Original Article

Clinical Importance of the Hemoglobin, Albumin, Lymphocyte, Platelet Score in Metastatic Pancreatic Cancer

Metastatik Pankreas Kanserinde Hemoglobin, Albümin, Lenfosit, Trombosit Skorunun Klinik Önemi

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ABSTRACT

Introduction: Pancreatic adenocarcinoma is one of the deadliest cancers. Effective, simple and practical methods that can be used in daily life are still lacking to predict the prognosis of patients with advanced pancreatic cancer and a promising biomarker is needed to predict prognosis. Our study's objective was to demonstrate the correlation between the HALP score and prognosis in patients with metastatic pancreatic cancer.

Methods: Patients diagnosed with metastatic pancreatic cancer from 4 centers in Turkey between 2016 and 2022 were included. Demographic data, hemogram parameters, biochemistry values, as well as the treatments received were recorded. Survivals were also recorded

Results: There were 280 patients in our study. The median PFS was 7.53 months, while the median OS was 11.53 months for the whole population. Median PFS was 7.1 months for the HALP-Low group and 14.8 months for the HALP-High group. The HALP-Low group exhibited a significantly shorter median progression-free survival (PFS) compared to the HALP-High group, with a statistically significant difference between the two groups ($p<0.001$). Median OS was 10.57 months for the HALP-Low group and 18 months for the HALP-High group. The HALP-Low group demonstrated a significantly shorter median overall survival (OS) compared to the HALP-High group, with a statistically significant difference between the two groups ($p<0.001$)

Discussion and Conclusion: In conclusion, the HALP score is an inexpensive, practical, literature-contributing marker and, if validated by prospective studies, can be used in routine clinical practice to predict the prognosis of patients with metastatic pancreatic cancer.

Keywords: HALP score, Overall survival, Metastatic Pancreatic cancer, Progression-free survival

ÖZET

Giriş ve Amaç: Pankreas adenokarsinomu en ölümcül kanserlerden biridir. Metastatik pankreas kanserli hastaların prognozunu tahmin etmek için günlük hayatta kullanılabilecek etkili, basit ve pratik yöntemler halen eksiktir ve prognozu tahmin etmek için umut verici bir biyobelirteç gerekmektedir. Çalışmamızda metastatik pankreas kanserinde HALP skorunun prognoz ile ilişkisini göstermeyi amaçladık.

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Yöntem ve Gereçler: 2016-2022 yılları arasında Türkiye'de 4 merkezden metastatik pankreas kanseri tanısı alan hastalar dahil edildi. Demografik veriler, hemogram parametreleri, biyokimya değerleri ve alınan tedaviler kaydedildi. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) da kaydedildi.
Bulgular: Çalışmamızda 280 hasta vardı. Tüm popülasyon için medyan PFS 7,53 aydı, medyan OS ise 11,53 aydı. Medyan PFS, HALP-Düşük grup için 7,1 ay ve HALP-Yüksek grup için 14,8 aydı. HALP-Düşük grubun median PFS'si HALP-Yüksek gruba göre daha kısaydı ve gruplar arasında istatistiksel olarak anlamlı bir fark vardı (p: <0,001).
Tartışma ve Sonuç: Sonuç olarak, HALP skoru ucuz, pratik, literatüre katkıda bulunan bir belirteçtir ve prospektif çalışmalarla doğrulanırsa, metastatik pankreas kanseri olan hastaların prognozunu tahmin etmek için rutin klinik uygulamada kullanılabilir.

Anahtar Kelimeler: HALP skoru, Genel sağkalım, Metastatik Pankreas kanseri, Progresyonsuz sağkalım

Introduction

Pancreatic ductal adenocarcinoma (PC) is a highly lethal cancer, responsible for 496,000 new cases and 466,000 deaths in the United States in 2018. It ranks as the 7th leading cause of cancer-related deaths. PC is increasing in both sexes and the median age at diagnosis is around 40 years [1]. Although surgery is a curative treatment option, 80% of patients are metastatic or locally advanced at the time of diagnosis [2]. Although chemo-therapy, immunotherapies and targeted therapies are being developed, 5-year survival is around 5% [3,4]. There is currently a lack of effective, straightforward, and feasible methods for predicting the prognosis of individuals with advanced pancreatic cancer, despite the existence of proto-oncogenes like BRCA and PALB2, as well as some molecular tests such as tumor mutation burden and a promising biomarker is needed to predict prognosis. Developments in the field of cancer and inflammation and the lack of biomarkers in patients with PC have led to the need for many studies.

