Impact of Blood Type on Treatment Response and Survival in HER2-Negative Metastatic Gastric Cancer

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What is already known on this topic?

- *The ABO blood group is associated with prognosis in some cancer types.*
- *Non-O blood group may be linked to poorer survival in gastric cancer.*
- *Lower thrombosis risk in blood group O may contribute to better outcomes.*

What this study adds on this topic?

- *Overall survival was longer in patients with blood group O (15.7 months vs. 12.9 months).*
- *Blood type can be a guide in treatment planning.*
- *Eastern Cooperative Oncology Group performance status emerged as a stronger determinant of survival.*

Abstract

Objective: Metastatic gastric cancer is one of the most lethal malignancies. Recent studies indicate that the O blood group has better survival than the non-O blood group. In this study, the aim was to evaluate the impact of blood group O and non-O blood groups on survival outcomes and treatment responses in gastric cancer patients.

Methods: Between January 2012 and June 2024, 187 patients with metastatic gastric cancer treated at Kartal Dr. Lütfi Kırdar City Hospital were retrospectively analyzed. Patients were divided into 2 groups: O blood group (n = 82) and non-O blood group (n = 105). The prognostic role of blood groups and their impact on survival outcomes was investigated.

Results: Median overall survival was 15.7 months in the O blood group and 12.9 months in the non-O blood group (P = .04). There was no significant difference between the groups in terms of progression-free survival (7.9 months versus 7.0 months, P = .11). Disease control rates were 69.5% in the O Rh +/– group and 63.3% in the other groups. In subgroup analyses, a borderline significant interaction (P = .08) was observed between the blood group and Eastern Cooperative Oncology Group (ECOG) PS (Performance Status). In multivariate analysis, ECOG performance score was found to be an independent prognostic factor (hazard ratio = 1.6, P = .003), whereas blood group was not found to be an independent prognostic factor (P = .16).

Conclusion: The study found that patients with blood group O exhibited better survival rates in metastatic gastric cancer; however, the blood group was not identified as an independent predictor of survival. The primary determinant of survival outcomes remained the patient's performance status. Therefore, while blood group may serve as an additional prognostic indicator, its utility requires further validation through larger scale studies.

Keywords ABO blood groups, metastatic gastric cancer, O Rh blood type, prognosis

Introduction

Gastric cancer is the fourth most common cause of cancer-related deaths worldwide.[1] Gastric cancer, particularly in its metastatic stage, has a poor prognosis and significantly reduced survival. Identifying prognostic factors is crucial for disease management and treatment planning. Various studies have explored these factors, identifying clinical and pathological markers that influence prognosis.[2,3] Like other malignancies, gastric cancer requires dependable biomarkers to differentiate between patient cohorts that respond to treatment and those that do not.[4]

Researchers have long studied the relationship between the ABO blood group and the development and prognosis of gastric cancer. Previous studies suggest that blood group A in particular may be associated with the development of gastric cancer, whereas blood group O may be associated

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with a better prognosis.[5] Blood types are among the biomarkers of prognostic significance in cancer patients.[6] The underlying prognostic significance of blood groups has been the subject of many studies.[7] One explanation attributed to this issue is that, irrespective of the initial malignancy, it has been observed that blood groups in cancer patients may predispose them to thrombosis and influence survival outcomes.[8] Subgroups of blood types in gastric cancer display various survival features, according to research.[9] Although it has been suggested that those with the O blood group have better survival rates in gastric cancer patients, this finding was not directly confirmed in the study of Yu et al.[10] The effects of the ABO blood group on response to treatment in metastatic gastric cancer patients have not been adequately investigated. However, there is still limited data on the prognostic significance of blood groups in metastatic gastric cancer cases and their relationship with responses to treatment. Most previous research has concentrated on the correlation between blood type and the prevalence of stomach cancer, with scant data regarding the influence of blood group variations on the efficacy of current treatments.[11]

Research indicates that individuals with non-O blood groups have lower survival rates compared to those with O blood groups. People who have non-O blood groups face a substantially elevated risk of developing venous thromboembolic events than those who have blood group O.[12-14] This study aimed to assess the influence of blood types on survival outcomes in patients with HER-2-negative metastatic gastric cancer and to compare those with and without blood type O based on real-world data.

