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Research Article

Prognostic Significance of HALP Score in Early Stage Triple-Negative Breast Cancer

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Abstract

Objectives: Triple-negative breast cancer (TNBC) is an aggressive and poor prognostic subtype of breast cancer. This study aims to evaluate the prognostic value of clinicopathological factors and novel inflammatory marker HALP (hemoglobin, albümin, lymphocyte, platelet) score in early-stage TNBC patients.

Methods: It was one center, retrospective study. We analyzed some parameters of TNBC patients and the effects of these parameters on overall survival (OS) and disease-free survival (DFS). The cut-off value of the HALP score was accepted as 32,4, which was calculated with the X-tile program. Chi-square test was used to compare 5 and 10 years survival rates, Kaplan-Meier and Cox regressions tests were used to estimate median survivals.

Results: There were 166 patients, the median age was 50, median follow-up time was 64 (range, 2-262) months, median OS was not reached, median DFS was 185 months. In multivariate analysis, HALP score was found not a prognostic factor, stage, tumor necrosis, lymph node extracapsular extension was found a negative prognostic factor for both OS and DFS.

Conclusion: Although, in other studies, HALP score was reported prognostic factor in some cancer types, in our study not found a prognostic factor in early-stage TNBC. But future studies should be done about HALP score in metastatic breast cancer.

Keywords: Hemoglobin, triple-negative breast neoplasms, prognosis

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Triple-negative breast cancer (TNBC) is defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) on the cancer cell surface. TNBC accounts for nearly 15% of all breast cancer subtypes. It is commonly diagnosed in younger women.[1] However, in recent studies, it has been reported that the rate of TNBC is lower.[2] It is generally high grade, and the most common histology is invasive ductal carcinoma.[3] TNBC patients have a poorer overall survival (OS) and disease-free survival (DFS) than other breast cancer subtypes.[4] There are some well-known prognostic factors in non-metastatic TNBC like pathological features (stage, grade, subtype, ki-67, lymphovascular invasion, tumor lymphocyte invasion) and patient features (age, sex, race, menopausal status, smoking).[5] Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index [(platelet × neutrophil)/ lymphocyte] have been used to predict the breast

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cancer prognosis. Hemoglobin, albumin levels, and other nutrition indices affect the OS in cancer patients. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a novel inflammatory marker. This score can simultaneously evaluate nutritional status and inflammation. The prognostic importance of the HALP score has been demonstrated in some tumor types, especially in prostate cancer.[6] We decided to investigate the early stage TNBC patients' features, and factors (especially HALP score) that have effects on prognosis.

Methods

It was a single center, retrospective study. This study was performed by retrospectively screening early-stage TNBC (from stage I to III) patient files who were diagnosed between January 2009 and June 2019, admitted to Cumhuriyet University Hospital. All of the patients enrolled in the study had pathologically confirmed TNBC histology. We used descriptive statistics to show clinicopathological characteristics. Data about the medications of the patients were recorded from their medical charts. The parameters that may affect the outcome such as age, sex, comorbidities like hypertension (HTN) and diabetes mellitus (DM), menopausal status, performance status (PS), type of surgery, chemotherapy regimen, pathological features (stage, grade, ki-67, lymphovascular invasion [LVI], perineuronal invasion [PNI], tumor necrosis, lymph node extracapsular invasion) were noted. The HALP score was calculated as hemoglobin (g/L) × albumin (g/L) levels × lymphocyte count (/L)/platelet count (/L). The cut-off value of the HALP score was accepted as 32,4, which was calculated with the X-tile software v3.6.1 (Yale University).[6]

We analyzed the OS, which was defined as the time elapsed from the date of diagnosis to the date of death from any cause. For OS, death was accepted as an event time. The follow-up time was defined as the time from the date of diagnosis to the date of death or last follow-up. The statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) version 22 (SPSS Inc, Chicago, IL). Univariate analysis was performed by using the Kaplan–Meier method to estimate the OS of different patient groups, and the groups were compared with the log-rank test. Cox regression analysis was used to determine the association of factors with the OS in the multivariate analysis. In the multivariate analysis, confounders were included if they were significant at a 0.05 level in the univariate analysis (log-rank test) or thought to be important for OS or the effect of the factors. The results were expressed as median OS, PFS, and hazard ratios (HRs) with 95% confidence intervals (CIs). The association between the clinicopathological data and the HALP score was evaluated by the chi-square and Mann-Whitney U tests. A p-value smaller than 0.05 was considered statistically significant.

