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The Role of Biomarkers In Predicting Neoadjuvant Treatment Response In Gastric Cancer

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ABSTRACT

Gastric cancer remains an important health problem in terms of both its incidence and mortality. The standard treatment for non-metastatic locally advanced disease is neoadjuvant chemotherapy, followed by surgery. In this study, we investigated the role of the HALP score and other immunonutritional biomarkers in predicting the response to treatment in patients with locally advanced gastric cancer receiving neoadjuvant chemotherapy.

A retrospective evaluation was conducted on patients who received neoadjuvant chemotherapy for gastric cancer and were treated and followed up at the Van Yüzüncü Yıl University Faculty of Medicine, Dursun Odabaşı Medical Center, and Van Training and Research Hospital between 2015 and 2024. In this study, the following parameters were examined: pretreatment hemogram parameters, tumor biomarkers, disease stage at the time of diagnosis, and tumor invasion characteristics. The objective of this study was to ascertain the relationship between these parameters and response to neoadjuvant treatment.

A total of 183 patients were included in the study, of which 62 (33.9%) were female and 121 (66.1%) were male. A statistically significant correlation was identified between the treatment response status of patients and the type of surgery, neural invasion, vascular invasion, TNM classification, HER2 status, and neoadjuvant regimen status ($p < 0.05$).

Our findings indicate that age, neural invasion, vascular invasion, HER2 status, and chemotherapy regimen, among clinicopathological features, and tumor markers (CEA and CA 19-9), white blood cell, lymphocyte, and monocyte counts, among laboratory values, can predict the response in neoadjuvant patients.

Keywords: Gastric cancer, neoadjuvant treatment, response evaluation, biomarkers

Introduction

Gastric cancer (GC) continues to represent a significant global health concern. It is the fifth most commonly diagnosed malignancy, with more than one million new cases per year, and the third most common cause of cancer-related deaths, with more than 750,000 deaths (1). In a study that compared surgery with epirubicin, cisplatin and infused 5-fluorouracil (ECF) administered perioperatively to patients with potentially operable gastric cancer, it was reported that progression-free survival and overall survival were significantly better in patients receiving perioperative ECF (2). Based on these data, ECF was employed in perioperative treatment for a considerable period of time. In the subsequent FLOT4 study, the standard perioperative regimen ECF/ECX was compared with FLOT (5-Fluorouracil, leucovorin, oxaliplatin and docetaxel). In this study, the median overall survival was found to be statistically significantly longer in the FLOT arm (3). The FLOT regimen has become the standard perioperative treatment regimen for appropriate patient populations.

The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend neoadjuvant chemotherapy for locally advanced non-metastatic stage patients with adequate organ function (4, 5). Neoadjuvant chemotherapy mainly aims to provide tumor downstaging and R0 resection for advanced gastric cancer cases (6). For patients receiving neoadjuvant chemotherapy, the pathological response rate or degree of tumor regression is among the main factors affecting overall survival (7).

Inflammation plays an important role in cancer progression and management. Furthermore, Hanahan et al. identified inflammation as a hallmark of cancer (8). Lymphocytes are vital components of the immune system. They can stop tumor progression by inhibiting tumor proliferation and metastasis through mechanisms of cytotoxicity (9). Platelets are a crucial source of cytokines that can facilitate tumor growth by enhancing angiogenesis (10, 11). Recent studies have demonstrated that inflammatory and nutritional markers can predict the treatment response and survival in patients with cancer. The HALP score comprises four parameters:

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hemoglobin, albumin, lymphocytes, and platelets. It was devised by Chen et al. to predict the prognosis of gastric carcinomas (12). These four markers serve as fundamental indicators of the immune and nutritional status of patients with cancer. Furthermore, it has been demonstrated that the neutrophil/lymphocyte ratio (NLR), platelet/neutrophil ratio (PLR), CRP/albumin, and carcinoembryonic antigen/albumin (CEA/albumin) can predict the response to treatment in patients with locally advanced gastric cancer undergoing neoadjuvant chemotherapy (13, 14).

The identification of a reliable indicator to predict tumor response and prognosis in patients receiving perioperative chemotherapy before treatment is a key objective of ongoing research. This will ultimately enable the optimization of the treatment strategy. In addition to the clinicopathological characteristics of patients, whole blood biochemistry and tumor markers routinely examined before chemotherapy, and various biomarkers generated from these tests, have been used to predict response to treatment. However, there is no clear consensus among the study results.

