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The frequency and prognostic significance of ABO/Rh blood groups in male breast cancer patients

A multicenter study

Izzet Dogan, MD[a], Murat Ayhan, MD[b], Mustafa Gurbuz, MD[c], Ahmet Kucukarda, MD[d], Esra Aydin, MD[a], Yuksel Urun, MD, Professor[c], Irfan Cicin, MD, Professor[d], Pinar Saip, MD, Professor[a]

Abstract

The study evaluated the distributions and prognostic significance of ABO and rhesus (D) groups in male breast cancer (MBC) patients. The data of 137 patients were retrospectively reviewed. Clinical, histopathological data and ABO/Rh blood groups of the patients were recorded. The ABO/Rh blood group distributions were compared to the healthy men control group (n = 120,160) by the chi-square test. Overall distributions of ABO blood groups were different between the patients (17.5% AB, 38% A, 19% B, and 25.5% O) and control group (7.88% AB, 42.06% A, 15.22% B, and 34.84% O) ($P < .001$). There were significant differences between the patients and control group with respect to AB vs non-AB blood group distributions ($P < .001$, odds ratio: 2.43, 95% CI) and O vs non-O blood group distributions ($P = .016$, odds ratio: 0.62, 95% CI). However, A vs non-A and B vs non-B blood group distributions were not significantly different. The distribution of the Rh factor was similar between patients and the control group ($P = .93$). In univariate analysis, ABO/Rh blood groups were not a prognostic factor on OS ($P = .29$). The frequency of the AB blood group in MBC patients is increased than in the healthy control group. AB blood group may be a risk factor for MBC, whereas O blood group may be a protective factor.

Abbreviations: ER = estrogen receptor, FBC = female breast cancer, IHK = immunohistochemistry, MBC = male breast cancer, OS = overall survival, PR = progesterone receptor.

Keywords: ABO blood groups, male breast cancer, prognosis, risk factors

1. Introduction

In males, breast cancer is uncommon. Breast lumps, nipple retraction, axillary adenopathy, and nipple or skin ulceration are the most prevalent clinical symptoms. Male breast cancer (MBC) is caused by some risk factors such as advanced age, obesity, and hyperestrogenemia. Genetic alterations, such as BRCA 1-2, CHECK2, and PALB2 mutations, may also play a role in MBC development. The estrogen receptor (ER) and progesterone receptor (PR) are expressed more often in MBC cells than in female breast cancer (FBC) cells.[1] There are no randomized studies that may guide the therapeutic management of MBC. A radical mastectomy is the most common treatment for MBC. Radiotherapy, chemotherapy, anti-HER2 therapy, and endocrine therapy are all options for adjuvant treatment, just as they are for FBC. Patients with MBC have a worse prognosis than those with FBC.[2] In prior investigations, pathological prognostic variables have been the focus. The presence of distant metastases has been identified as an independent risk factor for the prognosis of MBC patients.[3]

The ABO blood system, which was discovered in 1900, divides human blood into different categories depending on the presence or lack of antigens A and B on the surfaces of erythrocytes. The ABO blood types gene is found on chromosome 9q34 and encodes glycosyltransferases, which catalyze the transfer of nucleotide source sugars to H antigens to produce ABO blood type antigens.[4] At this present, the underlying mechanisms through which the ABO blood type or related genetic variations of the ABO gene locus interact with cancer development and progression are unknown and are being researched. Dysregulation of the ABO glycosyltransferases' enzymatic activity might be one of the causes. This protein regulates intercellular adhesion and cellular membrane transmission, as well

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This published paper contains all of the data produced or analyzed during this investigation.

The local ethics committee approved this study at the Istanbul University Faculty of Medicine (Number: 2019/1397). For this type of research, informed consent is not required.

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[a]Medical Oncology, Istanbul University Institute of Oncology, Istanbul, Turkey, [b]Department of Medical Oncology, Dr. Lutfi Kirdar Kartal City Hospital, Istanbul, Turkey, [c]Department of Medical Oncology, Ankara University School of Medicine, Ankara, Turkey, [d]Department of Medical Oncology, Trakya University School of Medicine, Edirne, Turkey.