Methods

This retrospective cohort study was conducted at Kartal Dr. Lütfi Kırdar City Hospital. Patients diagnosed with metastatic gastric cancer who started first-line chemotherapy between January 2012 and June 2024 were included in the study. The sample size calculation was based on the survival difference between the O Rh blood group and other blood groups as stated in the literature, with 80% power and a 5% type 1 margin of error, and was determined to be a minimum of 180 patients. Patients over 18 years of age, with histopathologically proven metastatic gastric adenocarcinoma, with Eastern Cooperative Oncology Group (ECOG) performance status 0-2, with at least 1 measurable lesion, and who had received at least 1 cycle of chemotherapy were included in the study. Patients who had previously received chemotherapy for metastatic disease, had a history of a second primary malignancy, were HER-2 positive, had ECOG performance status >2, or lacked available follow-up data were excluded.

Demographic, clinical, and pathological data were obtained from the hospital electronic record system and patient files using a standardized data collection form. ECOG performance status was recorded for all patients at the time of diagnosis. All pathological specimens were evaluated by experienced gastrointestinal system pathologists. HER-2 status was primarily evaluated by immunohistochemical (IHC) staining. FISH (Floresan in situ hibridizasyon) analysis was performed in cases with an IHC result of 2+. Cases with a HER2/CEP17 ratio ≥2.0 in FISH analysis were considered positive. Patients were followed prospectively from the time of diagnosis, and data were updated every 3 months. Laboratory evaluations were performed in the central laboratory of the hospital, and internal and external quality control procedures were applied for all tests.

Treatment Intervention

Treatment protocols were determined according to patients' performance status, comorbidities, and preferences. The FOLFOX (FOL = Folinic acid (Leucovorin) F = Fluorouracil (5-FU) OX = Oxaliplatin) regimen involved administering oxaliplatin 85 mg/m², leucovorin 400 mg/m², and 5-FU 400 mg/m² as a bolus, followed by a 46-hour infusion of 2400 mg/m². The FOLFIRI (FOL – Folinic acid (leucovorin) F – Fluorouracil (5-FU) IRI – Irinotecan) regimen involved administering irinotecan 180 mg/m², leucovorin 400 mg/m², and 5-FU. In the DCF (Docetaxel – Cisplatin – Fluorouracil) regimen, docetaxel 75 mg/m², cisplatin 75 mg/m², and 5-FU 750 mg/m²/day were given for 5 days. In the EOX/ECF (EOX → Epirubicin + Oxaliplatin + Capecitabine, ECF → Epirubicin + Cisplatin + 5-Fluorouracil) regimen, epirubicin 50 mg/m^2, oxaliplatin 130 mg/m^2, or cisplatin 60 mg/m^2, and capecitabine 1000 mg/m^2 were used twice daily or in a 5-FU infusion. Treatment responses were evaluated according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumorsz) criteria.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 software (IBM SPSS Corp.; Armonk, NY, USA). Compliance with normal distribution was evaluated by the Kolmogorov–Smirnov test. Chi-square or Fisher's exact test was used for categorical variables, and the Mann–Whitney *U* test was used for continuous variables. The Kaplan–Meier method was used for survival analyses, and the log-rank test was used to compare groups. Cox regression analysis was used to determine prognostic factors. Overall survival was calculated as the time from the start of treatment to the date of death or the last visit. Progression-free survival (PFS) was defined as the time interval in months between the start of chemotherapy and disease progression, death, or last visit, whichever occurs first.

Ethical Approval

The study protocol was approved by the ethics committee of Kartal Dr. Lütfi Kırdar City Hospital (Approval no: 2024/010.99/6/17; Date: July 26, 2024) and was conducted in accordance with the principles of the Declaration of Helsinki. The study was retrospective and informed consent was not required since the information about the patients was obtained from their past visits. Institutional approval was obtained for the use of anonymized patient information in accordance with ethical standards.

Results

Patients Characterictic

The study cohort consisted of 187 patients, with a median age of 57 years (range: 26-85). Of these, 31% were female. The most common pathological type was adenocarcinoma, followed by signet ring cell carcinoma. Most of the patients had poor differentiation (70%). Approximately one third of the patients had a history of previous gastrectomy. At the time of diagnosis, 81.8 % of patients were de novo metastatic. The most common metastatic sites were the liver and peritoneum, respectively. The baseline clinical and demographic data are summarized in Table 1.