Results

This study included 166 patients with early-stage TNBC. The median age was 50 (range 25-83). The ratio of patients who became postmenopausal after cancer treatment was 58%. The cancer history of the family in patients was 27%. Comorbidity was present in 67 patients (40%). There were 23 (14%) stage I, 87 (52%) stage II, and 53 (34%) stage III patients (Table 1).

Table 1. Descriptive Characteristics of Patients

	n	%
Age (median, range), year	50 (25-83)	
Menopausal status		
Pre-menopausal	69	42
Post-menopausal	97	58
Comorbidity	67	40
HTN	39	24
DM	22	13
Hearth failure	9	5
Family cancer history	45	27
Histopathology		
Invasive ductal carcinoma	121	73
Medullary carcinoma	19	11
Metaplastic	11	7
Apocrine	5	3
Mixed	4	2
Others	6	4
Stage		
I	23	14
II	87	52
III	53	34
Grade		
I	22	13
II	40	24
III	104	63
Ki 67 (median, range) %	50 (0-100)	
Pathological features		
PNI	34	21
LVI	66	40
Tumor necrosis	21	13
Multicenter/multifocal	69	42
Ductal carcinoma in-situ	73	44
Extracapsular invasion	45	27

DM: Diabetes Mellitus; HTN: Hypertension; LVI: Lymphovascular Invasion; PNI: Perineuronal Invasion.

Modified radical mastectomy was performed on 80 (49%), breast-conserving surgery was performed on 77 (46%) patients, Axillary dissection was performed on 133 (80%), and sentinel lymph node biopsy was performed on 21 (13%) patients. Neoadjuvant chemotherapy was received in 11 patients. There wasn't a complete response, there were 4 partial responses, and 4 stable diseases, 4 progressions. Adjuvant chemotherapy was received on 142 (86%), and adjuvant radiotherapy was received on 124 (75%) patients. There were 15 (9%) local, and 58 (35%) distance recurrences (Table 2).

The median follow-up time was 64 months (range 2–262) for the entire group. For all stages, the median OS was not reached, the 5 years and 10 years OS rates were 69% and 53% respectively. In univariate analysis, there wasn't a significant difference between HALP-score <32,4 group, and ≥32,4 group, in terms of 5-years, 10-years OS rates, and median OS. ECOG PS, stage, LVI, extracapsular invasion, surgery types, neoadjuvant treatment, and Ca 15-3 level were found prognostic factors for OS (Table 3). In multivariate analysis, both extracapsular invasion and neoadjuvant CT were found negative prognostic factors (Table 4). Survival curves of independent prognostic factors affecting OS are shown in Figure 1.

Table 2. Treatments and outcomes.

	n	%
Breast surgery		
No	9	5
Modified radical mastectomy	80	49
Breast-conserving surgery	77	46
Axillary surgery		
No	12	7
Sentinel lymph node biopsy	21	13
Axillary dissection	133	80
Neoadjuvant CT	11	6
Complete response	-	-
Partial response	4	18
Stable disease	5	46
Progression	4	36
Adjuvant CT	142	86
Adjuvant RT	124	75
Results		
Local recurrence	15	9
Secondary primer	7	4
Bilateral breast cancer	8	5
Distance recurrence	58	35
Bone	32	19
Brain	25	16
Lung	24	15
Liver	20	12

CT: Chemotherapy; RT: Radiotherapy.