**Correspondence: Izzet Dogan, MD, Department of Medical Oncology, Istanbul University Institute of Oncology, Çapa/Fatih- Istanbul 34093, Turkey (e-mail: dr.izzetdogan@gmail.com).*

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as the immune response to the host.[5,6] Antigens from the ABO blood type modify the inflammatory state of the host, which may impact cancer growth and spread.[7]

During the preceding several decades, many researchers investigated the link between ABO blood types and cancer risk. The relationship between cancer and ABO blood groups was firstly discovered by Aird *et al* in gastric cancer.[8] Previous studies have shown a link between ABO blood groups and gastric, pancreatic, pleura, colorectal, bladder, ovarian cancers.[9–11] Also, some studies determined that ABO blood groups might affect overall survival (OS) in a variety of cancer types.[12–14] Various studies showed that A blood group was more commonly observed in FBC[9,15] and ABO/ Rh groups did not affect OS.[16,17] In the literature, data on the relationship and prognostic significance of ABO/Rh groups in MBC was extremely rare. The purpose of the study was to evaluate the distributions and prognostic significance of ABO blood and rhesus (D) groups in MBC patients.

2. Methods

2.1. Patients, control groups, and data collection

Our study was designed as a case-control study. We included MBC patients diagnosed and treated between 2000 and 2018 in 4 different tertiary oncology centers outpatients clinics in the study. The local ethics committee approved this work (number: 2019/1397). The patients with MBC were identified by the hospital data processing system. The serologically confirmed ABO blood groups, clinical features, histopathological types, ER, PR, HER2/neu receptors, tumor grades, tumor stage at diagnosis, BRCA mutations, features of metastasis, and treatment (surgery, radiotherapy, chemotherapy, hormonotherapy) data of the patients were retrospectively recorded from hospital database registry system. Immunohistochemistry (IHK) was used to examine ER and PR status. HER2 overexpression was also determined using IHK (score 3+) and in situ hybridization. The staging was carried out in line with the American Joint Committee on Cancer's eighth edition.

The distribution of the ABO/Rh blood groups was identified for the patients. For comparing ABO/ Rh groups distributions, all-volunteer healthy men donors of Istanbul University Medical School Blood Center between 2014 and 2018 were used as a control group. We compared the distributions of ABO/Rh blood groups among the patients and control groups and calculated odds ratios according to ABO/Rh groups. Also, the relationship of ABO/Rh with age at diagnosis, tumor stage, histological subtype, ER, PR, HER2 status, and BRCA mutations were evaluated.

The follow-up time and recurrence status of the patients with early or locally advanced disease were also recorded. The death status of the patients was determined through the death notification system of the Ministry of Health. The time from diagnosis to death from any cause was defined as OS. The prognostic effect of the ABO/Rh blood groups for OS was evaluated in univariable and multivariable analysis.

2.2. Statistical analysis

IBM SPSS 25 was used to perform the statistical analysis (IBM, Chicago, IL). A *P*-value of <.05 was considered statistically significant. All variables were subjected to descriptive statistics. In order to examine the differences between groups and determine the odds ratio, we employed the chi-square and Fisher-exact statistical tests. Kaplan–Meier survival analysis with log-rank tests was used to assess the significance of the survival rates in this study. For multivariate analysis, we employed the Cox regression model.

Table 1

Characteristics of the patients.

	Number of patients total number: 137	%	Actual (%)
Age at diagnosis (years)	Median age 60 (25–82)		
Tumor localization			
Left sight	75	54.7	56
Right sight	59	43.1	44
Unknown	3	2.2	
Stage at diagnosis			
Stage 1	23	16.8	18.3
Stage 2	48	35	38.1
Stage 3	45	32.8	35.7
Stage 4	10	7.4	7.9
Unknown	11	8	
Surgery type			
Modified radical mastectomy	100	73	81.3
Segmenter mastektomy + SLNB	23	16.8	18.7
Unknowns	14	10.**2**	
Radiotherapy			
Adjuvant	89	65	69
Neoadjuvant	1	0.7	0.8
No	39	28.5	30.2
Unknown	8	5.8	
Chemotherapy			
Adjuvant	93	67.9	72
Neoadjuvant	9	6.6	7
No	27	19.7	21
Unknown	8	5.8	
Hormonotherapy			
Yes (Tamoxifen and others)	112	81.3	90.3
No	12	8.8	9.7
Unknown	13	9.5	
Histological type			
Invasive ductal carcinoma	110	80.3	84.6
Other types (invasive lobular carcinoma, mixed type, micropapillary, etc)	20	14.6	15.4
Unknown	7	5.1	
ER status			
Positive	120	87.6	94.5
Negative	7	5.1	5.5
Unknown	10	7.3	
PR status			
Positive	95	69.3	75.4
Negative	31	22.6	24.6
Unknown	11	8	
HER2 overexpression			
Positive	27	19.7	21.8
Negative	97	70.8	78.2
Unknown	13	9.5	
Grade			
1	3	2.2	2.7
2	67	48.9	60.4
3	41	29.9	36.9
Unknown	26	19	

ER = estrogen receptor, PR = progesterone receptor, SLNB = sentinel lymph node biopsy.