Treatment Response and Survival Outcomes

The partial response rate was 52.4% in the O blood group and 40% in the other blood groups. The objective response rate (ORR) and disease control rate (DCR) in the O group were 52.4% and 69.5%, respectively, compared to 41% and 63.3% in the other groups. There were no statistical differences between the 2 groups. Median overall survival was 14.0 months (95% confidence interval [CI]: 10.8-15.1) in the whole cohort. According to blood group type, median overall survival (OS) was 15.7 months (95% CI: 13.1-18.3) in the O Rh +/– group and 12.9 months (95% CI: 10.8-15.1)

Table 1. Baseline Clinical and Demographic Findings in the Whole Cohort, and Categorized by Blood Group Type

			Blood Group		
		Whole Cohort n = 187 [n (%)]	**O Rh ± n = 82 [n (%)]**	**Other n = 105 [n (%)]**	***P***
Age (years) (median)		60 (min 21-max 83)	60 (min 28-max 83)	60 (min 21-max 83)	.91
Gender	Female	58 (31)	26 (31.8)	32 (30.5)	.85
	Male	129 (69)	56 (68.2)	73 (69.5)	
Gastrectomy		59 (31.5)	31 (37.8)	28 (26.6)	.10
ECOG PS	0	102 (54.5)	53 (64.6)	49 (46.6)	.01
	≥ 1	85 (45.5)	29 (35.4)	56 (53.4)	
Pathology	Adenokarsinom	134 (71.6)	59 (71.9)	75 (71.4)	.16
	Signet cell carcinom	45 (24.0)	22 (26.8)	23 (21.9)	
	Other	8 (4.4)	1 (1.3)	7 (6.7)	
Signet cell component		66 (35.2)	28 (34.1)	38 (36.1)	.77
Differentiation	Well	5 (2.8)	3 (3.7)	2 (1.9)	.26
	Modarate	51 (27.2)	27 (32.9)	24 (22.8)	
	Poor	131 (70)	52 (63.4)	79 (75.3)	
CEA (median) (range)		3.8 (0.3-5163)	4.2 (0.6-3058)	3.8 (0.3-5163)	.76
CA 19-9 (median) (range)		38 (0.6-10 000)	40.3 (0.6-8612)	37.5 (0.8-10 000)	.86
De novo metastatasis		153 (81.8)	69 (84)	84 (76)	.46
Liver metastastasis		84 (44.7)	38 (46.3)	46 (43.4)	.68
Peritoneum metastastasis		70 (37.2)	27 (32.9)	43 (40.6)	.28
Bone metastastatis		21 (11.2)	7 (8.5)	14 (13.2)	.31
Lung metastastasis		37 (19.7)	17 (20.7)	20 (19.0)	.77
Chemotherapy	FOLFOX	103 (54.8)	39 (47.6)	64 (60.4)	.02
	FOLFIRI	17 (9)	7 (8,5)	10 (9,4)	
	DCF	56 (29.8)	26 (31.7)	30 (28.3)	
	EOX/ECF	12 (6.4%)	10 (12.2)	2 (1.9)	

Mann–Whitney U test was used for continuous variables and chi-square test was used for categorical variables. $P < .05$ was considered statistically significant.
CA, Cancer Antigen; CEA, Carcinoembryonic Antigen; ECOG, Eastern Cooperative Oncology Group.

in the other blood groups. There was a statistically significant difference between the 2 groups (log-rank $P = .04$) (Figure 1). Interms of PFS, median PFS was 7.9 months (95% CI: 6.6-9.2) in the O Rh +/− group and 7.0 months (95% CI: 5.7-8.2) in the other groups, but this difference did not reach statistical significance (log-rank $P = .11$) (Figure 2). The survival time for O Rh-positive patients (n = 74) was 16.1 months (95% CI: 13.2-19.0) and for O Rh negative patients (n = 8) was 13.8 months (95% CI: 10.1-17.5) with no significant difference (log-rank $P = .42$). The survival time was the longest in group O (15.7 months) followed by group A (13.5 months), group B (12.1 months), and group AB (11.8 months) (log-rank $P = .09$). Treatment responses and survival outcomes are outlined in Table 2.

Cox Regression Analysis of Overall Survival

In univariate analysis, ECOG PS 0 and blood group O predicted prolonged OS ($P < .05$). Eastern Cooperative Oncology Group PS ≥1 was associated with increased mortality risk (hazard ratio [HR]: 1.6, 95% CI: 1.1-2.2, $P = .003$) and non-O blood groups showed higher mortality risk compared to O blood group (HR: 1.4, 95% CI: 1.0-1.9, $P = .04$). However, in multivariate analysis, ECOG performance status was found to be an independent prognostic factor (HR: 1.6, 95% CI: 1.1-2.2, $P = .003$), whereas blood group was not identified as an independent prognostic factor (HR: 1.2, 95% CI: 0.9-1.7, $P = .16$) (Table 3).