The median DFS was 185 months. 5-years and 10-years DFS rates were 61% and 52%, respectively, for all stages. In univariate analysis, there was a statistically meaningful difference between HALP-score <32,4 group (72 mo., CI. 18,8-125,1), ≥32,4 group (185 mo., CI. 31,5-331,4) in terms of median DFS (p=.04). But in multivariate analysis, this significant difference was disappeared. Also, there wasn't a significant difference between HALP-score <32,4, and ≥32,4 groups, in terms of 5-years and 10-years DFS rates. In univariate analysis, histopathology, ECOG performance status, stage, LVI, extracapsular invasion, surgery types, tumor necrosis, neoadjuvant treatment, CEA, and Ca 15-3 level were found prognostic factors for PFS (Table 5). In multivariate analysis, tumor necrosis, extracapsular invasion, and neoadjuvant CT were found negative prognostic factors for DFS (Table 6). Survival curves of independent prognostic factors affecting DFS are shown in Figure 2.

Discussion

In this study, we assessed the prognostic effect of preoperative HALP score and other features in early-stage TNBC. HALP score didn't find as a prognostic factor for OS and DFS. But, previous studies investigating the prognostic features of the HALP score in cancer were generally assessed in metastatic stages or after surgery.[7] The lack of prognostic significance of the HALP score in our study may be due to we did it in early-stage patients and used preoperative values. The HALP score can reflects the nutritional and immune status of patients, which had been shown to have a prognostic role in some cancer types.[8] HALP score consists of four parameters. Actually, when these four parameters are evaluated separately, all four parameters have prognostic importance. Anemia was reported as a bad brognostic factor for breast cancer recurrence.[9] Lower preoperative blood albumin concentration was reported significant independent negative predictor of cancer-specific survival in early stage breast cancer.[10] Low lymphocyte (high neutrophil/lymphocyte ratio) is associated with an adverse OS and DFS in patients with breast cancer.[11] High platelet (high platelet/lymphocyte ratio) is associated worse prognosis in breat cancer.[12]

Although there are a lot of literature data about prognostic factors of TNBC, many aspects of this disease are still in the dark. In our analysis, well-known prognostic factors about breast cancer were assessed, also. 5-years OS

Table 3. The prognostic factors affecting overall survival.

Univariate analysis	n	The 5-year OS (%)	The 10-year OS (%)	The median OS (month)	p
Menopausal status					
Pre-menopausal	69	68	57	NR	.76
Post-menopausal	97	70	51	136	
Histopathology					
IDC	121	66	49	120	.10
Others	45	76	66	NR	
ECOG PS					
ECOG 0	107	78	63	NR	<.001
ECOG 1	41	62	49	118	
≥ ECOG 2	18	15	8	38	
Stage					
I	20	100	89	NR	<.001
II	84	81	61	NR	
III	50	51	38	69	
IV	12	0	0	9	
Grade					
I	22	72	60	NR	.23
II	40	75	61	NR	
III	104	66	49	109	
LVI					
No	82	77	59	NR	.011
Yes	66	56	47	91	
Tumor necrosis					
No	54	84	77	NR	.008
Yes	69	59	50	36	
Extracapsular invasion					
No	109	83	68	NR	<.001
Yes	45	52	32	64	
Surgery types					
MRM	80	65	48	118	.017
BCS	77	82	67	NR	
Neoadjuvant CT					
No	155	72	55	NR	.001
Yes	11	27	-	36	
CEA					
≤5.2	119	73	53	NR	.134
>5.2	24	48	48	42	
Ca 15-3					
≤25	103	76	64	NR	.001
>25	39	52	31	63	
HALP score					
<32.4	34	48	15	108	.09
≥32.4	29	60	23	NR	

CEA: Carcinoembryonic Antigen; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; IDC: Invasive ductal carcinoma; LVI: Lymphovascular Invasion; NR: Not-reached; PS: Performance Status.

rates of stages I, II, III were found 100, 80, 5% respectively. Similar rates were reported in other studies. In a study, it is reported that stage I, II-III 5-years OS rates were 95%, 80%, respectively.[13] In our study premenopausal patients' rate was 42% and we found menopause situation doesn't affect the OS and PFS. In a study, similar premenopausal rates were reported but they found premenopausal status as a bad prognostic factor for disease progression in

Table 4. Independent prognostic factors affecting overall survival.

