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The relation between ABO blood groups and clinicopathologic characteristics of the patients with gastric adenocarcinomas

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ABSTRACT

Objective: This study aimed to examine the association between blood groups and clinicopathological factors that could affect the prognosis of patients with gastric cancer.

Material and Methods: In this retrospective single-center study, patients with gastric adenocarcinoma were obtained from a prospectively maintained database. The association between blood groups and clinicopathologic characteristics including sex, age, tumor location, tumor size, tumor stage, metastatic lymph node ratio (MLR), lymphovascular invasion, and perineural invasion were analyzed.

Results: The study included 91 female and 221 male patients. The blood group distribution was A>O>B>AB both in the patients and healthy donors. Non-O blood types were more common in cancer patients than in healthy donors (p= 0.038). However, there was no significant association between sex, age, tumor location, tumor stage, lymph node status, lymphovascular invasion, and perineural involvement and blood groups. ≥7 lymph node involvement and MLR of >0.6 were significantly more common in patients with blood group A than in those with non-A blood groups (p= 0.034 and p= 0.018; respectively).

Conclusion: The findings of this study suggest that blood group A patients are associated with higher MLR and N3 involvement, so it is possible that these patients with gastric cancer have a poorer prognosis.

Keywords: ABO blood group, gastric cancer, outcome, pathologic characteristics

INTRODUCTION

Gastric cancer is a leading cause of cancer deaths worldwide. It is estimated that more than one million new cases of gastric cancer will occur annually, with approximately 750.000 of these cases resulting in death from the disease. Moreover, it is responsible for one in every 12 cancer-related deaths (1). Its prevalence among men is twice that of women (1,2).

The fact that the geographical distribution of gastric cancer shows a substantial variation suggests that there are numerous factors affecting its incidence, survival, and mortality (3). In addition to genetic predisposition, environmental factors and nutritional habits appear to have an important role in the development of gastric cancer. A diet high in salt, nitrite, or ultra-processed foods and fatty acids, as well as diets that are low in whole grains, seeds, fruit, and vegetables, has been linked to an elevated risk of gastric cancer (4). The association between Helicobacter pylori and gastric carcinoma is well-documented, with this microorganism accounting for approximately 90% of non-cardia gastric cancer (5).

ABO blood group antigens are complex carbohydrates expressed on red blood cells (RBCs) (6). These antigens have been the focus of many studies since their discovery. Although blood group antigens are markers on the surface of RBC membranes, they are highly expressed on lymphocytes, platelets, and the gastrointestinal mucosal epithelium (7). It has been suggested that the clinical use of the ABO blood-group system may be expanded beyond transfusion, immunohematology, and transplantation medicine (8). Aird et al. were the first to investigate the link between blood groups and gastric adenocarcinoma in an early-1950s study of almost 3.500 patients (9). The authors found that gastric

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cancer was more prevalent in patients with the blood group A, whereas the rate was lower among those with the O blood group compared to normal population. Since that time, numerous studies have been conducted to investigate the relation between blood groups and various types of cancer (10). It is currently believed that individuals with blood group A are at a higher risk of developing cancer than those with non-A blood groups. Conversely, those with blood group O are thought to be at a lower risk than those with non-O blood groups (11).

Although there is a well-established association between ABO blood groups and certain cancer characteristics, there has been a paucity of knowledge regarding the link between blood groups and the prognosis of these diseases, as well as the clinicopathologic features affecting the prognosis. In this study, we analyze the association between blood groups and the clinicopathologic characteristics that may influence the prognosis of patients with gastric adenocarcinomas. Additionally, the study presents a comparative analysis of the frequency of blood groups in patients with gastric cancer versus the general population.

MATERIAL and METHODS

Study population

Approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (approval no: 2024/178).

The study was conducted at a tertiary care hospital over the period of seven years from January 2017 and December 2023 and involved 312 patients with pathologically diagnosed gastric adenocarcinomas. Patients with gastric cancers other than adenocarcinomas and with Siewert type I-II cancers were excluded from the study. Patients with distant metastases (stage IV) were also not included since they were treated with chemotherapy instead of surgical resection (Figure 1). As a control group, 6.382 healthy blood donors who donated to the blood unit of the same hospital over the course of a year, between January 2017 and December 2018, were also enrolled.

