chemotherapy as an independent prognostic factor for OS (p=0.001), while LDH levels approached statistical significance (p=0.082) (Table 3).

Table 1. Clinical, pathological and laboratory characteristics of the patients

Variables	n (%)
Age, years, median	60 (20-83)
<60 years	22 (45.8%)
≥60 years	26 (54.2%)
Sex	
Male	37 (77.1%)
Female	11 (22.9%)
ECOG performance status	
0	2 (4.2%)
1	25 (52.1%)
2	15 (31.3%)
3	5 (10.4%)
4	1 (2.1%)
Histological type	
Small cell NEC	39 (81.3%)
Large cell NEC	2 (4.2%)
Mix (NEC + other component)	7 (14.6%)
Primary tumour site	
Colorectal	10 (20.8%)
Unknown	10 (20.8%)
Pancreas	6 (12.5%)
Gastric	7 (14.6%)
Other	15 (31.3%)
Ki-67	
≤85%	18 (43.9%)
>85%	23 (56.1%)
LDH	
≤246	17 (35.4%)
>246	31 (64.6%)

ECOG: Eastern Cooperative Oncology Group, NEC: Neuroendocrine carcinoma, LDH: Lactate dehydrogenase

Progression-Free Survival (PFS)

The median PFS for the cohort was not reported in detail due to the limited number of progression events. Univariate analysis showed that receiving chemotherapy was the only factor significantly associated with longer PFS (p<0.001). Consequently, multivariate analysis was not performed for PFS (Table 4, Figure 2).

Response Rates

The overall response rate did not show significant associations with any clinical or laboratory variables, including HALP scores. However, when considering the disease control rate (DCR), patients with mixed histological subtypes demonstrated a significantly higher DCR compared to other subtypes (p=0.028). No other variables were found to be significantly associated with DCR.

Discussion

This study aimed to evaluate the prognostic significance of the HALP score in patients with EPNECs, a rare and biologically aggressive tumor group. Although our findings did not demonstrate statistically significant associations, the observed trends suggest that lower HALP scores may be linked to inferior clinical outcomes. This aligns with existing literature highlighting the prognostic value of immunonutritional markers in oncology.

The prognostic utility of the HALP score has been extensively studied in various cancers. For instance, Shen et al. [12] demonstrated that a low HALP score before first-line treatment with etoposide was independently associated with shorter PFS in patients with SCLC, who are 65 years or older, a pulmonary NEC subtype. Similarly, Yang et al. [13] identified the HALP score as a significant prognostic factor for OS in SCLC patients undergoing chemotherapy, highlighting its role as a reliable biomarker in this patient population.

In comparison to SCLC, studies focusing on HALP scores in EPNECs are scarce. Our findings contribute to filling this gap by exploring the potential role of HALP scores in a distinct,

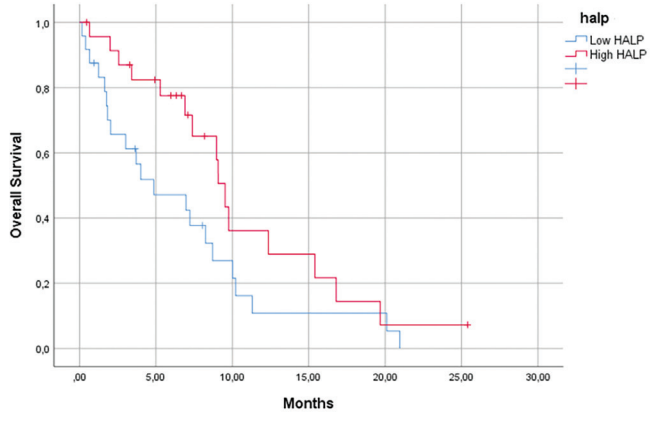

Figure 1. The Kaplan-Meier curves of overall survival for HALP

HALP: Hemoglobin, albumin,lymphocyte, platelet

non-pulmonary NEC cohort. While SCLC and EPNECs share significant biological characteristics, including their aggressive clinical course, their prognosis and therapeutic strategies differ in important ways. Both malignancies are typically treated with etoposide and platinum-based chemotherapy regimens, and demonstrate rapid progression if left untreated. However, subtle differences in biological behavior and treatment outcomes between the two entities warrant further investigation [2,14,15].