Multivariate analysis	Hazard ratio	95% confidence interval	p
Extracapsular invasion			
No	1		<.001
Yes	4.43	1.93-10.05	
Neoadjuvant CT			
No	1		.046
Yes	2.84	1.02-7.95	

CT: Chemotherapy; RT: Radiotherapy.

TNBC.[14] Also, in another study, ≤35 years old patients were found to have a worse prognosis.[15] In this study, HTN and DM were found don't affect the OS and PFS. In a retrospective study, HTN was reported as a negative prognostic factor for DFS and OS, but DM was not.[16] We found lymph node extracapsular extension (ECE) decreases the 5-years OS rate 4.4 times and 5-years DFS rate 6.6 times compared to the absence of ECE. In a study, ECE positivity was reported as a bad prognostic factor for 5-years OS (2.5 times) and DFS (2.1 times) rates in TNBC patients.[17] We found NACT negatively affects the OS and DFS. But, this result may be misleading. Our NACT received group was very small (11 patients). NACT received patients group was in more advanced stages (2 patients stage II, 9 patients stage III) than the non-NACT received group. A complete response to NACT is a well-known good prognostic factor but there was no complete response in our study. In many studies, it was reported that NACT is associated with high rates of clinical response and more cosmetically acceptable surgery. However, NACT has not been shown to improve OS or DFS compared with the same regimen received after surgery.[18] Despite the low NACT rate, our breast-conserving surgery (BCS) rate was 46%. Guo et al.[19] were reported from National Cancer Institute (NCI), TNBC patients' BCS rate was nearly 50%. Sentinel lymph node biopsy (SLNB) is recommended especially for those who have clinically negative axillary lymph nodes in patients with early breast cancer (T1 or T2) and patients with ductal carcinoma in situ (DCIS) when mastectomy is performed. In our study, SLNB performed patients rate was 13%, stage I patient rate was 12%.

Patients with TNBC have a higher rate of recurrence, decreased DFS compared to other subtypes of breast cancer. We found tumor necrosis increases the recurrence rate 3.38 times (95% CI, 1.34-8.53) but does not affect the OS. In a study, tumor necrosis found independent negative prognostic factors for recurrence.[20] In univariate analysis, stage, ECOG, and LVI were found to affect the DFS but they lost independence in the multivariate analysis. But, in multiple previous published studies, these factors demonstrated important prognostic factors for DFS.[21, 22]

There were some limitations of this study. This was a retrospective study, we couldn't reach some data from patients' files. There weren't important molecular and genetic data that can affect outcomes. Many new molecular prognostic factors emerging nowadays and precision medicine are becoming increasingly important in TNBC treatment decisions.[23] Our patients couldn't all newly released drugs. New drugs (like immunotherapy and targeted drugs) are