Clinicopathological data

The standard agglutination test was used for the determination of the blood groups of the patients and the healthy controls. In addition, data on demographic features and pathological characteristics including tumor location, size, and differentiation degree, number of metastatic lymph nodes, tumor-node-metastasis (TNM) stage, metastatic lymph node ratio (MLR), lymphovascular invasion and perineural tumor invasion was obtained from the hospital database (12).

Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD) or median with range values, while categorical data were expressed as number (n) and percentage (%), depending on distribution assumptions. The differences in clinicopathologic characteristics between the blood groups were analyzed using chi-square or Fisher's exact test. All p values were two-sided, and the significance level was set at $p < 0.05$. Jamovi (version 2.5) software was used for data analyses (Sydney, Australia).

RESULTS

The study included 221 male patients (70.8%) and 91 female patients (29.2%), with a mean age of 66.2 ± 12.7 years. About half of the patients (n= 154, 49.4%) had blood group A, 89 (28.5%) had blood group O, 46 (14.7%) had blood group B, and 23 patients (7.4%) had blood group AB. Blood groups were

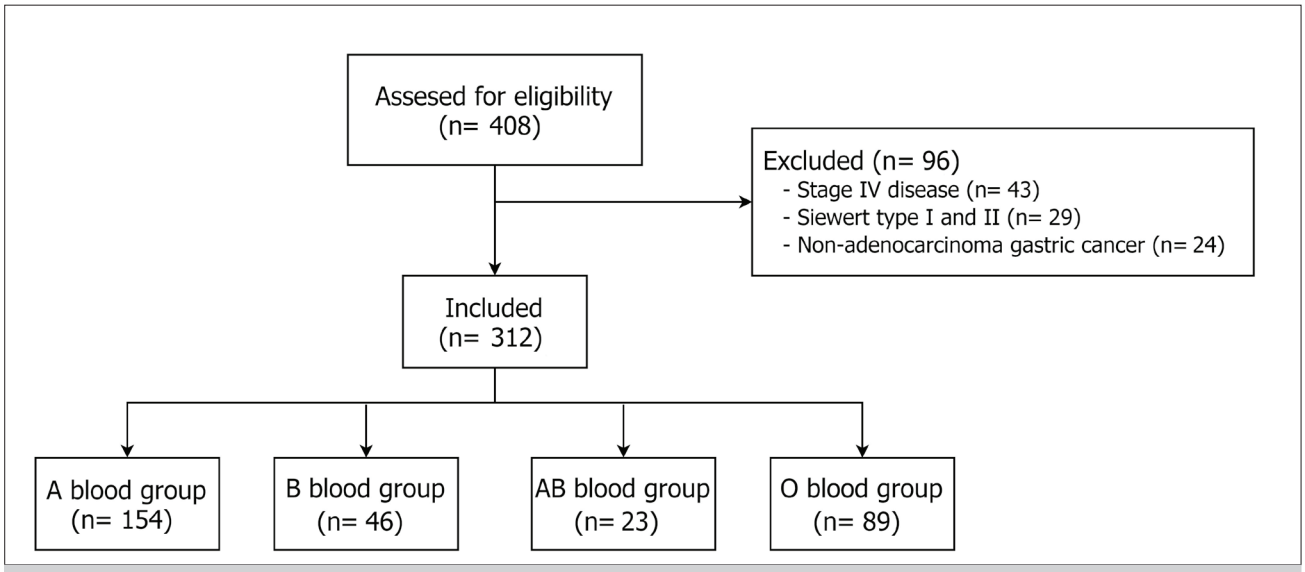

Figure 1. CONSORT flow diagram.

