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Research Article

Prognostic Importance of HALP (Hemoglobin, Albumin, Lymphocyte and Platelet) Score in Ovarian Cancer Patients

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Abstract

Objectives: The HALP score, which is the combination of hemoglobin, albumin, lymphocyte, and platelets has been confirmed as an important risk biomarker in several cancers. The aim of this study was to investigate prognostic value of the HALP score in patients with ovarian cancer.

Methods: In this study we retrospectively enrolled 185 patients from single center. The relationship between post-operative survival outcomes and pre-operative HALP level was assessed using Kaplan-Meier and Cox regression analyses. As a result, the cutoff value of HALP was 27 and patients were then divided into HALP ≤27group and HALP >28 group.

Results: A total of 185 women were included in the analysis. 89,7% patients had high grade and %86 patients were advanced stage (62 % were stage III and 24 % were stage IV) serous ovarian cancer. The median survival in the entire population was 54 months (95% CI, 37.57-70.43). Statistical differences were found for HALP score values with stages, platinum resistance status and latest status. In platinum-resistant and platinum-sensitive disease, the area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.618 (95% CI, 0.530-0.707), (p=0.008). In patients with high HALP scores, the median progression-free survival was 45 months (95% CI, 0,0-105,32) and in patients with low HALP scores, the median progression-free survival was 15 (95% CI, 13.27-16.72) months and the difference between them was statistically significant (p<0.001).

Conclusion: Our study showed that a lower HALP was associated with higher stage and platinum resistance and this score was also an independent factor for poorer oncological outcomes.

Keywords: Ovarian cancer, HALP score, Hemoglobin, Albumin, Lymphocyte, Platelet

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Ovarian carcinoma is the third most common gynecologic malignancy and it is also the most common cause of death from gynecologic malignancies.[1] The state of inflammation and nutrition may be an etiological factor for this type of cancer. Various cytokines are released as a result of chronic inflammation.[2-5] These cytokines prevent both the defense cells from functioning and prepare the environment where tumor cells can grow up and develop. Malnutrition also weakens immunity by negatively affecting this inflammatory process. While the peripheral cells provide the necessary energy for the tumor tissue, this situation aggravates malnutrition. C-reactive protein (CRP), neutrophil/lymphocyte ratio, prognostic nutrition index (PNI), platelet/lymphocyte ratio (PLR), interleukin 1 (IL-1), Systemic Inflammation

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Response Index (SIRI), Pan-immune Inflammation Value (PIV) and interleukin 6 (IL-6) may be considered among the inflammatory markers that has been subject of various studies and whose relationship with cancer has been investigated. [6-10] Auersperg et al. pointed out that cytokines secreted by malignant cells in ovarian cancer can enhance cancer progress because of the autocrine effect.[11]

The hemoglobin-albumin-lymphocyte-platelet (HALP) index is a novel score based on a combination of inflammatory and nutritional deficiency concepts. The HALP score may be a promising cancer prognostic biomarker. It may be associated with cancer-related anemia, nutritional deficiency and advanced malignancy. To our knowledge, this is the first study exploring the potential prognostic utility of the HALP score in ovarian cancer. The aim of this study was to investigate whether pre-treatment HALP scores are associated with clinical outcome and survival outcomes in ovarian cancer patients.

Methods

Inclusion and Exclusion Criteria

Stage I-IV and grade I-III serous ovarian cancer patients aged 18 years and over were included in this study. Patients who had not previously been diagnosed with cancer and did not have a rheumatological disease requiring any immunosuppressive treatment were included in the study. Patients with a second malignancy, active infectious disease, or receiving immunosuppressive treatment for any reason were not included in the study.

Study Selection and Ethical Approval

This study is a retrospective study conducted after written consent was obtained from the Ondokuz Mayis University Faculty of Medicine Clinical Research Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki. Ovarian cancer patients diagnosed from January 2017 to December 2020 were included in the study.