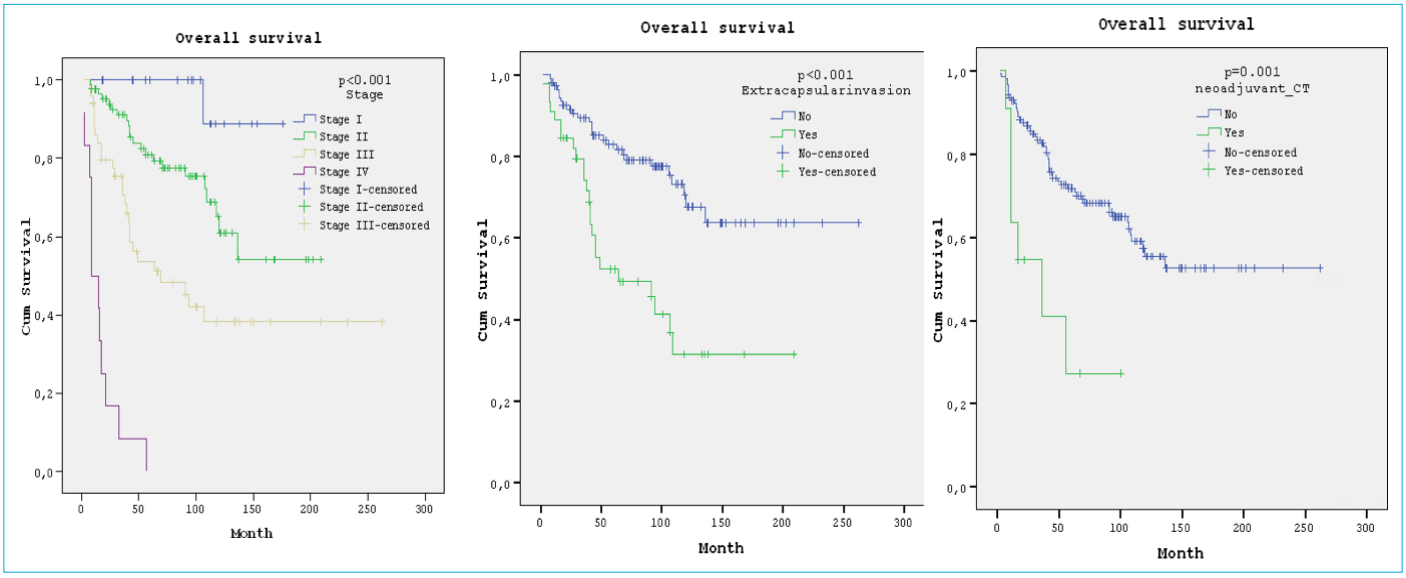

Figure 1. Effects of the stage, extracapsular extension, and NACT on overall survival.

Table 5. Factors affecting disease-free survival

Univariate analysis	n	The 5-year DFS (%)	The 10-year DFS (%)	The median DFS (month)	p
Menopausal status					
Pre-menopausal	69	58	50	195	.828
Post-menopausal	97	64	53	185	
Histopathology					
IDC	121	56	46	73	.016
Others	45	74	68	NR	
ECOG PS					
ECOG 0	107	73	62	NR	<.001
ECOG 1	41	49	43	45	
≥ ECOG 2	18	17	-	24	
Stage					
I	20	94	94	NR	<.001
II	84	76	62	NR	
III	50	38	30	32	
Grade					
I	22	67	56	NR	.196
II	40	67	64	185	
III	104	55	45	108	
LVI					
No	82	76	65	185	<.001
Yes	66	41	39	47	
Tumor necrosis					
No	54	77	74	NR	.002
Yes	69	51	48	70	
Extracapsular invasion					
No	109	77	69	NR	<.001
Yes	45	40	25	41	
Surgery types					
MRM	80	55	46	73	.020
BCS	77	76	65	195	
Neoadjuvant CT					
No	155	64	54	185	.002
Yes	11	23	-	11	
CEA					
≤5.2	119	66	58	NR	.035
>5.2	24	33	33	49	
Ca 15,3					
≤25	103	68	61	NR	.002
>25	39	47	35	45	
HALP score					
<32.4	34	40	15	72	.04
≥32.4	29	56	19	185	

CEA: Carcinoembryonic Antigen; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; IDC: Invasive ductal carcinoma; LVI: Lymphovascular Invasion; NR: Not-reached; PS: Performance Status.

more effective than chemotherapy. But there are a limited number of studies about novel inflamatory marker HALP score and cancer prognosis. To our best knowladge it was the firts study about HALP score assessment in early-stage TNBC. In conclusion, this study gives many ideas about TNBC and contributes to the literature.