Table 2

The distribution of ABO/Rh blood groups in patients and control group distribution of ABO/Rh blood groups.

Blood antigens	Patients group (N = 137) (%)	Control group (N = 120,160) (%)	*P*-value
ARh+	45 (32.8)	44,660 (36.56)	**0.002**
ARh–	7 (5.1)	6726 (5.51)	
BRh+	21 (15.3)	15,580 (12.75)	
BRh–	5 (3.6)	3010 (2.46)	
ABRh+	22 (16.1)	8285 (6.78)	
ABRh–	2 (1.5)	1339 (1.1)	
ORh+	29 (21.2)	35,500 (29.06)	
ORh–	6 (4.4)	7060 (5.78)	

Bold values are statistically significant.

3. Results

3.1. Patient characteristic, treatment modality, and data collection

Clinicopathological features and treatment modalities of the patients are presented in Table 1. One hundred thirty-seven patients and 120,160 healthy male control groups were included in the study from 4 tertiary oncology centers. At the time of diagnosis, the average age was 60 (25–82 years). The median follow-up period was 47.6 months. The most common histological type of tumor was invasive ductal carcinoma (84.6%). Among the patients, 43% presented with stage 3/4 disease at diagnosis. The ratio of BRCA mutant patients was 32%. Ninety (69.8%) patients received either adjuvant or neoadjuvant radiation treatment. Radiation was administered in 25 to 28 portions with a median dosage of 50 Gy. There were 102 (79%) patients who had chemotherapy as an adjuvant or neoadjuvant treatment. Anthracycline- and taxane-based chemotherapy was the most common treatment. Trastuzumab treatment was provided to individuals with Her2/neu positive disease. One hundred twelve (90.3%) patients were received adjuvant endocrine therapy.

The distribution of ABO/Rh blood types in patients and the control group is shown in Table 2. ABO/Rh blood groups distributions were statistically significantly different ($P < .001$) between the patients (17.5% AB, 38% A, 19% B, and 25.5% O) and control group (7.88% AB, 42.06% A, 15.22% B, and 34.84% O). The distribution of the Rh factor was similar between patients and the control group ($P = .93$). There were statistically significant differences between the patients and the control group for of AB vs non-AB blood group ($P < .001$, odds ratio: 2.43, 95% CI) and O vs non-O blood group ($P = .016$, odds ratio: 0.62, 95% CI). However, there was no statistically significant difference between the A and non-A blood groups or between the B and non-B blood groups. Table 3 is presented the odds ratios for MBC, according to ABO/RH blood groups.

In addition, when the clinicopathological characteristics of the patients and the distribution of blood groups were examined, there were no significant differences between ABO/Rh blood groups and age, histological features (ER, PR, HER2/neu receptor, grad), tumor stage, recurrences status, and BRCA mutation status.

3.2. Survival outcomes and prognosis

During the study period, 37 individuals (or 27%) died. The median OS was 120 months (72.4–169.2). The ratio of the 5-year survival was 73.3%. In univariate analysis, the Rh factor was a prognostic factor on OS ($P = .03$) (Fig. 1), but ABO blood groups were not ($P = .29$) (Fig. 2). In multivariate analysis, the effect of the Rh factor on OS was not confirmed. Also, we examined the AB blood group vs non-AB blood group and O blood group vs non-O blood group for survival impact (Figs. 3 and 4). We did not detect a statistically significant effect.