Discussion

Our study aimed to evaluate the impact of blood group O versus non-O on survival outcomes and treatment response in metastatic gastric cancer. These findings suggest a potential association between blood type and prognosis, with patients having blood group O showing improved overall survival. However, no significant differences in PFS were observed.

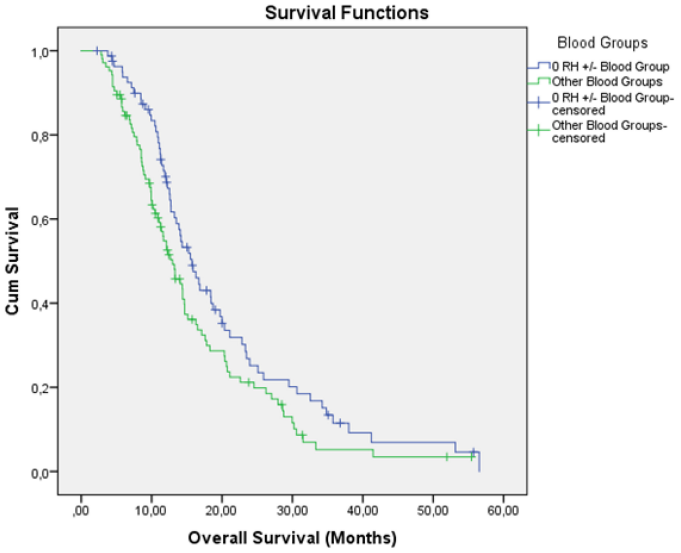

Figure 1. Overall survival according to blood groups in metastatic gastric cancer patients: Blue line represents O Rh ± blood group (median overall survival [OS]: 15.7 months), and the green line represents other blood groups (median OS: 12.9 months) ($P = .04$). The difference was statistically significant between groups.

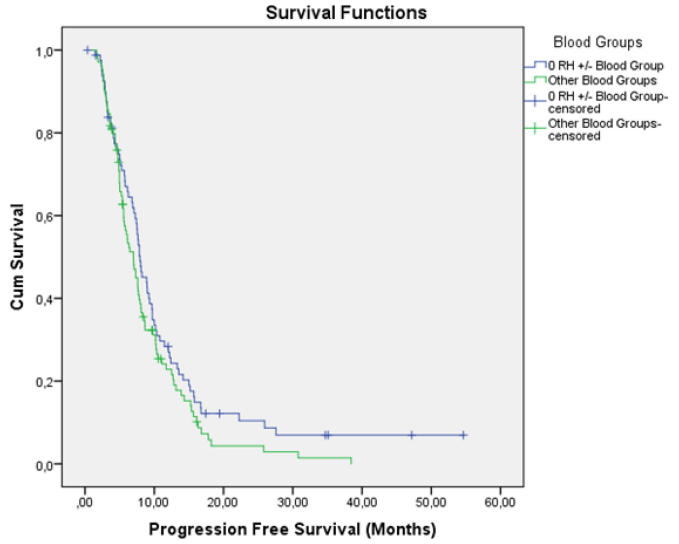

Figure 2. Progression-free survival according to blood groups in metastatic gastric cancer patients: Blue line represents O Rh ± blood group (median progression-free survival [PFS]: 7.9 months), while the green line represents other blood groups (median PFS: 7.0 months) ($P = .11$).

The impact of the relationship between blood types and cancer on survival is becoming an increasingly interesting area of research. The conflicting results of studies in this field show that new studies are needed.[15-17] Although studies have found that the non-O blood group is associated with worse survival, the underlying pathophysiologic reasons are not fully understood. Multiple mechanisms have been identified as responsible for this phenomenon according to recent evidence.

The thrombotic risk associated with non-O blood groups appears to be a major factor. It has been asserted that 1 reason for this is that the non-O blood group may constitute a risk factor for venous thromboembolism. This risk becomes more apparent, especially in cancer patients, and it has been reported that the non-O blood group significantly increases the risk of VTE (SHR: 1.79) after the third month of treatment.[8] Non-O individuals have 25%-30% higher levels of von Willebrand factor and factor VIII, which increase thrombotic risk.[14] The hypercoagulable state in non-O patients can cause microvascular thrombosis, which may interfere with drug delivery and treatment effectiveness.