Table 1. The comparison of ABO blood distribution between patients and healthy donors

Groups	ABO blood types (%)						p*	p**	p***
	A	B	AB	O	non-A	non-O			
Healthy (n= 6382)	2859 (44.8)	942 (14.8)	397 (6.2)	2184 (34.2)	3523 (55.2)	4198 (65.8)	0.184	0.114	0.038
Gastric cancer (n= 312)	154 (49.4)	46 (14.7)	23 (7.4)	89 (28.5)	158 (50.6)	223 (71.5)			

p*, the comparison of ABO blood distribution between patients with gastric cancer and healthy donors; p**, differences between the blood group A and non-A blood group; p***, differences between the blood group O and non-O blood group.

similarly distributed between gastric cancer patients and healthy blood donors (p= 0.184). The order of frequency of blood groups was A>O>B>AB in both groups. Non-O blood groups were statistically more common in gastric cancer patients compared to healthy donors (71.5% vs. 65.8%, p= 0.038). However, when comparing the frequency of blood group A between the gastric cancer group and the healthy donor group, no significant difference was found (49.4% vs. 44.8%, p= 0.114) (Table 1).

The association between the blood groups and the clinicopathologic features of the patients with gastric adenocarcinomas is presented in Table 2. TNM stage I, II, and III patients were found to be 59 (18.9%), 65 (20.8%), and 188 (60.3%), respectively. No statistically significant difference was observed in sex (p= 0.885), age (p= 0.088), disease location (p= 0.270), size (p= 0.225), differentiation status (p= 0.144), stage (p= 0.097), lymph node involvement (p= 0.085), MLR (p= 0.084), and lymphovascular (p= 0.553) or perineural involvement (p= 0.159) between the blood groups.

In addition, regional metastatic lymph node involvement (N3) ≥7 and an MLR >0.6 were found to be significantly more common in the patients with blood group A than in those with blood group non-A (50.0% vs. 34.8%, p= 0.034 and 29.9% vs. 16.5%, p= 0.018; respectively). In addition, perineural invasion was more common in A blood groups than in non-A blood groups (39.6% vs. 29.7%, p= 0.067), but this difference was not statistically significant. However, our findings indicated that there was no statistically significant difference between patients with O blood type and those with non-O blood types regarding all clinicopathologic parameters (Table 2).

DISCUSSION

The relation between the ABO blood-group system and some tumors, systemic disorders (such as cardiovascular disease), and some infectious diseases has been known for many years

Table 2. Clinicopathological characteristics of the patients with gastric adenocarcinoma divided by different ABO blood groups

Groups	ABO blood types (%)						p*	p**	p***
	A (n= 154)	B (n= 46)	AB (n= 23)	O (n= 89)	non-A (n= 158)	non-O (n= 223)			
Sex							0.885	0.819	0.774
Male	110 (71.4)	34 (73.9)	15 (65.2)	62 (69.7)	111 (70.3)	159 (71.3)			
Female	44 (28.6)	12 (26.1)	8 (34.8)	27 (30.3)	47 (29.7)	64 (28.7)			
Age, years							0.107	0.061	0.959
<60	54 (35.1)	8 (17.4)	5 (21.7)	27 (30.3)	40 (25.3)	68 (30.5)			
≥60	100 (64.9)	38 (82.6)	18 (78.3)	62 (69.7)	118 (74.7)	155 (69.5)			
Tumor location							0.270	0.459	0.267
Upper	43 (27.9)	17 (37.0)	3 (13.1)	20 (22.5)	40 (25.3)	63 (28.2)			
Middle	50 (32.5)	15 (32.6)	9 (39.1)	38 (42.7)	62 (39.2)	74 (33.2)			
Lower	61 (39.6)	14 (30.4)	11 (47.8)	31 (34.8)	56 (35.5)	86 (38.6)			
Tumor size (cm)							0.225	0.931	0.199
<5	86 (55.8)	20 (43.5)	14 (60.9)	55 (61.8)	89 (56.3)	120 (53.8)			
≥5	68 (44.2)	26 (56.5)	9 (39.1)	34 (38.2)	69 (43.7)	103 (46.2)			
Differentiation status							0.144	0.271	0.803
Well	11 (7.1)	3 (6.5)	6 (26.1)	10 (11.2)	19 (12.0)	20 (9.0)			
Moderate	57 (37.0)	19 (41.3)	8 (34.8)	34 (38.2)	61 (38.6)	84 (37.7)			
Poor	86 (55.9)	24 (52.2)	9 (39.1)	45 (50.6)	78 (49.4)	119 (53.3)			