In this study, we aimed to investigate the role of the HALP score and other immunonutritional biomarkers in predicting the response to treatment in patients with locally advanced gastric cancer receiving neoadjuvant chemotherapy.

Materials and Methods

In our study, patients who received neoadjuvant chemotherapy for gastric cancer and were followed up at Van Yüzüncü Yıl University Medical Faculty Dursun Odabaşı Medical Centre and Van Training and Research Hospital between 2015 and 2024 were evaluated retrospectively.

The inclusion criteria were as follows: (1) age >18 years, (2) cytological or histological diagnosis of gastric carcinoma, (3) adequate organ function for chemotherapy, and (4) at least two cycles of chemotherapy. The exclusion criteria were as follows: (1) age <18 years, (2) no pathological or cytological diagnosis, and (3) clinical or radiological TNM stage 4.

Following a diagnosis of gastric cancer, a multidisciplinary council comprising relevant departments decided to administer neoadjuvant treatment. The patients were evaluated for surgical treatment two–four weeks after the conclusion of chemotherapy. Data, including demographic and clinicopathological characteristics, complete blood count, biochemical tests, serum tumor markers, and other parameters of the patients before neoadjuvant treatment, were retrospectively obtained from hospital file archives and digital data systems. The exact spelling of the parameters used in this study is as follows.

HALP Score = [hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)]/platelets (/L), *SII* = (platelets × neutrophils)/lymphocytes, *NLR* = neutrophils/lymphocytes, *PLR* = platelets/neutrophils, *SIRI* = (neutrophil × monocyte)/lymphocyte, *AISI* = (neutrophil × platelet × monocyte)/lymphocyte, *NMR* = neutrophil/monocyte, *LMR* = lymphocyte/monocyte. The parameters used in the calculations were obtained from the values obtained before neoadjuvant treatment.

The pathological response evaluation of patients who underwent surgery following neoadjuvant treatment was conducted in accordance with the Tumor Regression Grade (TRG) Becker criteria, as outlined below: Grade 1, complete (0% residual tumor; Grade 1a) or subtotal tumor regression (<10 The percentage of residual tumor per tumor bed is classified as Grade 1b; Grade 2 is assigned to cases of partial tumor regression (10-50% residual tumor per tumor bed), while Grade 3 is given to cases of minimal or no tumor regression (50% residual tumor per tumor bed) (15). Patients with pathological response status of grades 1 and 2 were defined as responders, and patients with grade 3 were defined as non-responders.

Statistical Analysis: The The SPSS 27.0 software was used for data analysis. Descriptive statistics were used to evaluate patient characteristics and parameter frequencies. Frequency (n) and percentage (%) for categorical (qualitative) variables and mean, standard deviation (mean±ss), and minimum and maximum values for numerical (quantitative) variables are indicated. In cases where the normality assumption was deemed appropriate, parametric tests were applied; in cases where it was observed that it was not appropriate, non-parametric tests were applied. Mann-Whitney U test was used for non-normally distributed numerical variables, and the chi-square test was used for categorical variables. Confidence interval 95% and a two-way P significance value <0.05 were accepted.

The sample size of this retrospective study titled "The role of biomarkers in predicting response to neoadjuvant therapy in gastric cancer" was calculated using G*Power statistical program (ver.3.1.9.7)*. Accordingly, a "minimum of 147 patients (sample)" was determined by taking Power 0.95, Effect size 0.3 and Type-1 error (□) 0.05. However, in order to secure the sample number and keep the Power value high, the

sample number was increased and "183 samples" were used. The post-hoc Power (power of the test) recalculated according to this sample size increased to 97%.

Results

A total of 183 patients were included in the study, of whom 62 (33.9%) were female and 121 (66.1%) were male. The general demographic characteristics of patients are shown in Table 1. The majority of patients (81.4%) had clinical stage 3 disease, and the majority of patients (51.4%) had T3 tumors. N2 involvement was observed in 32.8% of cases, whereas N1 involvement was noted in 32.2% of cases. The majority of patients (90.7%) underwent curative surgery and 55.2% underwent total gastrectomy. Most patients (74.0%) underwent D2 lymph node dissection, which represents the standard surgical procedure for this type of surgery. Most tumors (58.5%) were located in the gastroesophageal junction, whereas 22.4% were located in the antrum-fundus region. Human epidermal growth factor receptor 2 (Her-2) was positive in 12.8% of patients. Most patients (84.7%) received FLOT as a neoadjuvant chemotherapy regimen. The additional clinical features are presented in Table 2.