ABO blood group antigens present on gastric epithelial cells directly affect tumor biology according to the second point. The A and B antigens function as bacterial adhesin receptors for

Table 2. Treatment Responses and Survival Outcomes

			Blood Group		
		Whole Cohort n = 187 [n (%)]	**O RH ± n = 82 [n (%)]**	**Other n=105 [n (%)]**	***P***
Treatment responses	CR	1 (0.5)	0	1 (1)	.31
	PR	85 (45.5)	43 (52.4)	42 (40)	
	SD	38 (20.3)	14 (17.1)	24 (22.9)	
	PD	63 (33.7)	25 (30.5)	38 (36.2)	
	ORR	46%	52.4%	41%	.11
	DCR	66.3%	69.5%	63.3%	.41
Progression		163 (87.1)	71 (86.5)	92 (87.6)	.83
Progression-free survival (PFS)	Median PFS (months)	7.5 (95% CI: 6.9-8.1)	7.9 (95% CI: 6.6-9.2)	7.0 (95% CI: 5.7-8.2)	.11
Exitus		150 (80)	65 (79)	85 (80.9)	.77
Overall survival (OS)	Median OS (months)	14.0 (95% CI:10.8-15.1)	15.7 (95% CI: 13.1-18.3)	12.9 (95% CI:.10.8-15.1)	.04

ORR (Objective Response Rate): CR + PR rates; DCR (Disease Control Rate): CR + PR + SD ratios. Chi-square test was used for treatment response comparisons. $P < .05$ was considered statistically significant; Survival analyses were performed using Kaplan–Meier method with log-rank test.
CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease.

Table 3. Cox Regression Analysis of Survival

		Univariate Analysis		Multivariate Analysis	
Variables		**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Gender	Female (references)	0.79 (0.56-1.13)	.21		
	Male				
ECOG PS	PS 0 (references)	1.6 (1.1-2.2)	.003	1.6 (1.1-2.2)	.003
	≥ 1				
Liver metastatasis	Present (references)	1.0 (0.7-1.4)	.80		
	Absent				
Peritoneum metastastasis	Present (references)	1.1 (0.8-1.6)	.37		
	Absent				
Blood groups	O Rh ± (references)	1.4 (1.0-1.9)	.04	1.2 (0.9-1.7)	.16
	Other groups				

In subgroup analyses, a borderline significant interaction was found between blood group and ECOG PS ($P = .08$), no significant interaction was observed with other factors. Multivariate analysis included variables with $P < .10$ in univariate analysis. Hazard ratio for progression-free survival was calculated from log-rank analysis.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

Helicobacter pylori, which modifies the gastric environment and could influence cancer development.[18] The absence of A and B antigens in blood group O individuals enables better immune surveillance because their immune system can detect tumor-associated antigens more effectively.

As a result, cancer patients with blood type O may have longer survival. In this study, better overall survival (15.7 months vs. 12.9 months, $P = .04$) was observed in patients with blood group O. The analysis showed that ECOG performance status was significantly different between blood groups (64.6% ECOG 0 in O group vs. 46.6% in non-O groups, $P = .01$). Eastern Cooperative Oncology Group PS was the strongest independent prognostic factor (HR: 1.6, $P = .003$), and the borderline significant interaction between blood group and ECOG PS ($P = .08$) suggests that blood group effects may be more pronounced in patients with better functional status.

Consistent with the current study, a study conducted in patients with gastric cancer showed that blood group A had higher mortality rates compared to blood group O.[19] Unlike the current study, the research by Doğan et al[17] revealed no significant difference in overall survival between blood group O and non-O blood groups. Once more, in contrast to the current data, a study of breast cancer patients found no significant correlation between survival and blood group.[20] The different results stem from multiple factors including population heterogeneity (blood group O frequency varies from 40% to 50% across ethnicities), methodological differences (this study focused specifically on HER2-negative metastatic gastric cancer), varying control for confounding factors, and potential stage-specific effects of blood groups.