4. Discussion

In this case-control study, we found essential data on blood group distribution and prognostic significance in MBC patients. Although we found that the AB blood group was more common in MBC patients, we showed that it was not a prognostic factor for OS. Since the 1960s, researchers have studied the link between ABO blood groups and cancer. Blood type A was associated with an excess risk of developing stomach[9] and pancreatic cancer.[18] Blood type AB was associated with an increased risk of developing nasopharyngeal carcinoma[19] and postmenopausal ovarian cancer.[20] Also, B Blood type was found as a risk factor for ovarian[21] and esophageal cancer development.[10] In our study, we found that the AB blood group ratio was 2.4 and the O blood group ratio 0.62 in MBC patients compared to the healthy population. A meta-analysis found that blood type A may have a higher risk than other blood groups in FBC.[15] But, Yuksel et al did not detect any link between HER2 positive breast cancer and ABO blood type or Rh factor.[22]

The underlying mechanisms of the ABO blood group with cancer development and progression are still poorly understood. The variant alleles (O, B, and A) of a single gene are located on chromosome 9q34. Genetic variants of the ABO locus may play a role in cancer development.[23] Blood groups are carbohydrate

Table 3

Odds ratios for male breast cancer according to ABO/RH blood group distribution.

	Patients, N (%)	Control group, N (%)	*P*-value	Odds ratio 95% CI
A	52 (38)	51,386 (42.06)	$P = .256$	0.819
non-A	85 (62)	68,774 (57.94)		(0.580–1.156)
B	26 (19)	18,590 (15.22)	$P = .257$	1.280
non-B	111 (81)	101,570 (87.78)		(0.835–1.962)
AB	24 (17.5)	9624 (7.88)	**$P < .001$**	2.439
Non-AB	113 (82.5)	110,536 (92.12)		(1.569–3.791)
0	35 (25.5)	42,560 (34.84)	**$P = .016$**	0.626
non-0	102 (74.5)	77,600 (65.16)		(0.426–0.919)
Rh–	20 (14.6)	18,135 (14.85)	$P = .935$	0.981
Rh+	117 (85.4)	104,025 (85.15)		(0.610–1.576)

Bold values are statistically significant.

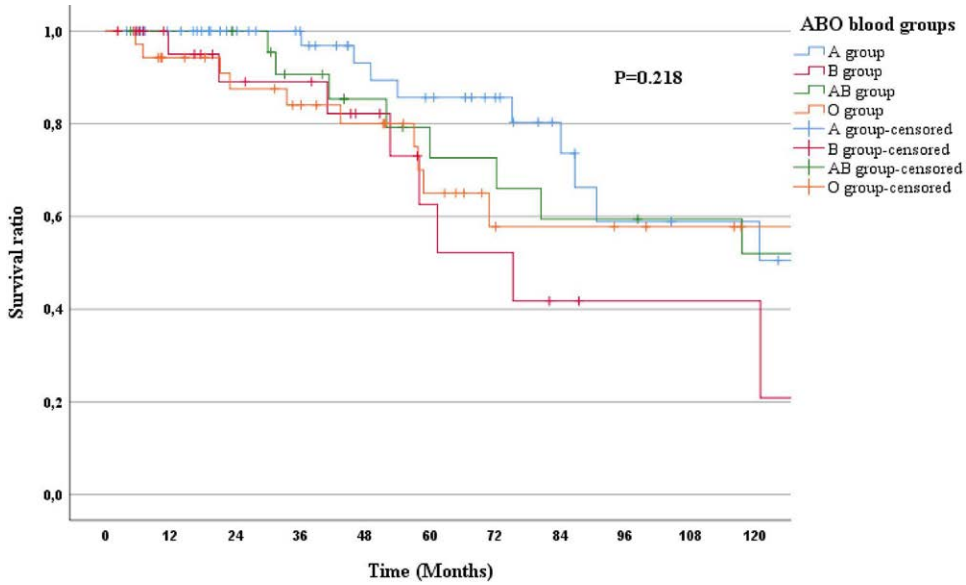

Figure 1. Kaplan–Meier survival curves for OS by Rh factors.