Only 1.1% of the patients stopped treatment, and 85.2% did not undergo dose reduction. Most patients (74.3%) received granulocyte colony-stimulating factor) (G-CSF) prophylaxis. Among the patients, 33.3% had a complete or near-complete pathological response, 31.7% had a moderate response, and 35.0% had a poor or no response. Recurrence occurred in 22.4% of patients. Other toxicity and treatment response characteristics are shown in Table-3.

There was a statistically significant relationship between the treatment response status of the patients and the type of surgery, neural invasion, vascular invasion, TNM, Her-2 status, and neoadjuvant regimen status ($P<0.05$). Palliative surgery (17.2%), neural invasion (85.2%), vascular invasion (90.2%), TNM stage 3 (78.7%), T4 (49.2%), N3 (42.6%), Her-2 negative (89.3%), and docetaxel, cisplatin, and 5-fluorouracil (DCF) regimen (14.1%) were more common in patients who did not respond to treatment. The relationship was not significant for the other characteristics ($P>0.05$) (Table-4).

The mean age was 63.48 ± 9.48 years in the group that did not respond to treatment (n=64) and 66.27 ± 8.49 years in the group that responded (n=119). There was a significant difference in age between the two groups ($P = 0.044$). This was higher in patients who responded to the treatment.

The mean number of involved lymph nodes was 7.25 ± 6.51 in the non-responding group (n=64) and 2.59 ± 5.26 in the responding group (n=119). There was a significant difference in the retained lymph node values between the groups ($P = 0.001$). The number of involved lymph nodes was higher in patients who did not respond to the treatment.

The mean CEA value was 737.6 ± 570.93 in the group that did not respond to treatment (n=64), and 7.81 ± 16.59 in the group that responded (n=119). A significant difference was observed in CEA values between the two groups ($P = 0.019$). CEA levels were higher in patients who did not respond to treatment.

The mean carbohydrate antigen 19-9 (CA 19.9) value was 520.23 ± 182.98 in the non-responders (n=64) and 85 ± 29.69 in the responders (n=119). A significant difference was observed between the CA 19.9 values of the groups ($P = 0.002$).

The mean white blood count was 8.09 ± 2.31 in the non-responders (n=64) and 7.43 ± 2.33 in the responders (n=119), respectively. There was a significant difference between the groups ($P = 0.018$), with measurements being higher in patients who did not respond to treatment.

The mean lymphocyte count was 2.02 ± 0.66 in the non-responding group (n=64) and 1.81 ± 0.72 in the responding group (n=119). A significant difference was observed between the two groups ($P = 0.049$). This measurement was higher in patients who did not respond to treatment.

The mean monocyte count was 0.56 ± 0.22 in the non-responders (n=64) and 0.51 ± 0.47 in the responders (n=119). A significant difference was observed between the two groups ($P = 0.007$). This measurement was higher in patients who did not respond to treatment. No significant differences were found in the other measurements ($P > 0.05$). The parameters examined for treatment response are shown in Table 5.

Discussion

In the present study, we found that age, neural invasion, vascular invasion, HER2 status, and chemotherapy regimen, among clinicopathological features, and tumor markers (CEA and CA 19-9), white blood cell, lymphocyte, and monocyte counts among laboratory values, could predict response in patients receiving neoadjuvant chemotherapy. However, the HALP score, SII, NLR, PLR, SIRI, AISI, NMR, and LMR were not found to be related to response.