Data Collection

We collected relevant demographic and clinicopathological data at baseline, including age, stage according to the FIGO (International Federation of Gynecology and Obstetric) staging system criteria (8th edition), grade, CA125 level, treatment modality, surgical procedure, disease-free survival and overall survival. The HALP index was calculated as haemoglobin (g/L) x albümin (g/L) levels x lymphocyte count (/L)/ platelet count (/L). We categorised participants into two age groups (<65 and ≥65 years), in line with age proupings used in many studies.[12] In addition, it was noted whether she was alive or not from the patient records.

Statistical Analysis

Statistical analyses were performed with SPSS 21.0 for windows. Data were presented as mean±standard deviation (SD), as median (min-max) as frequence (%). The Shapiro–Wilk test was used to analyze normal distribution assumption of the quantitative outcomes. Data were analysed by Mann–Whitney test for non-normal data. Results were evaluated using the nonparametric Kruskal–Wallis for comparison between groups. The relation between variables was assessed by Spearman rank correlation for non-normal data. The area under the ROC curve (AUC) was evaluated as the measure of a diagnotic test's discriminatory power. Confidence intervals can be computed for AUC. In this article, sensitivity, specificity, positive predictive and negative predictive values were evaluated.

Kaplan-Meier method was used for survival analysis with the log-rank test used to statistical difference. A univariate Cox proportional hazards regression model was used to evaluate the prognostic value of each variable for OS. Multivariate Cox proportional hazards regression models were used to analyze independent prognostic factors. A p value less than 0.05 was considered as statistically significant.

Results

A total of 185 women, with a median age of 55.28±11.32 years were included in the analysis. Primary treatment was optimal surgery in 71,9% cases and debulking surgery was performed in 28,1% of these patients. The demographic characteristics of the patients are given in Table 1. 82% of the patients were 65 years of age or younger and 159 (86

Table 1. Demografic characteristics of the study population.

Variable	n (%)
Age at diagnosis	
≤65 years	152 (82)
>65 years	33 (18)
Grade	
Grade 1	5 (2.7)
Grade 2	14 (7.6)
Grade 3	166 (89.7)
Stage at diagnosis (FIGO)	
Stage I	13 (7)
Stage II	13 (7)
Stage III	115 (62)
Stage IV	44 (24)
Surgical procedure	
Total abdominal hysterectomy+ bilateral salphingoophorectomy + sentinel lymph node dissection.)	133 (71.9)
Debulking	52 (28.1)

%) patients had locally advanced stage. Most patients had high grade tumor (89.7%) and 7% were stage I, 7% were stage II, 62% were stage III and 24% were stage IV (Supplementary Table 1).

In this study, the optimal cut-off value for the HALP score to discriminate between healthy and dead patients was determined as 0.27. Then, the patients were divided into ≤0.27 and >0.28 groups. The cut-off value with the highest sensitivity and specificity was taken as the cut-off value in the ROC analysis of the HALP score of the patients whose cut-off value was followed by ovarian cancer. According to this value, sensitivity and specificity were found to be 0.78 and 0.60, respectively.

The comparison of the HALP values of the patients according to various parameters and the discriminative power of the HALP score for these parameters are given in Supplementary Table 3. Statistical differences were found for HALP values with these parameters.

There was a statistical difference between the HALP score and the stages at the time of diagnosis, but there was no significant difference only between stages I and II (p=0.54). The differences between the other stages (stages I-III, stages I-IV, stages II-III, stages III-IV) were statistically significant (p<0.001). The relationship between HALP score and grade was evaluated and there was a significant difference between grade 2 and 3 (Supplementary Table 2).

AUC values were also found to be statistically significant. In the ROC curve for stage I-II and stage III-IV, AUC was 95% CI 0.863 (0.81-0.92), p<0.001 (Supplementary Figure 1). In platinum-resistant and platinum-sensitive disease, the AUC of the ROC curve was 95% CI 0.618 (0.53-0.71), with statistical significance (p=0.008). There was also a statistically significant difference between those who died, and HALP score AUC 95% CI 0.689 (0.61-0.77) ROC curve, (p<0.001).

