# The Frequency and Prognostic Significance of ABO/Rh Blood Groups in Male Breast Cancer Patients: A Multi-center Study

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# Abstract

**Purpose:** The study evaluated the distributions and prognostic significance of ABO and rhesus (D) groups in MBC patients.

**Patients and methods:** 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.

**Results:** Overall distributions of ABO blood groups were different between the patients (17.5% AB, 38% A, 19% B, 25.5% O) and control group (7.88% AB, 42.06% A, 15.22% B, 34.84% O) ($p<0.001$). There were significant differences between the patients and control group with respect to AB vs. nonAB blood group distributions ($p<0.001$, Odds Ratio: 2.43 CI 95%) and O vs. nonO blood group distributions ($p=0.016$, Odds Ratio: 0.62 CI 95%). However, A vs. nonA and B vs. nonB blood group distributions were not significantly different. The distribution of the Rh factor was similar between patients and the control group ($p=0.93$). In univariate analysis, ABO/Rh blood groups were not a prognostic factor on OS ($p=0.29$).

**Conclusions:** 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.


# 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 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 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 overall survival (OS) [16, 17]. In the literatüre, 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.

## Material And Methods

# Patients, control groups, and data collection

We included MBC patients diagnosed and treated between 2000 and 2018 in four 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 overall survival was evaluated in univariable and multivariable analysis.

# Statistical analysis

IBM SPSS 25 was used to perform the statistical analysis (IBM, Chicago, IL). A p-value of less than 0.05 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.

## Results

# Patient characteristic, treatment modality, and data collection

Clinicopathological features and treatment modalities of the patients are presented in Table 1. 137 patients and 120,160 healthy male control groups were included in the study from four 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 25–28 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. 112 (90.3%) patients were received adjuvant endocrine therapy.

| Table 1 Characteristics of the patients | | | |
|---|---|---|---|
| | *Number of Patients* | *(%)* | *Actual-%* |
| **Age at diagnosis, years** | | | |
| Median age 60 (range: 25-82) | 137 | | |
| **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[1] | 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 (IDC) | 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 | |
| [1]SLNB: Sentinel Lymph Node Biopsy | | | |

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 ($p < 0.001$) 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 ($p = 0.93$). There were statistically significant differences between the patients and the control group for of AB vs. nonAB blood group ($p < 0.001$, Odds Ratio: 2.43, 95%CI) and O vs. nonO blood group ($P = 0.016$, Odds Ratio: 0.62, 95%CI). However, there was no statistically significant difference between the A and nonA blood groups or between the B and nonB blood groups. Table 3 is presented the odds ratios for MBC, according to ABO/RH Blood groups.

Table 2
The distribution of ABO/Rh blood groups in patients and control groupDistribution 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) | 6,726 (5.51) | |
| **BRh+** | 21 (15.3) | 15,580 (12.75) | |
| **BRh-** | 5 (3.6) | 3,010 (2.46) | |
| **ABRh+** | 22 (16.1) | 8,285 (6.78) | |
| **ABRh-** | 2 (1.5) | 1,339 (1.1) | |
| **ORh+** | 29 (21.2) | 35,500 (29.06) | |
| **ORh-** | 6 (4.4) | 7,060 (5.78) | |

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 = 0.256 | 0.819 |
| **non-A** | 85 (62) | 68,774 (57.94) | | (0.580–1.156) |
| **B** | 26 (19) | 18,590 (15.22) | P = 0.257 | 1.280 |
| **non-B** | 111 (81) | 101,570 (87.78) | | (0.835–1.962) |
| **AB** | 24 (17.5) | 9,624 (7.88) | **P < 0.001** | 2.439 |
| **Non-AB** | 113 (82.5) | 110,536 (92.12) | | (1.569–3.791) |
| **O** | 35 (25.5) | 42,560 (34.84) | **P = 0.016** | 0.626 |
| **non-O** | 102 (74.5) | 77,600 (65.16) | | (0.426–0.919) |
| **Rh-** | 20 (14.6) | 18,135 (14.85) | P = 0.935 | 0.981 |
| **Rh+** | 117 (85.4) | 104,025 (85.15) | | (0.610–1.576) |

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.

# 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 five-year survival was 73.3%. In univariate analysis, the Rh factor was a prognostic factor on OS (p = 0.03) (Fig. 1), but ABO blood groups were not (p = 0.29) (Fig. 2). In multivariate analysis, the effect of the Rh factor on OS was not confirmed. Also, we examined the AB blood group vs. nonAB blood group and O blood group vs. nonO blood group for survival impact. (Figs. 3 and 4). We did not detect a statistically significant effect.