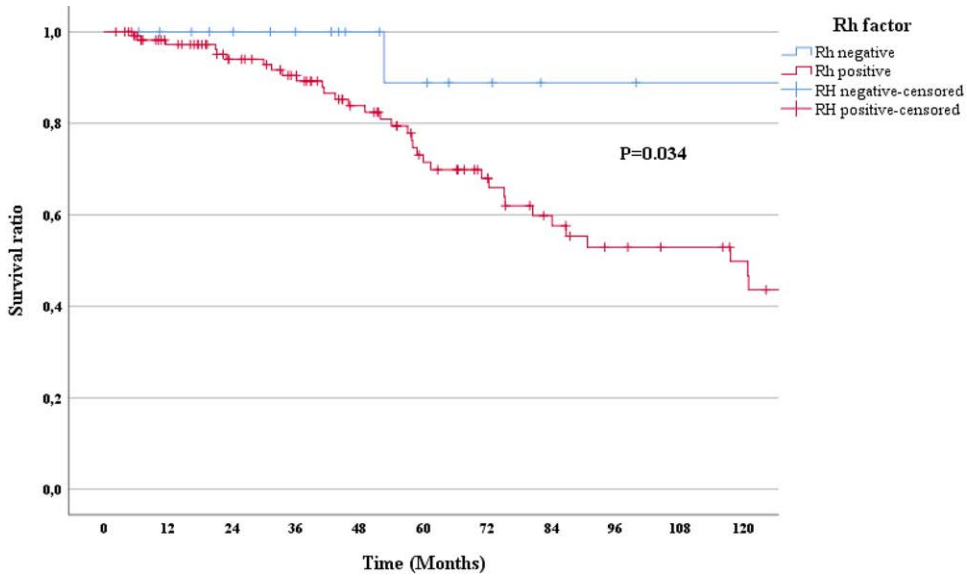

Figure 2. Kaplan–Meier survival curves for OS by ABO blood groups.

antigens found on the surface of epithelial cells such as epidermis, genital tract, bronchopulmonary, and gastrointestinal cells.[24] The blood type isoantigens are constantly expressed in healthy breast tissue, but the A and B isoantigens are likely to disappear in breast cancer.[25] In addition, the antigens of the ABO blood type may affect the host's inflammatory response, and persistent inflammation may lead to cancer formation.[26]

Many studies have been assessed the relationship between ABO blood group antigens and survival in various types of cancers. Although the results of studies on the prognostic importance of the blood group are still controversial, statistically significant results were obtained in some studies involving a high number of patients. According to Fukumoto et al's results that ABO blood type was a significant prognostic factor in resected non-small cell cancer patients. The patients with blood type O had higher 5-year overall and disease-free survival rates than patients with other ABO blood groups.[14] Sun et al discovered that the A blood group was significantly associated with an increased mortality ratio (HR = 1.38, 95% CI) compared to the O blood group in gastric cancer after adjusting for demographic and clinical features.[27] Similarly, Xu et al found that blood type AB is a favorable prognostic factor for gastric cancer patients, but blood type A is an unfavorable prognostic factor for gastrectomy patients.[13] In FBC, data on the prognostic significance of the ABO blood group is unclear and contradictory. In a prospective study, Gates et al found no evidence of a link between blood type and overall or breast cancer-specific survival. The hazard ratios of death due to any cause were 1.00 for blood type A, 1.35 for AB, and 0.81 for B, compared to patients with blood type O.[16] Inversely, in a study that included non-metastatic breast cancer patients, when comparing with A and O blood types to those with other blood groups, it was shown that overall and disease-free survival periods were longer in the A and O blood groups.[28] In a nationwide study from the Kore, breast cancer patients with blood type O had a better prognosis when they were <40 years old than patients with blood group non-O.[29] Also, Yu et al showed that triple-negative breast cancer and its prognosis were not linked to a particular ABO blood type or Rh factor status.[17] In our study,

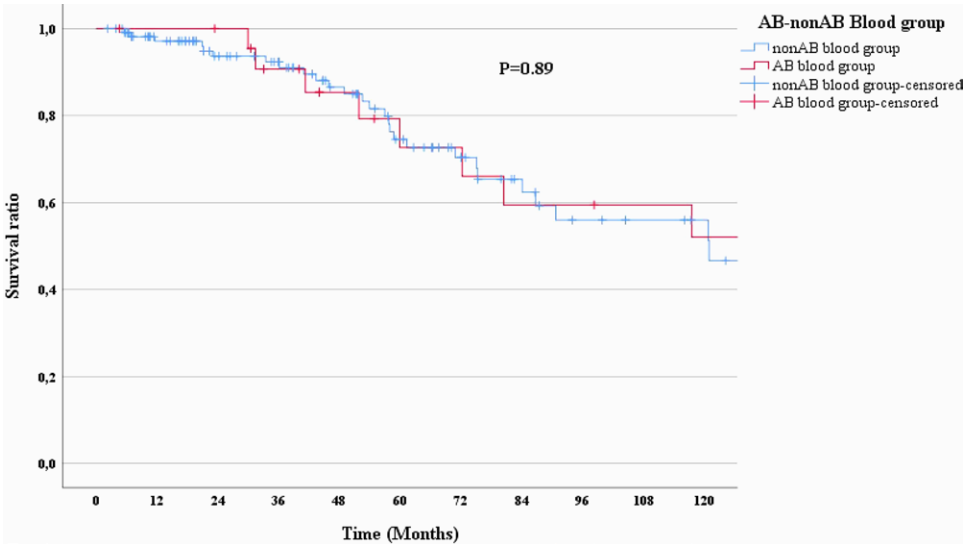

Figure 3. Kaplan–Meier survival curves for OS by A and non-A blood groups.