When the correlations between HALP score and different variables were evaluated, there was no correlation between age and HALP score (rho=-0.064 p=0.38). There was a moderate negative correlation between HALP score and CA125 (rho =-0.434 p<0.001). The median survival in the entire population was 54 (95% CI, 37.57-70.43) months. The median survival above 65 years of age could not be calculated due to the small number of patients, and the median survival of those aged 65 and below was calculated as 50 (95% CI, 31.33-68.66) months (Supplementary Figure 2). When evaluated in terms of overall survival, when stage I-II, stage II-IV, platinum sensitive and platinum resistant patients were evaluated, stage IV and platinum resistant patients had statistically lower median survival time (p<0.001) (Supplementary Table 3). In addition, a statistically significant difference was found when the survival times of those with high and low HALP scores were compared. In the other words, the median survival was 61.71 (95% CI, 27.49-48.51) months in patients with low HALP scores, and the median survival could not be calculated in patients with high HALP scores (p<0.001) (Fig. 1d).

The median progression-free survival in the general population was 17 (95% CI, 12.66-21.33) months (Supplementary Figure 3a). As with overall survival, there was a significant correlation between stage at diagnosis, platinum resistance, high HALP score and progression-free survival (Supplementary Figure 3). Accordingly, as the stage at diagnosis increased, progression-free survival decreased significantly (p<0.001) (Supplementary Figure 3b). In patients with high HALP scores, the median progression-free survival was 45 months and in patients with low HALP scores, the median progression-free survival was 15 (95% CI, 13.27-16.72) months (p<0.001) (Supplementary Figure 3c). Likewise, progression-free survival was lower in platinum-resistant patients, with a median of 11 (95% CI, 9.03-12.98) months. In platinum-sensitive patients, the median progression-free survival was 23 (95% CI, 14.05-31.96) months, which was significantly higher (p<0.001) (Supplementary Figure 3d).

Considering the HALP score in patients receiving treatment between 0-3 and 3-6 months in platinum resistant patients, it was lower in patients who relapsed in the 0-3 months period, which was statistically significant (p<0.001). The AUC was 0.985 (95% CI, 0.96-1.00) (sensitivity 93.9% and specificity 100%) (Supplementary Figure 4).

Discussion

Our study showed that low HALP score was correlated with advanced stage, high grade, platinum resistance, high CA125 level, shortened progression-free survival and poor survival which could be defined as poor prognostic factors.

Anemia and hypoalbuminemia, which indicate nutrition and inflammation, have been documented to be associated with the progression of various cancers.[12-15] Inflammatory response and nutritional status play an important role in cancer progression and metastasis. Cancer-related anemia, which is associated with advanced stage, is seen in 30% of cancer patients.[13] Anemia is induced by imbalance in inflammatory process due to increased hepcidin and reactive O2 stress products.[14,15]

It has been suggested that tumor necrosis factor-α (TNFα) and interleukin-6 (IL-6), secreted by tumor cells reduce hemoglobin levels by altering the hemopoietic environment. The level of hemoglobin was significantly related to tumor progression in cancer patients. Increasing body of evidence suggests that anemia is an independent factor