In a study investigating the factors associated with tumor response in gastric cancer patients receiving

Table 1: Distribution of Demographic Characteristics

		n	%
Gender	Woman	62	33,9
	Male	121	66,1
Age	<65	61	33,3
	≥65	122	66,7
Comorbidity status	Yok	99	54,1
	Var	84	45,9
Comorbidities	Hyper tension	50	27,3
	Diabetes melitus	30	16,4
	Ischaemic heart disease	24	13,1
	Cerebro vascular event	4	2,2
	Chronic kidney disease	3	1,6
	Congestive heart failure	1	0,5
	Chronic obstructive pulmonary disease	4	2,2
	Other	14	7,7
Smoking	None	136	74,3
	There is	47	25,7

Frequency analysis of patients characteristics

neoadjuvant therapy, tumor location, smoking history, clinical T and N stages, and tumor differentiation were shown to be associated with tumor response (16). Another retrospective study showed that age < 60 years, poor differentiation, and weight loss during neoadjuvant chemotherapy were independent risk factors for the effect of neoadjuvant chemotherapy, but clinical T and N stage did not affect the response (17). In our study, sex, clinical T and N stage, tumor location, and tumor differentiation were not associated with response. Age, HER-2 status and neoadjuvant chemotherapy regimen were associated with response. In patients who did not respond to treatment, the mean age was lower, HER-2 negative and DCF regimens were more common. In a study evaluating 53 patients with locally advanced gastric cancer who received neoadjuvant chemotherapy, HER2 was shown to be an independent predictor of response (18). In a study evaluating the efficacy of FLOT and modified DCF in neoadjuvant treatment, both regimens showed similar efficacy (19). In our study, the proportion of patients who received the DCF regimen was higher in the group of patients who did not respond to treatment.

In a retrospective study conducted to identify histopathological factors predicting response to neoadjuvant treatment in gastric cancer, including 80 patients, the presence of vascular or perineural invasion predicted poor response to treatment (20). In our study, the rates of lymphovascular and perineural invasion were significantly higher in patients who did not respond to treatment.

Tumor markers have shown little utility as a screening method in the general population owing to their low sensitivity and specificity in detecting early primary tumors; however, they can be used clinically to monitor tumor recurrence and as prognostic factors, as higher levels are observed in advanced disease (21). CEA and CA 19-9 are widely used markers of gastric cancer (22). In our study, CEA and CA 19-9 levels were lower in the group with pathological response.

In a study examining the role of the HALP score in gastric cancer, sex, age, histological subtypes, tumor location, adjuvant or palliative treatment status, TNM stage, CEA and CA19-9 levels, and overall survival of patients in the low and high HALP groups were statistically similar between the two groups. (23). In another study in which only metastatic disease was included, overall survival was significantly longer in patients with high HALP scores than in those with low HALP scores (24). In our study, there was no statistically significant difference in the response to treatment between patients with low and high HALP scores.

In a study evaluating 238 locally advanced gastric cancer patients, TRG grade was significantly worse in patients with high NLR and PLR values (13). In another study evaluating 225 patients who underwent D2 dissection after neoadjuvant chemotherapy, high NLR and LMR change and preoperative anemia were associated with poor prognosis (25). In our study, the NLR, PLR, and LMR were not associated with response.

Table 2: Distribution of Clinical Characteristics

		n	%
Clinical stage	1	6	3,3
	2	28	15,3
	3	149	81,4
Clinical T stage	T0	1	0,5
	T1	4	2,2
	T2	30	16,4
	T3	94	51,4
	T4	54	29,5
Clinical N stage	N0	21	11,5
	N1	59	32,2
	N2	60	32,8
	N3	43	23,5
Type of surgery	Inoperable	2	1,1
	Curative	166	90,7
	Palliative	15	8,2
Gastrectomy type	Subtotal	71	39,2
	Total	100	55,2
	Local excision	10	5,5
Lymph node dissection	D1	47	26,0
	D2	134	74,0
Tumour localisation	Gastrocephalic junction	107	58,5
	Corpus-fundus	32	17,5
	Anthrum-fundus	41	22,4
	Linitis plsatica	3	1,6
Histopathological type	Stone ring cell	35	19,1
	Adenocarcinoma	130	71,0
	Mucinous	9	4,9
	Stone ring cell + Adenocarcinoma	6	3,3
	Stone ring cell + Mucinous	2	1,1
	Adenocarcinoma + Mucinous	1	0,5
Grade	Good differential	7	4,0
	centre differential	103	59,2
	less differential	62	35,6
	Undifferential	2	1,1
Neural invasion	None	86	48,0
	There is	93	52,0
Vascular invasion	None	77	43,0
	There is	102	57,0
ypTNM	0	22	12,9
	1	22	12,9
	2	59	34,5
	3	68	39,8
ypT	0	22	12,2
	1	17	9,4
	2	26	14,4
	3	79	43,9
	4	36	20,0
ypN	0	78	43,3
	1	37	20,6
	2	24	13,3
	3	41	22,8
Her-2 status	Negative	136	87,2
	Positive	20	12,8