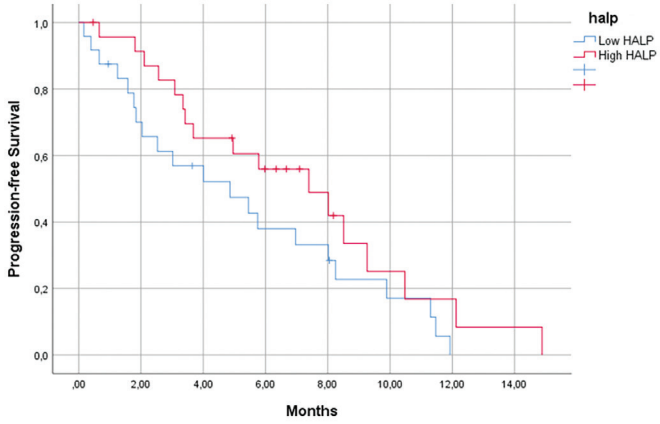

Figure 2. The Kaplan-Meier curves of progression free survival for HALP

HALP: Hemoglobin, albumin,lymphocyte, platelet

Table 2. The features of HALP groups

Variables	Low HALP (n: 24)	High HALP (n: 24)	p value
Age, years, median			
≤60 years	8 (33.3%)	14 (58.3%)	0.081
>60 years	16 (66.7%)	10 (41.7%)	
Sex			
Male	17 (70.8%)	20 (83.3%)	0.300
Female	7 (29.2%)	4 (16.7%)	
ECOG performance status			
0-1	11 (45.8%)	16 (66.7%)	0.130
2-4	13 (54.2%)	8 (33.3%)	
Histological type			
Small cell NEC	21 (87.5%)	18 (75.0%)	0.144
Large cell NEC	1 (4.2%)	1 (4.2%)	
Mix (NEC + other component)	2 (8.3%)	5 (20.8%)	
Ki-67			
≤85%	7 (35.0%)	11 (52.4%)	0.261
>85%	13 (65.0%)	10 (47.6%)	
LDH			
<246	4 (16.7%)	13 (54.2%)	**0.006**
≥246	20 (83.3%)	11 (45.8%)	
Chemotherapy			
Yes	21 (87.5%)	2 (8.3%)	0.637
No	3 (12.5%)	22 (91.7%)	

HALP: Hemoglobin, Albumin, Lymphocyte, Platelet, ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, NEC: Neuroendocrine carcinomas

In our study, the median OS of patients with EPNEC was notably shorter compared to reported outcomes in SCLC, highlighting the aggressive nature of this disease. Consistent with the literature, EPNECs are reported to have a worse prognosis and a poorer response to chemotherapy than SCLC. Tumor localization patterns in our cohort were also consistent with those reported in the literature, with the majority of cases originating in the gastrointestinal tract, followed by unknown primary sites [2]. These findings align with previously documented trends, providing a solid basis for investigating the prognostic role of HALP scores in EPNEC patients. Further research is needed to better understand the interplay of these clinical parameters and their impact on patient outcomes.

Beyond NEC, the HALP score has shown consistent prognostic value across a range of malignancies. A recent meta-analysis by Farag et al. [16] reviewed the prognostic ability of HALP scores in different cancer types and emphasized its robust association with outcomes such as PFS and OS across various solid tumors. Another meta-analysis by Xu et al. [17] involving 13, 110 patients reinforced these findings, highlighting the HALP score's utility as a simple yet effective biomarker for cancer prognosis. These meta-analyses provide strong evidence for incorporating the HALP score into clinical practice, given its ability to reflect both inflammatory and nutritional states, which are critical determinants of cancer progression and treatment response.

Various studies have demonstrated the potential of the HALP score as an immunonutritional biomarker, showing its association with prognosis in a variety of cancers [16,17]. A low HALP score has been linked to poorer survival outcomes, suggesting that it may serve as a valuable prognostic indicator. However, the clinical applicability of the HALP score remains an area of active exploration. Specifically, while a lower HALP score is often indicative of worse prognosis, it raises the question of whether immunonutritional interventions could positively impact survival outcomes in these patients. Given the association between low HALP scores and poorer survival, incorporating routine nutritional and immunological assessments into clinical practice may help identify high-risk patients. Furthermore, targeted nutritional interventions, such as high-protein diets or supplementation with immune-modulating nutrients, could be explored as part of a comprehensive treatment strategy.