The link between nutritional status and inflammation and cancer progression has been known for many years. Chronic inflammation accelerates the neovascularization process by increasing cytokines and this contributes to tumor growth [5,6]. Nutritional status contributes to prognosis by affecting the immune system through cytokines [7,8]. Cancer-related anemia is highly prevalent. In the presence of anemia, hypoxia occurs at the cellular level. This leads to genomic and proteomic changes (e.g. increased growth factors for example vascular endothelial growth factor). Thus, it increases tumor growth and metastasis potential [9]. Platelets are involved in inflammation-mediated cancer development through growth factors, chemokines and proinflammatory cytokines. It is known that thrombocytosis increases the metastasis potential and plays a poor prognostic role in many malignancies [10,11].

Recent research has demonstrated that hemoglobin, albumin, lymphocyte, platelet score (HALP score) has significant relevance in forecasting the development of renal cancer, non-small cell lung cancer (NSCLCL), gastric cancer, and small cell lung cancer. (SCLC) [12,15]. As far as we know, there have been no studies demonstrating the correlation between HALP score and prognosis in metastatic PC.

Our study aims to establish the association between HALP score and prognosis in metastatic PC.

Materials and Methods

Patients diagnosed with metastatic pancreatic cancer at Mardin Training and Research Hospital, Aydın Adnan Menderes University Hospital, Manisa Celal Bayar University, and Aydın Atatürk State Hospital between 2016 and 2022 were included. Patient records and hospital databases were examined for this

study. The patients' age, ECOG performance status, gender, comorbidities, hemoglobin at the time of metastasis, thrombocyte, lymphocyte, albumin and the treatments they received were recorded.

Patients with another malignancy, younger than 18 years of age, known hematologic disease, autoimmune disease, inflammatory bowel disease, history of steroid or anticoagulant use, non-metastatic patients whose data could not be securely accessed were excluded. HALP score had been calculated as × lymphocyte (/L) x albumin (g/L) x hemoglobin (g/L) / platelet count (/L). The cut-off for HALP score was determined as 0.6 with the X-tile program.

Statistical analyses were conducted using R version 2.15.3 (R Core Team, 2013). The study data were summarized using various descriptive statistics, including the minimum, maximum, first quartile, third quartile, median, mean, standard deviation, frequency, and percentage. These measures were utilized to provide a comprehensive overview and description of the study data. The normality of the quantitative data was assessed through the Shapiro-Wilk test and graphical analysis to determine if it followed a normal distribution. These methods were used to examine the distributional characteristics of the data and assess its adherence to the assumptions of a normal distribution. The Dunn-Bonferroni test and Kruskal-Wallis test were employed to compare quantitative variables among more than two groups when the data did not exhibit a normal distribution. These statistical tests were used to examine potential differences or relationships between the groups, considering the non-normal distribution of the data. Qualitative data were compared using Fisher's exact test, Pearson chi-square test, and Fisher-Freeman-Halton exact test. These statistical tests were employed to assess potential associations or differences among categorical variables. For evaluating progression-free survival (PFS) and overall survival (OS), univariable and multivariable Cox regression analyses were performed. A significance level of $p<0.05$ was considered to determine statistical significance in the results.