ECOG -PS	0	107	58,5
	1	72	39,3
	2	4	2,1
	3	1	0,5
Neoadjuvant regimen	EOF	3	1,6
	DCF	19	10,4
	FOLFOX	6	3,3
	FLOT	155	84,7

Frequency analysis of patients characteristics
ECOG -PS: Eastern Cooperative Oncology Group performance score
EOF: Epirubicin- oxazoplatin- 5 flourouracil
DCF: Docetaxel- cisplatin- 5 flourouracil
FOLFOX: 5 flourouracil - folinic acid – oxazoplatin
FLOT: 5 flourouracil – oxazoplatin- Docetaxel

Table 3: Distribution of toxicity and treatment response characteristics

		n	%
Toxicity	Grade 1	118	66,3
	Grade 2	46	25,8
	Grade 3	2	1,1
	Grade 4	12	6,7
Stop treatment	None	181	98,9
	There is	2	1,1
Dose reduction	None	156	85,2
	There is	27	14,8
Dose deferral	None	153	83,6
	There is	30	16,4
Granulocyte stimulating factor prophylaxis	None	47	25,7
	There is	136	74,3
Pathological response	Complete or near complete answer	61	33,3
	middle answer	58	31,7
	Weak, no answer	64	35.0
Response	There is	119	65,0
	None	64	35,0
adjuvant treatment	No	19	10,6
	Yes	161	89,4
Relapse	None	121	66,1
	There is	62	33,9
Relapse location	Local	3	1,6
	Liver	19	10,4
	Peritoneum	12	6,6
	Distant lymph node	4	2,2
	Lung	1	0,5
	Bone	5	2,7
	ovarian	3	1,6
	Other	6	3,3
Ex	None	125	68,3
	There is	58	31,7

Frequency analysis of patients characteristics

Table 4: Relationship between Clinical Characteristics and Treatment Response Status

		Responsse				p
		There is (n=119)		None (n=64)		
		n	%	n	%	
Clinical stage	1	5	4,2	1	1,6	0,740
	2	20	16,8	8	12,5	
	2	94	79,0	55	85,9	
Clinical T stage	T0	1	0,8	0	0,0	0,498
	T1	2	1,7	2	3,1	
	T2	22	18,5	8	12,5	
	T3	63	52,9	31	48,4	
	T4	31	26,1	23	35,9	
Clinical N stage	N0	17	14,3	4	6,3	0,492
	N1	43	36,1	16	25,0	
	N2	37	31,1	23	35,9	
	N3	22	18,5	21	32,8	
Type of surgery	Inoperable	0	0,0	2	3,1	0,046*
	Curative	115	96,6	51	79,7	
	Palliative	4	3,4	11	17,2	
Gastrectomy type	Subtotal	49	41,2	22	35,5	0,157
	Total	64	53,8	36	58,1	
	Local excision	6	5,0	4	6,5	
Lymph node dissection	D1	34	28,6	13	21,0	0,757
	D2	85	71,4	49	79,0	
Tumour localisation	Gastrocephalic junction	65	54,6	42	65,6	0,353
	Corpus-fundus	26	21,8	6	9,4	
	Anthrum-fundus	27	22,7	14	21,9	
Histopathological type	Linitis plsatica	1	0,8	2	3,1	0,095
	Stone ring cell	24	20,2	10	15,6	
	Adenocarcinoma	83	69,7	47	73,4	
	Mucinous	6	5,0	3	4,7	
	Stone ring cell + Adenocarcinoma	4	3,3	3	4,7	
	Stone ring cell + Mucinous	1	0,8	1	1,6	
	Adenocarcinoma + Mucinous	1	0,8	0	0,0	
Grade	Good differential	6	5,2	1	1,7	0,925
	centre differential	76	65,5	27	46,6	
	less differential	32	27,6	30	51,7	
	Undifferential	2	1,7	0	0,0	
Neural invasion	None	77	65,3	9	14,8	0,010*
	There is	41	34,7	52	85,2	
Vascular invasion	None	71	60,2	6	9,8	0,001*
	There is	47	39,8	55	90,2	
ypTNM	0	22	20,0	0	0,0	0,001*
	1	22	20,0	0	0,0	
	2	46	41,8	13	21,3	
	3	20	18,2	48	78,7	
yT	0	22	18,5	0	0,0	0,001*
	1	17	14,3	0	0,0	
	2	24	20,2	2	3,3	
	3	50	42,0	29	47,5	
	4	6	5,0	30	49,2	
yN	0	73	61,3	5	8,2	0,001*
	1	27	22,7	10	16,4	