Table 6. Independent prognostic factors affecting disease-free survival

Multivariate analysis	Hazard ratio	95% confidence interval	p
Tumor necrosis			
No	1		0.010
Yes	3.38	1.34-8.53	
Extracapsular invasion			
No	1		<.001
Yes	6.66	3.12-14.20	
Neoadjuvant CT			
No	1		.003
Yes	4.28	1.63-11.18	
HALP score			
<32.4	1	0.33-1.45	.33
≥32.4	0.6		

CT: Chemotherapy; HALP: Hemoglobin-albumin-lymphocyte-platelet; mo: month.

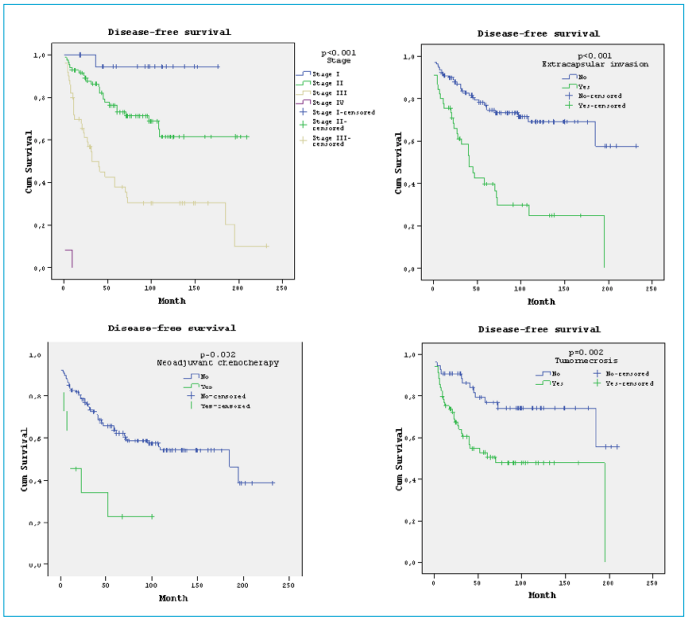

Figure 2. Effects of the stage, extracapsular extension, tumor necrosis, and NACT on DFS.

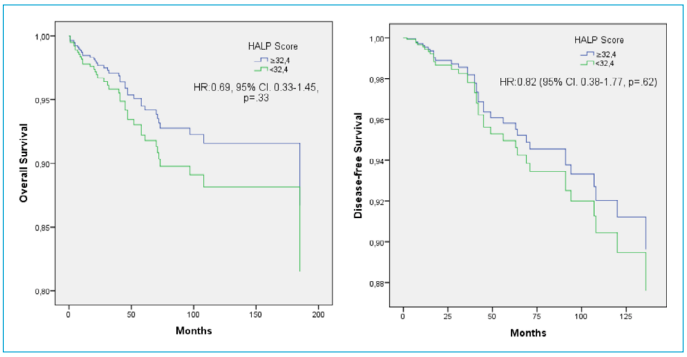

Figure 3. Effects of HALP score on disease-free and overall survival in triple-negative breast cancer patients.

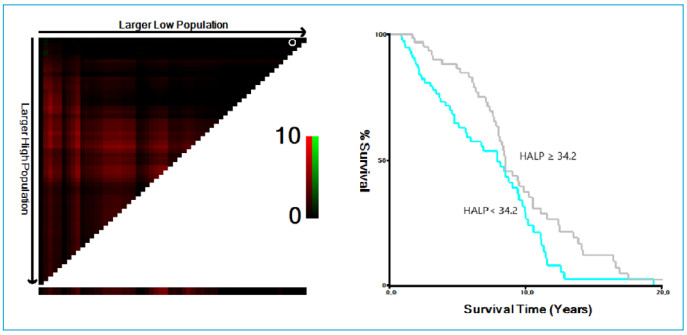

Figure 4. Cut-off value of HALP score as determined by X-Tile software program.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained from Cumhuriyet University Ethics Committe, at date 19/08/2021, number is 2021-08/45.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – C.A.; Design – M.Y.; Supervision – B.Y.; Materials – E.E.; Data collection &/or processing – N.D.; Analysis and/or interpretation – B.Y.; Literature search – C.A.; Writing – C.A; Critical review – B.Y.

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