This study was conducted and designed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. It received approval from the ethics committee of Diyarbakır Gazi Yaşargil Training and Research Hospital (Approval Date-No: 25.11.2022-2022/242). Informed consent was obtained from all patients Results

There were 280 patients in our study. The median age was 64.5 years (58, 72). 165 (58.9%) of our patients were male. ECOG performance scale was 0 or 1 in 182 (65%) of our patients. Most of our patients 230 (82.1%) were de-novo metastatic. Liver was the site of metastasis in 202 (72.1%) of our patients. The primary site of origin was the head of the pancreas in 184 (65.7%) of our patients. In metastatic 1st line chemotherapy, 59 (21.1%) patients received cisplatin + gemcitabine, 59 (21.1%) patients received single agent gemcitabine and 47 (16.8%) patients received FOLFIRINOX regimen. In our study, 254 (90.7%) patients were exited. No statistically significant differences were found concerning gender, ECOG performance status, and tumor localization.

Percentages between the group with a HALP score ≤ 0.6 (HALP-Low) and the group with a HALP score > 0.6 (HALP-High) ($p>0.05$). We observed a statistically significant difference between the HALP-Low group and the HALP-High group in terms of the proportion of patients receiving the 1st step chemotherapy ($p=0.002$).

The HALP-Low group had a higher percentage of patients receiving capecitabine. Detailed information on the general characteristics and demographics of the patients is provided in Table 1.

Table 1. Demographic and clinicopathological characteristics of the patients

	Total (n=280)	Low HALP score (≤0.6) (n=234)	High HALP score (>0.6) (n=46)	p
Age, year	64.5 (58, 72)	65 (59, 72)	63 (56, 71)	0.253
Gender				0.972
Female	115 (41.1)	96 (41)	19 (41.3)	
Male	165 (58.9)	138 (59)	27 (58.7)	
ECOG				0.761
0-1	182 (65)	153 (65.4)	29 (63)	
2-3	98 (35)	81 (34.6)	17 (37)	
Smoking (%)				0.788
No	151 (53.9)	126 (53.8)	25 (54.3)	
Active	121 (43.2)	102 (43.6)	19 (41.3)	
Former	8 (2.9)	6 (2.6)	2 (4.3)	
BMI				0.919
<20	44 (15.7)	37 (15.8)	7 (15.2)	
>20	236 (84.3)	197 (84.2)	39 (84.8)	
De-novo metastasis, n (%)				0.741
Yes	230 (82.1)	193 (82.5)	37 (80.4)	
No	50 (17.9)	41 (17.5)	9 (19.6)	
Liver metastasis				0.770
No	78 (27.9)	66 (28.2)	12 (26.1)	
Yes	202 (72.1)	168 (71.8)	34 (73.9)	
Lung metastasis				0.324
No	196 (70)	161 (68.8)	35 (76.1)	
Yes	84 (30)	73 (31.2)	11 (23.9)	
Periton metastasis				0.263
No	168 (60)	137 (58.5)	31 (67.4)	
Yes	112 (40)	97 (41.5)	15 (32.6)	
Others				0.543
No	222 (79.3)	184 (78.6)	38 (82.6)	
Yes	58 (20.7)	50 (21.4)	8 (17.4)	
First Line				0.002
FOLFOX	16 (5.7)	12 (5.1)	4 (8.7)	
FOLFIRINOX	47 (16.8)	39 (16.7)	8 (17.4)	
KAPOX	15 (5.4)	9 (3.8)	6 (13)	
Gemcitabine	59 (21.1)	49 (20.9)	10 (21.7)	
Gemcitabin+Capesitabin	25 (8.9)	24 (10.3)	1 (2.2)	
Gemcitabin+ Nab-paclitaxel	22 (7.9)	19 (8.1)	3 (6.5)	
Cisplatin+Gemcitabine	59 (21.1)	45 (19.2)	14 (30.4)	
Capesitabin	37 (13.2)	37 (15.8)	0 (0)	
Tumor location, n (%)				0.178
Head	184 (65.7)	159 (67.9)	25 (54.3)	
Body	55 (19.6)	42 (17.9)	13 (28.3)	
Tail	41 (14.6)	33 (14.1)	8 (17.4)	
Survival				0.401
Live	26 (9.3)	20 (8.5)	6 (13)	
Exitus	254 (90.7)	214 (91.5)	40 (87)	