Table 2. Clinicopathological characteristics of the patients with gastric adenocarcinoma divided by different ABO blood groups (continue)

Groups	ABO blood types (%)						p*	p**	p***
	A (n= 154)	B (n= 46)	AB (n= 23)	O (n= 89)	non-A (n= 158)	non-O (n= 223)			
TNM stage[§]							0.097	0.177	0.067
I	28 (18.2)	7 (15.2)	8 (34.8)	16 (18.0)	31 (19.6)	43 (19.3)			
II	26 (16.9)	8 (17.4)	5 (21.7)	26 (29.2)	39 (24.7)	39 (17.5)			
III	100 (64.9)	31 (67.4)	10 (43.5)	47 (52.8)	88 (55.7)	141 (63.2)			
Lymph node metastasis							0.085	**0.034**	0.258
N0 (0)	38 (24.7)	11 (23.9)	11 (47.8)	27 (30.3)	49 (31.0)	60 (26.9)			
N1 (1-2)	22 (14.3)	5 (10.9)	3 (13.1)	16 (18.0)	24 (15.2)	30 (13.5)			
N2 (3-6)	17 (11.0)	11 (23.9)	3 (13.1)	16 (18.0)	30 (19.0)	31 (13.9)			
N3 (≥7)	77 (50.0)	19 (41.3)	6 (26.0)	30 (33.7)	55 (34.8)	102 (45.7)			
MLR							0.084	**0.018**	0.129
0	38 (24.6)	11 (23.9)	11 (47.8)	27 (30.3)	49 (31.0)	60 (26.9)			
>0-0.3	46 (29.9)	14 (30.4)	4 (17.4)	27 (30.3)	45 (28.5)	64 (28.7)			
>0.3-0.6	24 (15.6)	11 (23.9)	5 (21.8)	22 (24.8)	38 (24.0)	40 (17.9)			
>0.6	46 (29.9)	10 (21.8)	3 (13.0)	13 (14.6)	26 (16.5)	59 (26.5)			
Lymphovascular invasion							0.553	0.666	0.789
No	83 (53.9)	25 (54.3)	16 (69.6)	48 (53.9)	89 (56.3)	124 (55.6)			
Yes	71 (46.1)	21 (45.7)	7 (30.4)	41 (46.1)	69 (43.7)	99 (44.4)			
Perineural invasion							0.159	0.067	0.459
No	93 (60.4)	31 (67.4)	19 (82.6)	61 (68.5)	111 (70.3)	143 (64.1)			
Yes	61 (39.6)	15 (32.6)	4 (17.4)	28 (31.5)	47 (29.7)	80 (35.9)			

MLR: Metastatic lymph node ratio.
[§]AJCC Cancer Staging Manual, 8th edition.
p*, differences between the groups (A, B, AB, and O); p**, differences between the blood group A and non-A blood group; p***, differences between the blood group O and non-O blood group.

although discrepancies in the results of the studies in this field mean that trials in this issue are ongoing (6). Recent studies have suggested a potential association between blood group antigens and tumor oncogenesis, tumor dissemination, and survival in several forms of cancer (8). Aird et al. have shown an association between the blood group A and gastric carcinoma, and numerous later studies have confirmed this association, while numerous studies have been conducted to investigate the influence of blood group types on the prognosis and survival of individuals diagnosed with cancer (9-11,13,14). Nevertheless, the results are rather conflicting, even within the same kind of tumor.