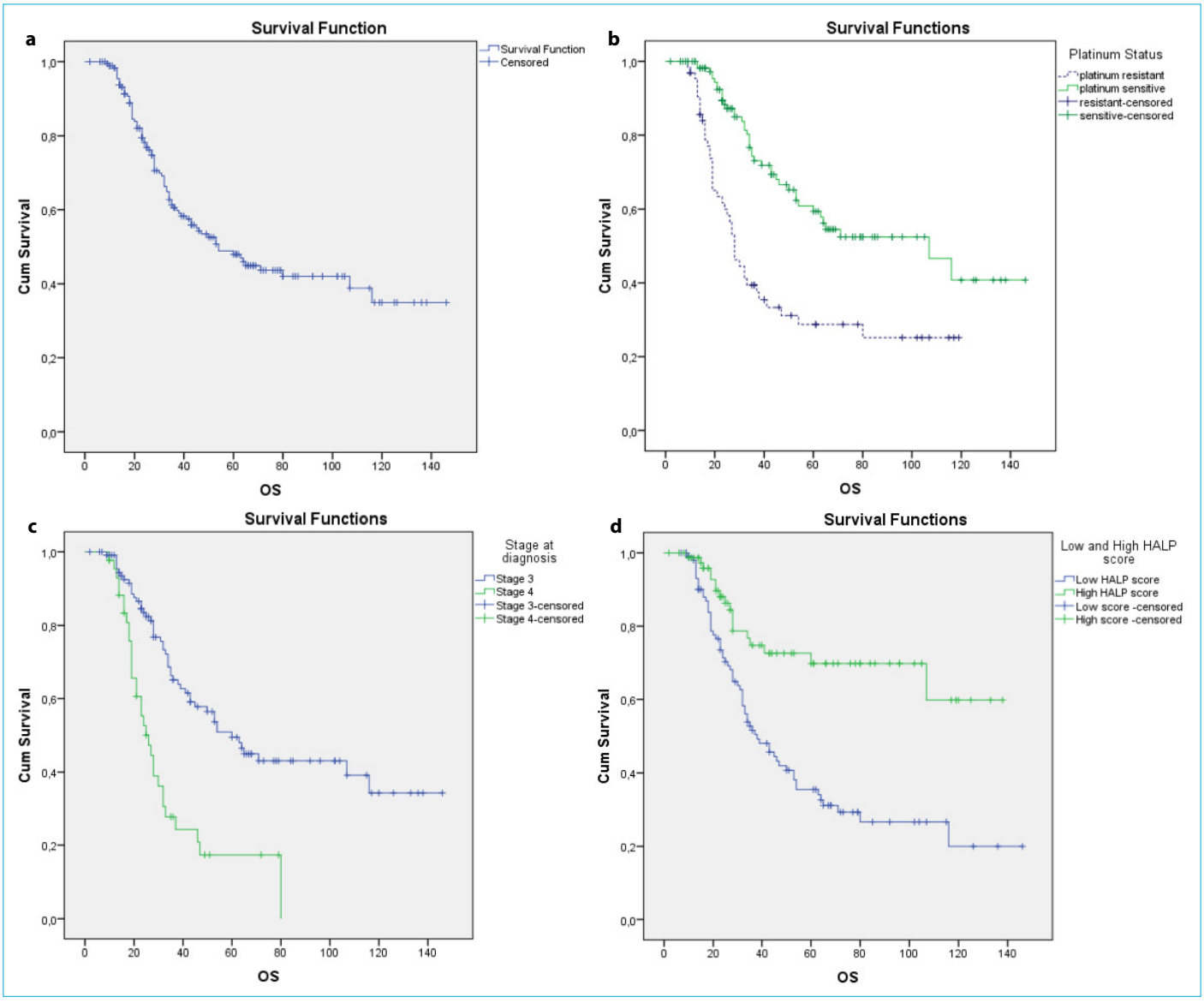

Figure 1. Survival curves for different parameters. **(a)** Overall survival (Kaplan Meier). **(b)** Overal survival in Platinum-resistant and platinum-sensitive patients **(c)** Overall survival in Stage 3 ve 4 patients **(d)** Overall survival in low and high HALP Score.

that adversely affects benefit of antineoplastic treatment and survival of the patients.[16] One study demonstrated that patients with advanced epithelial ovarian cancer had lower hemoglobin levels than in controls, with an inverse correlation between hemoglobin levels and stage and performance status.[17]