HALP: Hemoglobin-Albumin-Lymphocyte-Platelet-Ratio

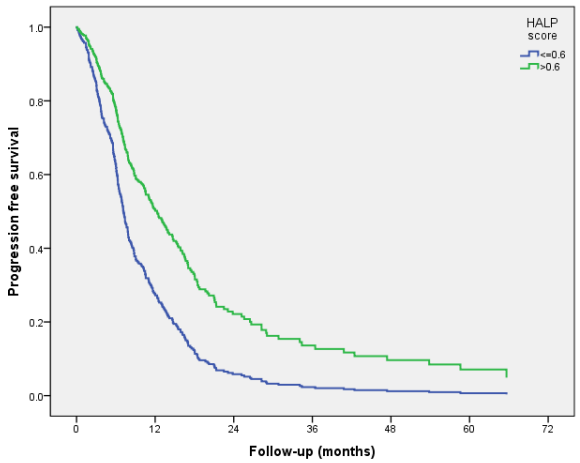

Figure-1: Progression free survival analysis functions

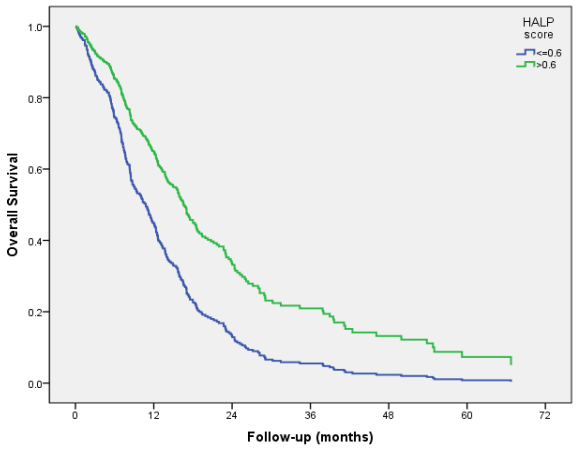

Figure-2: Overall survival analysis functions

For the whole population, median PFS was 7.3 (95% CI: 6.75-8.32) months and median OS was 11.53 (95% CI: 10.1-12.97) months. Median PFS was 7.1 (95% CI: 6.37-7.83) months for the HALP-Low group and 14.8 (95% CI: 12.36-17.24) months for the HALP-High group. The HALP-High group exhibited a significantly longer median PFS compared to the HALP-Low group, with a p-value of less than 0.001 indicating statistical significance (Figure 1).

The HALP-Low group had a median overall survival (OS) of 10.57 months (95% CI: 8.66-12.47), while the HALP-High group had a median OS of 18 months (95% CI: 14.51-21.49). The HALP-Low group exhibited a shorter median OS compared to the HALP-High group, and this difference was statistically significant (p<0.001). (Figure 2).

There were no statistically significant differences observed between the HALP-Low group and the HALP-High group in terms of gender, ECOG performance status, and tumor localization percentages respectively (p-values: 0.972, 0.761, 0.178,). Median PFS was higher and statistically significant in patients with an ECOG performance score of 0-1 compared to those with an ECOG performance score of 2-3, 8.33 (95% CI: 7.16-9.51) and 6.77 (95% CI 5.68-7.85), respectively (p<0.001).

Furthermore, the median OS was higher and statistically significant in patients with ECOG performance score 0-1 compared to those with ECOG performance score 2-3, 13.3 (95% CI: 11.43- 15.17) and 7.9 (95% CI: 6.26, 9.54), respectively (p:0.001).

Median PFS was 6.77 (95% CI: 6.12-7.41) months with de-novo metastatic disease and 16.43 (95% CI: 10.52, 22.34) months with recurrent metastatic disease and was statistically significant (p:0.001). Median OS was 10 (95% CI: 8.36-11.64) months with de-novo metastatic disease and 21.67 (95% CI: 15.41-27.93) months with recurrent metastatic disease, which was statistically significant (p:0.001). Univariate analyses of PFS and OS are shown in detail in Table 2.