In this study, we analyzed the link between blood groups and the clinicopathologic features that may have an impact on the prognosis of patients with gastric adenocarcinomas. There have been earlier studies investigating the association between blood groups and prognosis in gastric cancer although their results are inconsistent (15-17). As there are numerous factors affecting the prognosis of gastric cancer, we aimed to analyze the link between blood types and clinicopathological characteristics of gastric cancer rather than its prognosis. In line with other studies in the literature, the order of blood type frequencies were A> O> B> AB both in the patients and the healthy donors, and there was a male predominance in gastric cancer patients (16). In this study, non-O blood type was found to be more prevalent in patients with gastric cancer. Consistent with our findings, Zhang et al. have identified a lower gastric cancer risk (OR= 0.84) in patients with O blood group in their meta-analysis (11).

In earlier studies investigating the relation between the blood groups and gastric cancer survival, significant heterogeneity was present and different conclusions were documented. For instance, in a study investigating the link between blood types and clinicopathologic features of the patients with gastric cancer, the researchers have reported no significant association between blood groups regarding sex, tumor size, tumor stage,

degree of differentiation, and P53 expression. They have only reported that the subjects with blood group O were statistically significantly less likely to have angiolymphatic involvement than those with non-O blood groups (15). Furthermore, the expression of progestogen receptors, estrogen receptors, and carcinoembryonic antigen (CEA) was significantly higher in blood group A patients than in those with other blood groups. While there was no statistically significant difference between blood groups and survival, patients with blood group B had a longer survival than those with other blood groups. In another study, Xu et al. have analyzed the prognostic impact of the blood types in more than a thousand gastric cancer patients and reported that patients with blood group AB had a longer survival than those with non-AB blood groups ($p< 0.001$) (16). Furthermore, A blood group patients exhibited the poorest survival outcomes across all blood groups. In a study by Xiao et al., no significant difference has been found for the survival rates of patients across the four blood groups (17). The authors have also explored the prognostic impact of the blood types in gastric carcinoma patients with different preoperative CEA levels, and they have reported that among the patients with high preoperative CEA, the AB blood group was associated with longer survival than non-AB blood type.

Gastric cancer shows a significant geographic variation in incidence, and there are numerous factors that affect survival and mortality, with both genetic susceptibility and environmental triggers such as nutrition and infectious agents playing a crucial role in development, prognosis, and survival of gastric cancer (3-5). Tumor stage, lymph node status, MLR, tumor size and other histopathological tumor-related factors such as lymphatic, vascular or perineural invasion; tumor differentiation; and the Lauren classification are valuable prognostic factors in gastric cancer patients (18-21). Moreover, HER2 overexpression is considered to be a poor prognostic factor in patients with gastric cancer (22). When reviewing studies assessing prognostic features in gastric cancer specifically in relation with blood groups, tumor depth and stage, lymph node metastasis, blood group A, ER expression, and CEA elevation have been found as the most prominent factors (15-17). Considering the findings of above studies, there is a clear relationship between clinicopathological features and the prognosis of gastric cancer.

In the present study, among all clinicopathological features, seven or more regional lymph node involvement was more common in blood group A compared to non-A blood groups ($p= 0.034$) and patients with A blood group had a greater rate of MLR (>0.6) than those with the non-A blood groups ($p= 0.018$), while no relation was identified between the blood groups and patient demographics, tumor location, size, and stage, or lymphovascular invasion. Moreover, perineural invasion was more common in blood group A compared to non-A blood groups (39.6% vs. 29.7%, $p= 0.067$). According to these results, lymph node metastasis and MLR are significant prognostic indicators for gastric cancer patients undergoing radical D2 resection. Three staging systems have been used for decades to predict the prognosis of patients with gastric adenocarcinoma: Log odds of positive nodes (LODDS), nodal staging system, and MLR. When these systems compared with each other, the LODDS and MLR have exhibited a higher prognostic accuracy compared with TNM and nodal systems (23). A number of studies have employed a 0.2 to 0.3 cut-off for MLR, with the results indicating that a higher MLR is associated with a significantly lower survival rate and a higher recurrence for N3 disease (24-27). It is also a poor prognostic factor for stage III gastric cancer (28). In other words, an increased MLR in blood group A may indicate a worse prognosis in patients undergoing curative gastrectomy, given the large number of stage III patients in this study.