Serum albumin is a negative acute phase protein synthesized in the liver. Serum albumin level is affected by systemic factors such as inflammation and stress. Therefore, decreased albumin level maintains the systemic inflammatory response.[18] Many studies reported that poor survival outcomes were associated with hypoalbuminemia in different types of cancers.[19-21] Inflammatory cells can suppress the action of cytotoxic lymphocytes. Lymphocytes can cause systemic inflammation by releasing TGF-β (tumor growth factor- β) and IL-10 (interleukin-10). Platelet activation leads to the release of angiogenic growth factors to increase vascular permeability.[22] Tumor-promoting inflammation, in which neutrophils and platelets can promote carcinogenesis, angiogenesis, invasion or metastasis by secreting proinflammatory cytokines, is one of the hallmarks of cancer. Conversely, lymphocytes can inhibit tumor proliferation and migration through cytotoxicity.[23]

In chronic inflammation, the levels of cytokines such as NF-KB (Nuclear factor kappa-light-chain-enhancer of activated B cells), P53, HIF-α (hypoxia inducible factor 1-alpha), and VEGF (Vascular endothelial growth factor) change in the body. The alteration of these cytokines was reported

to dysregulate cancer apoptosis inhibition and promote neovascularization. Inflammation causes shortened erythrocyte survival, suppressed bone marrow function and hypoferremia, resulting in low hemoglobin levels.[24] In cancer patients, some cytokines such as thrombopoietin and IL-6 were found to stimulate platelet production and reactive thrombocytosis was associated with poor prognosis.[25,26] Cytokine signaling components often mediate the interaction between immune cells and tumor cells in the ovarian tumor microenvironment to regulate immune system reorganization. This immune regulation is thought to play a role in tumor resistance and progression.[27] Cong at al. reported that the HALP score had higher predictive ability than neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients with esophageal carcinoma.[28] However, in another study Guo at al. showed that low HALP score was significantly associated with tumor progression and appeared to be an unfavorable risk factor for prostate cancer.[4] Yang at al. suggested that the HALP score could be considered as a potential independent prognostic factor for esophageal squamous cell carcinoma.[7]

Njoku et al. examined the HALP score in gynecological cancers. They showed that HALP score was associated with adverse clinicopathologic factors but not cancer-specific or recurrence-free survival.[29] In our study, we found that both clinical features and survival were associated with HALP score in ovarian cancer. Similarly, Leetanoparn et al. found that a low HALP score was an independent predictive factor in cervical cancer.[30]

According to the results of many studies, low HALP score negatively affects survival.[29-31] Regarding survival, our study found that a high HALP score was independently associated with worse progression-free survival and overall survival. When evaluated in terms of overall survival, a statistically significant difference was found between early stage and advanced stage in terms of survival, as death did not occur in patients with early stage ovarian cancer.

While it is expected that the HALP score will decrease with aging due to the low level of albumin, which is a nutritional marker, there was no relationship between age and HALP score in our study. This can be explained by the fact that only 18% of the patients included in the study were over 65 years of age, did not have any additional comorbidities, and the majority of them were stage II patients.

Although cytoreductive surgery was performed in all stage IV patients in our cohort, residual tumor remained. Total abdominal hysterectomy and bilateral salpingo-oophorectomy and omentectomy and sentinel lymph node dissection was performed in all stage I and II patients and no postoperative residue was observed. Optimal surgery was performed in 99 of 115 stage III patients. Thirty-four of the 115 patients received neoadjuvant therapy. All of these patients were diagnosed as stage IIIC. After chemotherapy, stable disease was observed in 15 patients, while the remaining patients progressed. All of these patients were considered platinum resistant.

Colombo at al. suggested a prognostic nomogram using six variables (treatment free interval, performance status, size of the largest tumor, CA125, hemoglobin and the number of organ metastases) to provide an objective method for predicting survival after platinum-based therapy.[32] The HALP score can be evaluated within this nomogram and may serve as a guide for the diagnosis of platinum-resistant ovarian cancer. Patients with platinum-resistant ovarian cancer need more intensive treatment.

The HALP score was not previously evaluated in the first 6 months when platinum resistance was identified, and this score may lead to a change in treatment. Our study may bring this issue to the fore.