Multivariate analysis was conducted to identify independent prognostic factors for progression-free survival (PFS) and overall survival (OS). The HALP-Low group had a lower PFS compared to the HALP-High group [HR (95% CI)=2.288 (1.587, 3.301), p<0.001]. Additionally, individuals with de-novo disease status had a lower PFS compared

Table 2: Univariate analysis of PFS and OS

	mOS (95%CI)	p-value	mPFS (95% CI)	p-value
Age, year	-	0.132	-	0.715
Gender				
Female	10.97 (9.01 – 12.93)	0.823	7.8 (6.52- 9.08)	0.863
Male	12.33 (10.32 -14.34)		7.3 (6.47- 8.13)	
ECOG-PS				
0-1	13.3 (11.39 - 15.21)		8.33 (7.16- 9.51)	
2-3	7.9 (6.34 - 9.46)	<0.001	6.77 (5.68- 7.85)	0.001
Smoking		0.989		0.679
Never	10.77 (9- 12.93)		7.63 (6.64- 8.62)	
Active	12.67 (10.64-14.83)	0.995	7.53 (6.26- 8.8)	0.406
Former	14.17 (0-28.81)	0.883	5.87 (0 - 19.73)	0.679
BMI				
<20	11.77 (6,04- 17.49)		7.3 (5.86- 8.74)	
>20	11.5 (9.92- 13.08)	0.362	7.63 (6.8 -8.47)	0.362
De-novo metastasis, n (%)				
Yes	10 (8.4 - 11.6)	<0.001	6.77 (6.12- 7.41)	<0.001
No	21.67 (15.41- 27.93)		16.43 (10.52-22.34)	
Liver metastasis				
No	11.53 (8.73- 14.34)		7.8 (6.18- 9.42)	
Yes	11.77 (10,02- 13.38)	0.215	7.4 (6.54- 8.26)	0.085
Lung metastasis				
No	11.53 (10,01- 13.06)		7.63 (6.68- 8.59)	
Yes	12.4 (7.51-17.29)	0.302	7.4 (5.65- 9.15)	0.592
Periton metastasis				
No	11.13 (8.9-13.33)		7.9 (6.41- 9.16)	
Yes	12 (10.2-13.8)	0.893	7.2 (6.44-7.96)	0.244
Others				
No	11.77 (10.16- 13.24)		7.4 (6.69- 8.11)	
Yes	11.3 (7.32-15.28)	0.942	8.5 (6.67- 10.33)	0.248
Tumor location, n (%)		0.446		0.144
Head	12 (10.97 – 13.03)		7.87 (6.78- 8.95)	
Body	10.1 (7.14- 13.06)	0.237	6.33 (5.26- 7.41)	0.057
Tail	10.3 (5.72- 14.88)	0.914	8.67 (5.05- 12.28)	0.820
HALP score				
Low (≤0.6)	10.57 (8.66-12.47)	<0.001	7.1 (6.37-7.83)	<0.001
High (>0.6)	18 (14.51- 21.49)		14.8 (12.36- 17.24)	

PFS: Progression-free survival , OS: Overall Survival, CI: Confidence interval, PS: performance status, BMI: Body mass index, n: number, HALP: Hemoglobin-Albumin-Lymphocyte-Platelet Ratio

to those with relapse [HR (95% CI) = 3.942 (2.747-5.656), p<0.001].

Multivariate analysis showed that OS was lower in the HALP-Low group than in the HALP-High group [HR (95% CI) = 2.076 (1.437, 2.998), p<0.001]. OS was lower in those with de-novo disease status than in those with relapse [HR (95% CI) = 3.205 (2.243-4.579), p<0.001].

Discussion

Many studies have been conducted to predict the prognosis of patients with metastatic PC and prognostic factors have been identified. Unfortunately, no markers have been found to be used in daily clinical practice. Many studies have shown that hemoglobin levels affect survival in patients with malignancy [16]. Albumin is a negative acute phase reactant synthesized in the liver. Hypo-

albuminemia may be caused by malnutrition, hypercatobolism caused by cancer cells and increased inflammation due to cytokine release and this plays a role in the survival of cancer patients. Lymphocytes inhibit apoptosis by secreting TNF alpha and interferon gamma and contribute to prolonged survival by preventing tumor migration and invasion [17,18]. Platelets increase angiogenesis, migration and vascular permeability through growth factors and therefore play an important role in cancer formation and prognosis. The Halp score, in which these parameters are used together, is one of the indices that is thought to play a prognostic role in the evaluation of nutrition and immune system. We decided to do this study, which we thought would play a prognostic role in metastatic cancer. To the best of our knowledge, this study represents the first investigation to assess the prognostic significance of the HALP score in metastatic PC.