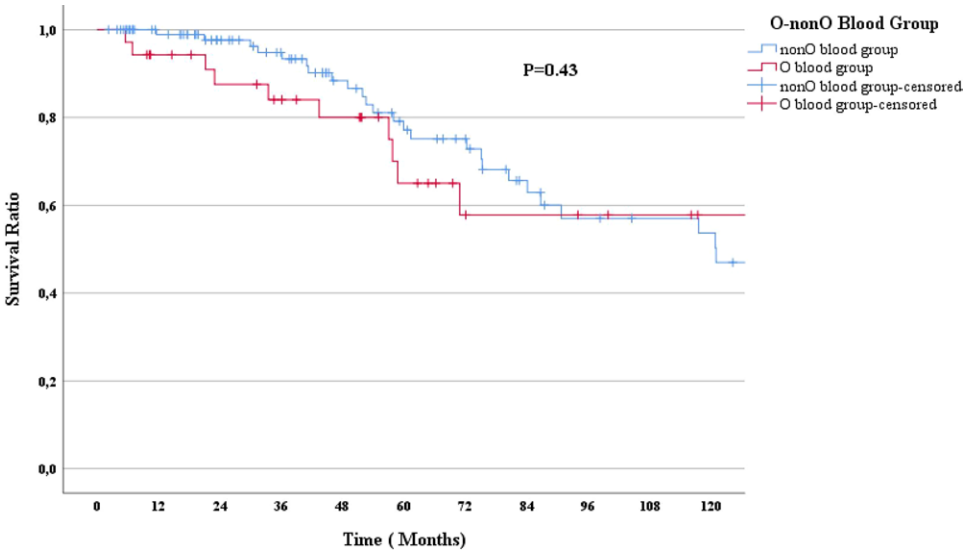

Figure 4. Kaplan–Meier survival curves for OS by O and non-O blood groups.

the ABO blood group's prognostic significance was not found in MBC patients. The Rh factor was detected as a statistically significant prognostic factor in univariate analysis, but it was probably biased and not confirmed in multivariate analysis.

The relationship between the blood group distribution of the patients and their clinicopathologic features has been investigated in different cancer types. In gastric cancer, Yu H et al found no link between ABO blood types and clinicopathological characteristics.[30] Furthermore, Qiu et al found no significant variations by ABO blood type in gastric cancer in terms of gender, tumor size, differentiation degree, P53 status, or tumor stage.[31] Data on the relationship between breast cancer clinicopathological features and ABO/Rh blood group is limited. According to the results of the retrospective study published by Serkan et al; the type, grade, stage, and hormonal state of breast cancer had no significant relationships with ABO blood grouping.[32] Similarly, we could not find a relationship between blood group characteristics and the age at diagnosis, tumor stage, histopathologic features, and BRCA mutation status of MBC patients.

Our study was a multicenter study. The study's limitations were the small number of patients due to being a rare tumor and its retrospective design. In addition, some data were missing and may have biased the statistical analysis.

In conclusion, we determined that the AB blood group's frequency was more common and the O blood group less common in MBC than the healthy control group. AB blood group may be a risk factor for MBC, and O blood group may be protective. In addition, we did not detect a relationship between ABO/Rh blood group distribution and clinicopathological features. To the best of our knowledge, this study is the first study to examine blood group distribution and its prognostic effect in MBC patients. However, there is a need for studies that will confirm our results involving large patient groups on this subject. Because the effect of the ABO/Rh blood types for cancer development is not well understood, further translational research is needed to clarify this problem.

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Author contributions

Idea and design: ID, PS, EA, YU, IC.
Data collection: ID, MA, MG, AK, EA.
Statistical analysis and writing: ID, MA, MG, EA, AK.
Revision of the article for important intellectual content: YU, IC, PS.

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