The HALP score can help predict prognosis and make more accurate decisions about the platinum sensitivity or resistance. Currently new therapeutic options like immunotherapies are available for platinum-resistant disease. Evasion of immune response is thought to be a mechanism of tumor resistance.[33] It has been suggested that there may be a relationship between the high level of the tumor infiltrating T cells (TILs) and progression-free survival. Since TILs are also associated with PD-L1 level, immunotherapies are the subject of new research in high-grade ovarian cancer.[27]

There are some limitations that should be noted in our study. The study was retrospective and all patients were recruited from a single center. Different results for the HALP score may be obtained with multicenter studies with a larger number of patients. Moreover, since there is no consensus on the cut-off value of the HALP score, it should be taken into account when interpreting the results for clinical use. The data focusing on HALP score is limited, so larger multicenter studies are necessary to confirm our findings.

Inconclusion, our study found that a lower HALP score was associated with higher stage, higher CA125 level and platin resistance and was also an independent factor for poorer oncological outcomes. The utilization of a HALP score index can improve the accuracy of determining oncological outcomes of ovarian cancer patients.

Disclosures

Ethics Committee Approval: Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Table 1. Distribution of stages at diagnosis

Stage at diagnosis	n (%)	Mean±SD	Median (Minimum-Maximum)
1	13 (7)	0.476±0.172	0.420 (0.230-0.830)
2	13 (7)	0.425±0.113	0.450 (0.210-0.644)
3	115 (62)	0.254±0.171	0.205 (0.037-0.930)
4	44 (24)	0.150±0.099	0.130 (0.026-0.537)
Total	185	0.257±0.177	0.201 (0.026-0.930)

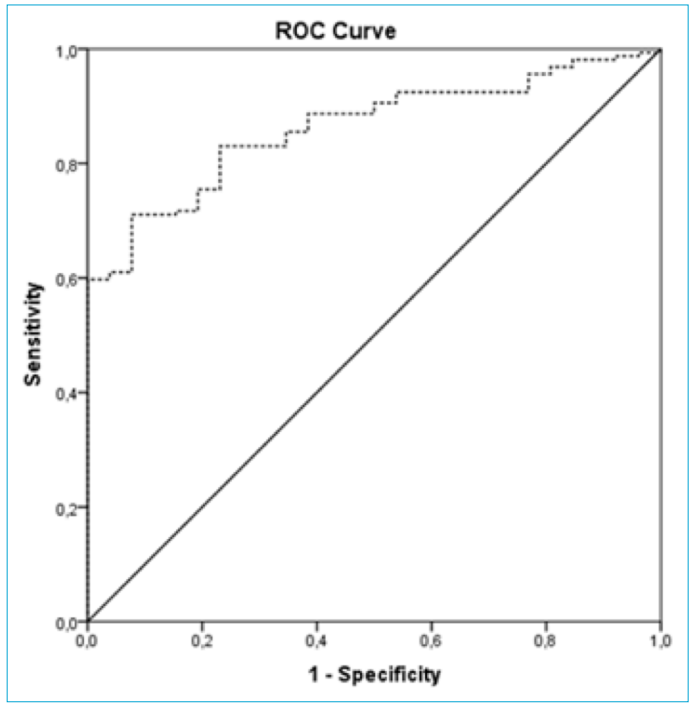
Supplementary Table 2. Comparison of HALP value according to various parameters

	Mean±SD	Median (Min-Max)	p
Stage			
Stage I-II	0.45±0.145	0.435 (0.21-0.83)	<0.001
Stage III-IV	0.225±0.161	0.166 (0.026-0.93)	
Platinum status			
Platinum resistant	0.228±0.202	0.132 (0.026-0.930)	0.008
Platinum sensitive	0.272±0.160	0.268 (0.037-0.830)	
Latest status			
Alive	0.305±0.178	(0.030-0.830)	<0.001
Dead	0.198±0.158	(0.026-0.930)	
Grade*			
Grade 1	0.294±0.244	0.205 (0.085-0.66)	0.006
Grade 2	0.411±0.186	0.378 (0.090-0.830)	
Grade 3	0.242±0.169	0.182 (0.026-0.930)	