In the recent study, it was found that patients with blood group O showed a longer survival time compared to other groups.[21] A value trial with comparable outcomes showed blood type O as an independent prognostic predictor (HR = 0.78), correlating with improved survival.[10] The studies demonstrating that cancer patients with blood type O experienced significantly prolonged lifespans supported the current study's thinking (16.0 months versus 11.0 months, $P = .001$).[22] Compared to blood group O, blood group A exhibited the poorest prognosis, with the lowest illness control rates observed in this category.[23] Similarly, in the current study, a higher ORR (52.4% vs. 41.0%) and DCR (69.5% vs. 63.3%) were found in the O blood group, and better response rates (53.8% vs. 45.3%) were obtained, especially in the O blood group. The improved treatment response in O group patients could be due to better tumor perfusion because of reduced thrombotic burden, which may enhance drug delivery. Genetic polymorphisms in drug-metabolizing enzymes (such as CYP2D6, CYP2C19, DPYD, UGT1A1, TPMT) have a major impact on drug metabolism and treatment response in cancer patients.[24]

The findings obtained from the current study seem to be partially compatible with the results in the literature. In particular, similar to the longer survival time shown by Sun et al[19] in patients with O blood group and the findings of Yu et al[10] in which O blood group was defined as an independent prognostic factor (HR = 0.78), a higher ORR (52.4% vs. 41.0%) and DCR (69.5% vs. 63.3%) were found in the O blood group in the current study. The poor prognosis and low DCRs shown by Xu et al[23] in the A blood group support these findings. The studies did not include blood group as an independent prognostic factor in their multivariate analysis (HR: 1.2, 95% CI: 0.9-1.7, $P = .16$), which suggests that its effect may be mediated by other factors, particularly performance status.

This study has some limitations. Firstly, the generalizability of the results is limited because it is a retrospective study reflecting a single center experience. In addition, retrospective examination of patient records may have caused some data to be missing and possible errors to be encountered. The small number of patients in specific subgroups, especially O Rh negative (n = 8), restricted the ability to conduct thorough Rh subgroup analyses. However, this study also has strengths. The fact that an adequate sample size was reached, patients were followed up regularly, and treatment protocols were standardized increases the reliability of this study. Furthermore, the focus on a homogeneous population of HER2-negative metastatic gastric cancer patients reduces confounding from molecular heterogeneity.

The research findings indicate that blood group O provides survival benefits yet should be evaluated together with other prognostic factors instead of being used as a standalone biomarker. Research should explore risk-stratified approaches that include intensified thromboprophylaxis for non-O patients and closer monitoring of their condition.

The recommendations for future studies are to investigate the relationship between blood groups and survival in larger patient groups with a multicenter and prospective design. It is thought that patients with non-O metastatic gastric cancer will have worse survival results. Furthermore, a future task will be to determine how, at subclass levels, blood groups affect the outcome of immunotherapy. Research should investigate how checkpoint inhibitor effectiveness varies between blood groups because O group patients may benefit from enhanced immune surveillance. Lastly, in light of blood groups prognosis, further in-depth studies combining blood groups with other parameters, like markers and genetic information, will be needed. The integration of blood group data with molecular profiling and circulating tumor DNA analysis and comprehensive thrombotic risk assessment could lead to more accurate prognostic models for developing personalized treatment strategies in metastatic gastric cancer.

To summarize, this research provides insight into the possible impact of blood groups on the prognosis of patients suffering from metastatic gastric cancer. While a trend toward better overall survival in patients with blood group O was observed compared to non-O blood groups, this factor alone did not emerge as an independent prognostic indicator. The association of blood groups and other clinical characteristics, especially the patient's performance status, seems to be intricate and needs more attention. It is believed that the blood type of a patient suffering from metastasized gastric cancer may improve their prognosis, and therefore it should be considered when designing their treatment protocol.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received for this study from the ethics committee of Kartal Dr. Lütfi Kırdar City Hospital (Approval no: 2024/010.99/6/17; Date: July 26, 2024)

Informed Consent: The requirement for informed consent was waived by the Ethics Committee of Dr. Lütfi Kırdar City Hospital due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Y., H.O.; Design – S.Y., Ö.A.; Supervision – S.Y., G.A., H.Ş.Y., A.T.; Resources – S.Y., A.D., A.T.; Materials – S.Y., E.T., N.S.B., H.Ş.Y.; Data Collection and/or Processing – S.Y., E.T., N.S.B., A.D., A.S.; Analysis and/or Interpretation – S.Y., Ö.A., S.A.E.; Literature Search – S.Y., E.T.; Writing Manuscript – S.Y., Ö.A., Ö.N.S., T.B.; Critical Review – S.Y., Ö.A., S.A.E., N.T., H.O.; Other –S.Y., E.T.

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