Studies have demonstrated a direct correlation between the ABO group genotype and the levels of inflammatory markers in the blood. This evidence suggests that blood-group antigens may influence the immune system response (29,30). Thus, ABO blood-group antigens and antibodies might have potential implications on tumor dissemination, angiogenesis, and lymphatic invasion. The results indicate a correlation between the ABO blood group and the predisposition to lymphatic invasion and tumorigenesis. Similarly, although a link between blood groups and the prognosis of gastric cancer could not be inferred, blood group A was associated with higher lymph node involvement.

The results indicate a correlation between the ABO blood group and a predisposition to lymphatic invasion and tumorigenesis.

Finally, there are several important limitations of this study that are noteworthy. First, the data comes from a retrospective single-center analysis; second, the high rate of advanced stage cancer limits its generalizability to every gastric cancer patient. Lastly, exclusion of stage IV patients can make tumor pathology biased and make findings not generalizable. In addition, the sample size of patients with AB blood group and B blood group was small, which could result in unsatisfactory statistical p values.

CONCLUSION

The relation between ABO blood groups and clinicopathological features and prognosis of gastric cancer has not been extensively studied. Although several studies have defined survival advantages for certain blood types, relevant studies are limited, and their results are inconclusive. The present study showed some association between the ABO blood groups and

clinicopathological characteristics in gastric cancer, especially with blood group A being associated with a higher MLR level and N3 involvement, estimating that patients having gastric adenocarcinoma with A blood group may have a worse prognosis. Although gastric carcinoma is more prevalent in patients with non-O blood groups, the relation between this blood type and tumor characteristics is relatively weak. There is need for further prospective multicenter studies with larger sample sizes to better define the influence of blood types on clinicopathological features and survival in gastric cancer.

Further prospective multicenter studies with larger sample sizes are needed to better define the influence of blood group on clinicopathological features and survival in gastric cancer.

Ethics Committee Approval: This study was obtained from University of Health Sciences Gülhane Scientific Research Ethics Committee (Decision no: 2024-178, Date: 24.04.2024).

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Mide adenokarsinomlu hastaların ABO kan grupları ile klinikopatolojik özellikleri arasındaki ilişki

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ÖZET

Giriş ve Amaç: Bu çalışmada mide kanseri teşhisi konan hastaların prognozunu etkileyebilecek kan grupları ile klinikopatolojik faktörler arasındaki ilişkinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif tek merkezli çalışmada, mide adenokarsinomlu hastalar prospektif olarak tutulan bir veri tabanından elde edilmiştir. Kan grupları ile cinsiyet, yaş, tümör yeri, tümör boyutu, tümör evresi, metastatik lenf nodu oranı (mLNO), lenfovasküler invazyon ve perinöral invazyon gibi klinikopatolojik özellikler arasındaki ilişki analiz edildi.

Bulgular: Çalışmaya 91 kadın ve 221 erkek hasta dahil edildi. Kan grubu dağılımı hem hastalarda hem de sağlıklı donörlerde A> O> B> AB şeklindeydi. O kan grubu olmayan kanser hastalarında sağlıklı donörlere göre daha yaygındı (p= 0,038). Ancak cinsiyet, yaş, tümör yerleşim yeri, tümör evresi, lenf nodu metastazı, lenfovasküler invazyon, perinöral tutulum ve kan grupları arasında anlamlı bir ilişki bulunmadı. ≥7 lenf nodu tutulumu ve >0,6 mLNO, kan grubu A olan hastalarda kan grubu A olmayanlara göre anlamlı derecede daha fazlaydı (sırasıyla p= 0,034 ve p= 0,018).

Sonuç: Bu çalışmanın bulguları, kan grubu A olan hastaların daha yüksek mLNO ve N3 tutulumu ile ilişkili olduğunu ve dolayısıyla mide kanseri teşhisi olan bu hastaların daha kötü bir prognoza sahip olabileceğini göstermektedir.

Anahtar Kelimeler: ABO kan grubu, mide kanseri, patolojik özellikler, sonuç

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