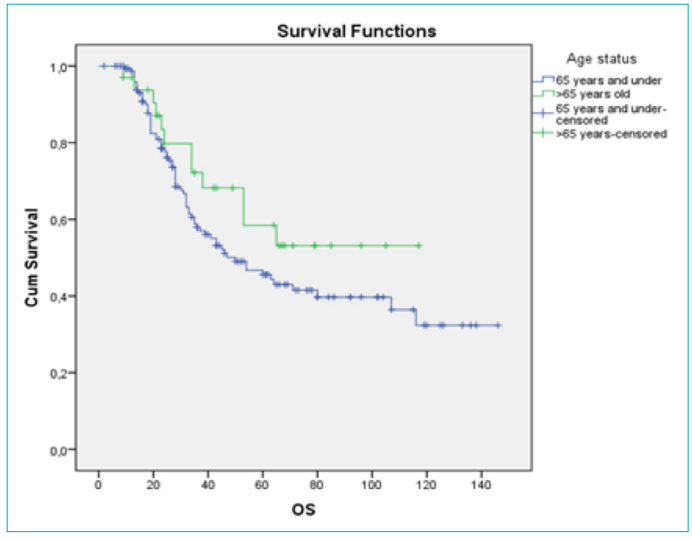
* In pairwise comparisons, p values for grades 1-2, 1-3 and 2-3 were p=0.308, p=0.748 and p=0.001, respectively.

Supplementary Table 3. Relationship between overall survival and platinum sensitivity and advanced stage

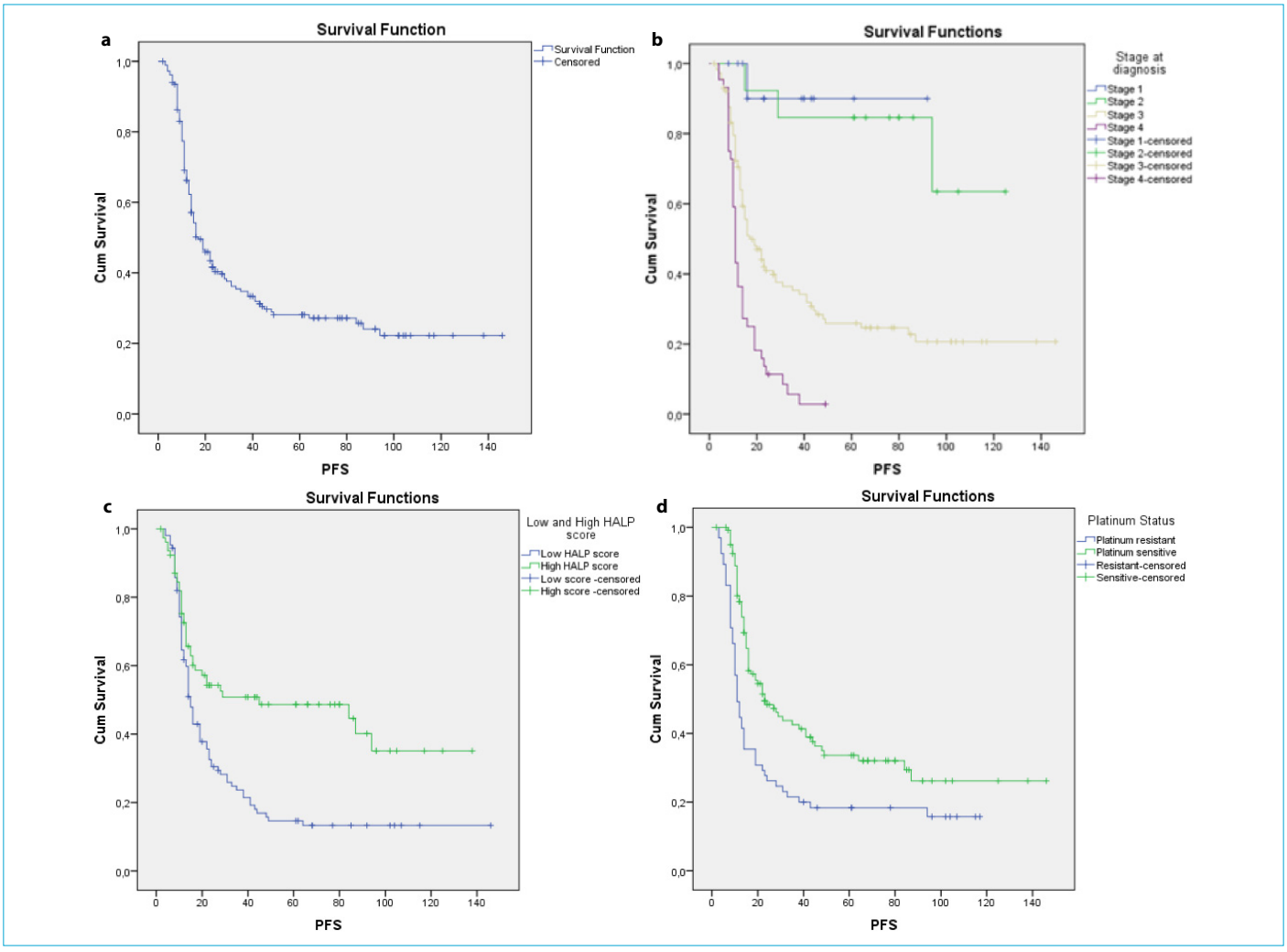
	Median (95% CI Min-Max)	p
Platinum status		
Sensitive	107 (56.97-157.04)	<0.001
Resistant	28 (23.75-32.25)	
Stage		
Stage 3	60 (46.05-73.95)	<0.001
Stage 4	26 (20.21-31.79)	