	2	4	3,4	20	32,8	
	3	15	12,6	26	42,6	
Her-2 status	Negative	86	86,0	50	89,3	0,001*
	Positive	14	14,0	6	10,7	
	0	79	66,4	28	43,8	
ECOG- PS	1	38	31,9	34	53,1	0,734
	2	1	0,8	2	3,1	
	3	1	0,8	0	0,0	
	EOF	1	0,8	2	3,1	
Neoadjuvant regimen	DCF	10	8,4	9	14,1	0,006*
	FOLFOX	3	2,5	3	4,7	
	FLOT	105	88,2	50	78,1	
	Grade 1	77	65,8	41	67,2	
Toxicity	Grade 2	33	28,2	13	21,3	0,242
	Grade 3	2	1,7	0	0,0	
	Grade 4	5	4,3	7	11,5	

*p<0,05 significant relationship, p>0,05 no significant relationship; Chi-square
ECOG -PS : Eastern Cooperative Oncology Group performance score
EOF: Epirubicin- oxazoplatin- 5 flourouracil
DCF: Docetaxel- cisplatin- 5 flourouracil
FOLFOX: 5 flourouracil - folinic acid – oxazoplatin
FLOT: 5 flourouracil – oxazoplatin- Docetaxel

Table 5: Comparison of Measurements according to Response to Treatment

	Response				p
	There is (n=119)		None (n=64)		
	Min-Max(M)	Meant±SS	Min-Max(M)	Meant±SS	
Age	37-80 (66)	66,27±8,49	37-83 (65,5)	63,48±9,48	0,044*
Height	130-180 (167)	164,6±9,69	147-184 (167)	164,12±10,33	0,787
Weight	38-178 (67)	69,37±15,56	46-85 (67,5)	67,26±11,08	0,525
body mass index	16,9-72,2 (25,1)	26,14±6,86	19,6-35 (24,4)	24,82±4,01	0,236
Neoadj cure number	1-8 (4)	4,39±1,04	1-8 (4)	4,38±1,2	0,907
Extracted LN	7-66 (34)	33,28±12,99	2-50 (33)	30,1±10,47	0,100
Retained LN	0-24 (0)	2,59±5,26	0-22 (5)	7,25±6,51	0,000*
Relapse duration	3,5-30,2 (16,4)	14,71±6,73	5-35,6 (10,6)	13,16±9,08	0,549
Survival time	4,1-73,9 (18,7)	21,08±12,98	2,6-55,5 (13,3)	18,53±11,81	0,194
Neadj start time	0-375 (18)	24,54±39,18	0-144 (15,5)	26,38±32,27	0,981
CEA	0,3-139 (3)	7,81±16,59	0,7-44941 (4,4)	737,6±570,93	0,019*
CA 19.9	0,3-2307 (10)	85±292,69	0,2-12000 (18,2)	520,23±182,98	0,002*
LDH	120-450 (200)	210,07±67,53	119-1192 (198,5)	226,77±147,26	0,847
ALB	26-46 (39)	38,5±4,23	25-49 (39)	38,27±5,64	0,774
CRP	0,3-169 (5)	11,3±18,62	1,7-114 (10)	15,06±20,7	0,269
WBC	3,9-19,9 (7,1)	7,43±2,33	4,1-15 (7,9)	8,09±2,31	0,018*
HB	57-165 (124)	122,42±25,3	47-165 (125)	124,71±21,48	0,520
PLT	132-474 (263)	267,96±76,47	109-533 (283,5)	283,08±92,11	0,237
NEU	1,8-17,3 (4,4)	4,76±1,93	1,6-12,6 (4,7)	5,26±2,21	0,076
LYM	0,2-4,6 (1,7)	1,81±0,72	0,7-4 (1,9)	2,02±0,66	0,049*