In all our patients, median PFS was 7.3 (95% CI: 6.75-8.32) months and median OS was 11.53 (95% CI: 10.1-12.97) months. The general characteristics and median survival times of the patient population in our study were found to be compatible with the literature [19]. The HALP-Low group had a shorter median PFS compared to the HALP-High group, and this difference was statistically significant ($p<0.001$) In this study, high HALP score was found to be a good prognostic indicator and our study is compatible with the literature [12,14,15].

The literature contains numerous studies highlighting the prognostic significance of the HALP score. For instance, a study involving 582 patients with resectable pançreatic cancer demonstrated that a high HALP score prior to surgery was identified as a prognostic factor for survival [20]. According to a study involving 355 patients diagnosed with esophageal squamous cell carcinoma, a high HALP score before surgery was identified as an independent and favorable prognostic indicator [21]. In a separate study conducted by Topal et al., which included 110 colorectal cancer patients who underwent surgical procedures, it was observed that the prognostic significance of a low HALP score was diminished in the presence of tumor budding [22]. Again, in a study in which 591 patients with locally limited gastrointestinal stromal tumors were followed up post-operatively, low HALP score predicted short PFS [23].

Numerous publications also exist on this topic concerning locally advanced or metastatic stages. For instance, in a study conducted by Ekinci et al. involving 123 patients diagnosed with metastatic renal cell carcinoma, a low HALP score was associated with a poor prognosis [14]. A study in gastric cancer showed that a low HALP score numerically indicates a poor prognosis. The reason for the lack of statistical significance was thought to be the fact that the number of metastatic patients was 58 (12). Similarly, in a study conducted by Güç et al. involving 401 patients with NSCLC, it was noted that a low HALP score was associated with unfavorable survival outcomes [13]. Again, in a study including patients with limited and diffuse stage SCLC, low HALP score was found to be poor prognostic [15].

Patients with an ECOG performance score of 0-1 demonstrated a significantly higher median PFS compared to those with an ECOG performance score of 2-3, with durations of 8.33 months and 6.77 months, respectively ($p<0.001$). Additionally, patients with an ECOG performance score of 0-1 exhibited a significantly higher median OS compared to those with an ECOG performance score of 2-3, with durations of 13.3 months and 7.9 months, respectively (p: 0.001). Our study findings align with the existing literature, confirming the association between ECOG performance score and survival outcomes [24].

Median PFS was 6.77 (95% CI: 6.12-7.41) months with de-novo metastatic disease and 16.43 (95% CI: 10.52, 22.34) months with recurrent metastatic disease and was statistically significant (p:0.001). Median OS was 10 (95% CI: 8.36-11.64) months with de-novo metastatic disease and 21.67 (95% CI: 15.41-27.93) months with recurrent metastatic disease, which was statistically significant (p:0.001). In a study by Miotke et al. survival of recurrent patients was 10.8 months and OS of recurrent patients was 7.3 months and our study was found to be favorable with the literature [25].

The retrospective design of our study and the relatively limited sample size of the HALP-low group are acknowledged limitations. While we adopted a HALP score cut-off value of 0.6 based on previous literature, the optimal threshold is still undetermined. Another issue that should be mentioned at the same time was that our patient groups were heterogeneous. It included Denovo and metachronous metastatic patients. Therefore, more specific, prospective, well-designed studies with a larger patient population are needed to investigate this issue in more detail.

A high HALP score represents a cost-effective and practical marker that contributes to the existing literature. If validated by prospective studies, it could be utilized in clinical practice to prognosticate patients with metastatic prostate cancer. Furthermore, a high HALP score was identified as an independent predictor of unfavorable prognosis in patients with metastatic pancreatic cancer

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