Although no significant differences were observed in our study between HALP groups and age or gender, the differences in cutoff values across studies may be related to variations in age-related factors, such as the decline in hemoglobin and albumin levels with age [18,19]. This can influence the prognostic value of the HALP score. Additionally, other variables such as gender, which may influence immune and inflammatory responses, could further affect the prognostic accuracy of the HALP score. Some studies have noted variations in baseline HALP scores between males and females. However, even when adjustments are made for sex, HALP has been shown to retain its prognostic significance. This suggests that while

gender-related differences in HALP scores may exist, they do not substantially impact their reliability as a biomarker [16].

The discrepancies in cutoff values may stem from variations in calculation methods, such as X-tile or other approaches, as well as differences in patient demographics and clinical parameters [20]. This highlights the critical need for standardization in HALP score calculations. Future studies should focus on how these variables impact the interpretation and utility of HALP scores across different cancer populations.

Although our study's findings did not reach statistical significance, which is likely because of the limited sample size, the numerical trend observed, aligns with these prior studies. The HALP score's numerical association with survival in EPNEC patients suggests that it may serve as a useful tool for risk stratification. Nevertheless, this numerical trend should be interpreted cautiously, particularly in light of the limited sample size. However, larger, prospective studies are needed to confirm these observations and establish definitive clinical guidelines.

Table 3. Prognostic factors of overall survival in patients

Univariate analysis	
Variables	**p value**
Age, ≤60 years vs >60 years	0.438
Sex, male vs female	0.411
ECOG performance status, 0-1 vs 2-4	0.287
Histological type, small cell NEC, large cell NEC vs mix (NEC + other component)	0.657
Ki-67, ≤85% vs >85%	0.966
LDH, <246 vs ≥246	**0.023**
HALP, high vs low	0.072
Chemotherapy, yes vs no	**<0.001**
Multivariate analysis	
Variables	**p value**
LDH, <246 vs ≥246	0.082
Chemotherapy, yes vs no	**0.001**

ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, NEC: Neuroendocrine carcinomas

Table 4. Prognostic factors of progression-free survival in patients

Univariate analysis	
Variables	**p value**
Age, ≤60 years vs >60 years	0.363
Sex, male vs female	0.402
ECOG performance status, 0-1 vs 2-4	0.089
Histological type, small cell NEC, large cell NEC vs mix (NEC + other component)	0.667
Ki-67, ≤85% vs >85%	0.826
LDH, <246 vs ≥246	0.247
HALP, high vs low	0.124
Chemotherapy, yes vs no	**<0.001**

ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, NEC: Neuroendocrine carcinomas

Study Limitations

The retrospective nature of our study and the relatively small cohort size are notable limitations, potentially impacting the statistical power of our analyses. In particular, the limited sample size may have increased the risk of type 2 error and reduced the generalizability of our results to broader EPNEC populations. Despite these limitations, the comprehensive evaluation of patient records and the focus on a rare cancer type are strengths that enhance the relevance of our findings. Furthermore, the uniformity in treatment protocols, with all patients receiving platinum plus etoposide-based chemotherapy at first line, minimizes potential confounding effects related to variability in treatment approaches.

Our study supports the potential utility of the HALP score as a prognostic marker in EPNECs. While the association observed in this cohort was not statistically significant, the numerical trend aligns with existing evidence from other cancer types and NEC subtypes. The HALP score's ease of measurement and cost-effectiveness make it an attractive biomarker for routine clinical use. Further research, particularly in the form of large-scale, prospective studies, is warranted to confirm these findings and explore the HALP score's role in guiding individualized treatment strategies.

Conclusion

Although the HALP score was not significantly associated with OS or PFS in our study, its correlation with LDH levels and observed trends suggest potential prognostic implications that deserve further exploration. Elevated LDH levels, a known marker of tumor burden and metabolic stress, were associated with worse survival outcomes. Furthermore, the absence of chemotherapy was another critical factor linked to poor prognosis. These findings underscore the importance of comprehensive metabolic and treatment-based assessments in the management of patients with extrapulmonary NEC. Future research should focus on validating these observations and exploring the potential benefits of interventions, such as immunonutritional support, tailored to specific metabolic profiles.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (1st Medical Research Scientific and Ethics Review Board) (decision no: TABED 1-24-777, date: 04.12.2024).

Informed Consent: Informed consent was waived due to the use of anonymized clinical data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.P., M.A.P., D.B., Ş.Y., Concept: P.P., Ş.Y., F.T.K., Design: P.P., Ş.Y., F.T.K., Data Collection

or Processing: P.P., S.S., M.A.P., D.B., F.T.K., Analysis or Interpretation: P.P., S.S., M.A.P., M.M., Literature Search: P.P., M.M., Ş.Y., Writing: P.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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