MONO	0-5 (0,5)	0,51±0,47	0-1,3 (0,5)	0,56±0,22	0,007*
HALP	4,1-118,6 (29,6)	34,17±19,32	6,7-86,7 (32,1)	38,14±20,6	0,197
SII	211,5-5289 (647,8)	849,83±724,9	121,8-3682,6 (661,2)	902,12±783,01	0,810
NLR	0,8-24,6 (2,7)	3,31±3,17	0,8-11,9 (2,5)	3,01±2,12	0,406
PLR	11,5-146,2 (60,2)	62,48±24,65	18,8-161,3 (57,4)	60,06±24,98	0,529
SIRI	0,3-12,3 (1,2)	1,76±1,88	0,4-6,3 (1,3)	1,71±1,31	0,706
AISI	49,2-3173,4 (302,5)	468,73±513,56	56,7-3315,9 (373,1)	530,08±552,98	0,333
NMR	0,7-33,3 (9,6)	10,06±4,37	4-115 (8,1)	11,3±14,18	0,167
LMR	0,3-8,9 (3,5)	3,84±1,6	1,4-12,3 (3,6)	3,9±1,81	0,810

*p<0,05 there is a significant difference, p>0,05 there is no significant difference; dependent group t/Mann Whitney tests
HALP: haemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)/platelets (/L)
SII: platelets×neutrophils /lymphocytes,
NLR: neutrophils/lymphocytes,
PLR = platelets/neutrophils,
SIRI neutrophil × monocyte /lymphocyte
AISI = (neutrophil × platelet × monocyte)/lymphocyte
NMR: neutrophil/monocyte
LMR =: lymphocyte/monocyte

The aggregate index of systemic inflammation (AISI) (26), systemic immune-inflammation index (SII) (27), and SIRI (28) have been found to be associated with prognosis in patients with gastric cancer, but no study has examined the relationship with neoadjuvant response. In our study, there was no significant relationship between the levels of AISI, SII, and SIRI in patients with and without a response to treatment.

The association between leukocytosis and poor prognosis has been confirmed in oropharyngeal, esophageal, and cervical cancer (29-31). Furthermore, in triple negative breast cancer molecular subtype, low white blood cell count (<6.75 G/L) was predictive of a higher pathological complete response rate (32). In our study, it was higher in patients who did not respond to the treatment. In a study evaluating more than 3,000 patients who underwent radical gastrectomy, high absolute neutrophil, monocyte, and platelet counts and low absolute lymphocyte counts were associated with poor prognosis of gastric cancer (33). In our study, the lymphocyte count was higher in patients who did not respond to neoadjuvant treatment. Monocyte count is a negative prognostic factor associated with inflammation. In a retrospective analysis of 278 patients with stage II and III gastric cancer who underwent curative gastrectomy, high monocyte levels were associated with poor prognosis (34). In our study, the monocyte count was higher in patients who did not respond to treatment.

Despite the limitations of our study, including its retrospective nature and lack of long-term follow-up, the findings are valuable as they highlight the potential of tumor markers and white blood cell, lymphocyte, and monocyte count values as predictors of neoadjuvant treatment response, a phenomenon that has not been previously reported in the literature. Further research is required in the form of large-scale, multicenter prospective studies with a larger number of patients to determine the factors predicting response to treatment and long-term survival in patients with locally advanced gastric cancer receiving neoadjuvant treatment.

Consequently, our findings indicate that age, neural invasion, vascular invasion, HER2 status, and chemotherapy regimen, among clinicopathological features, and tumor markers (CEA and CA 19-9), white blood cell, lymphocyte, and monocyte counts, among laboratory values, can predict the response in neoadjuvant treated patients. However, the HALP score, SII, NLR, PLR, SIRI, AISI, NMR, and LMR, which were the primary biomarkers of interest in this study, were not associated with response.

Ethics committee approval: Ethical approval was obtained from the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee with the decision dated 16.02.2024 and numbered 2024/02-13. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of interests: The authors declare no conflicts of interest.

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