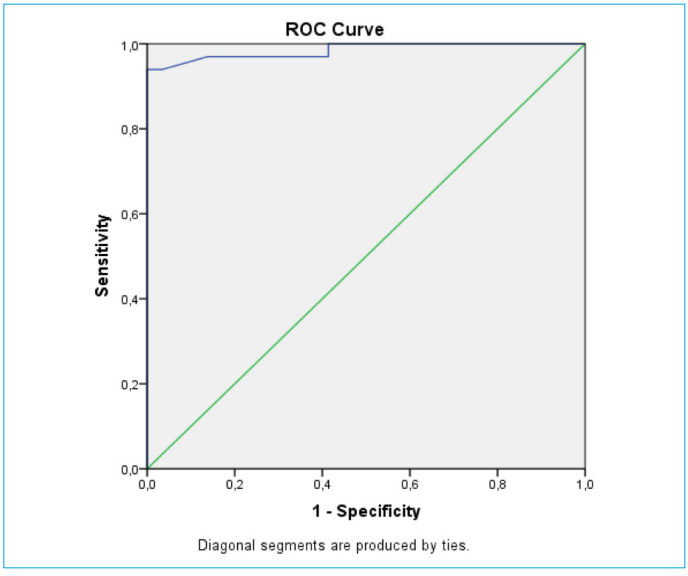
Supplementary Figure 1. ROC Curve in the differentiation of Stages 1-2 and 3-4.



Supplementary Figure 2. Overall survival curve by age.



Supplementary Figure 3. PFS curves for different parameters. **(a)** PFS in the general population (Kaplan Meier). **(b)** Relationship between stage at diagnosis and PFS **(c)** PFS in low and high HALP Scores **(d)** PFS by platinum resistance status.



Supplementary Figure 4. Relationship between HALP score and platinum resistance between 0-3 months and 3-6 months (sensitivity 93.9% and specificity 100% for Cut off value 0.13350).