## 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 male breast cancer patients, we showed that it was not a prognostic factor for overall survival. 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 male breast cancer 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 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 percent 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 less than 40 years old than patients with blood group non-O [29]. Also, Yu et al. showed that Triple-Negative Breast Cancer (TNBC) and its prognosis were not linked to a particular ABO blood type or Rh factor status [17]. In our study, 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 male breast cancer patients.

Our study was a multi-center 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.

# Conclusions

In conclusion, we determined that the AB blood group's frequency was more common and the O blood group less common in male breast cancer 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 male breast cancer 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.

# Declarations


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### Statement of Ethics

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

### Conflict of Interest

The authors declare that they have no conflicts of interest.


### Funding Sources

Neither financial nor of other nature

### 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

### Data Availability Statement

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

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# Figures

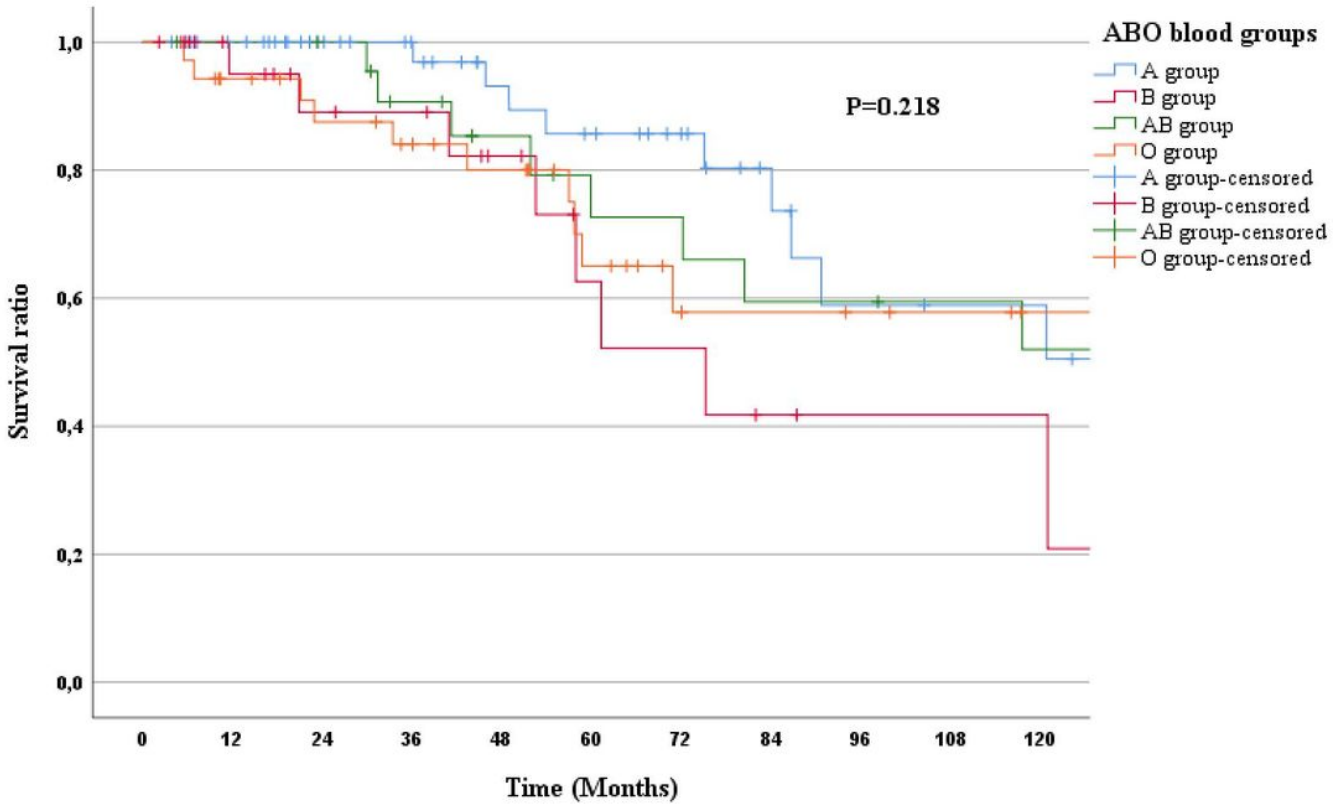


Figure 1

Kaplan-Meier survival curves for ABO blood Groups

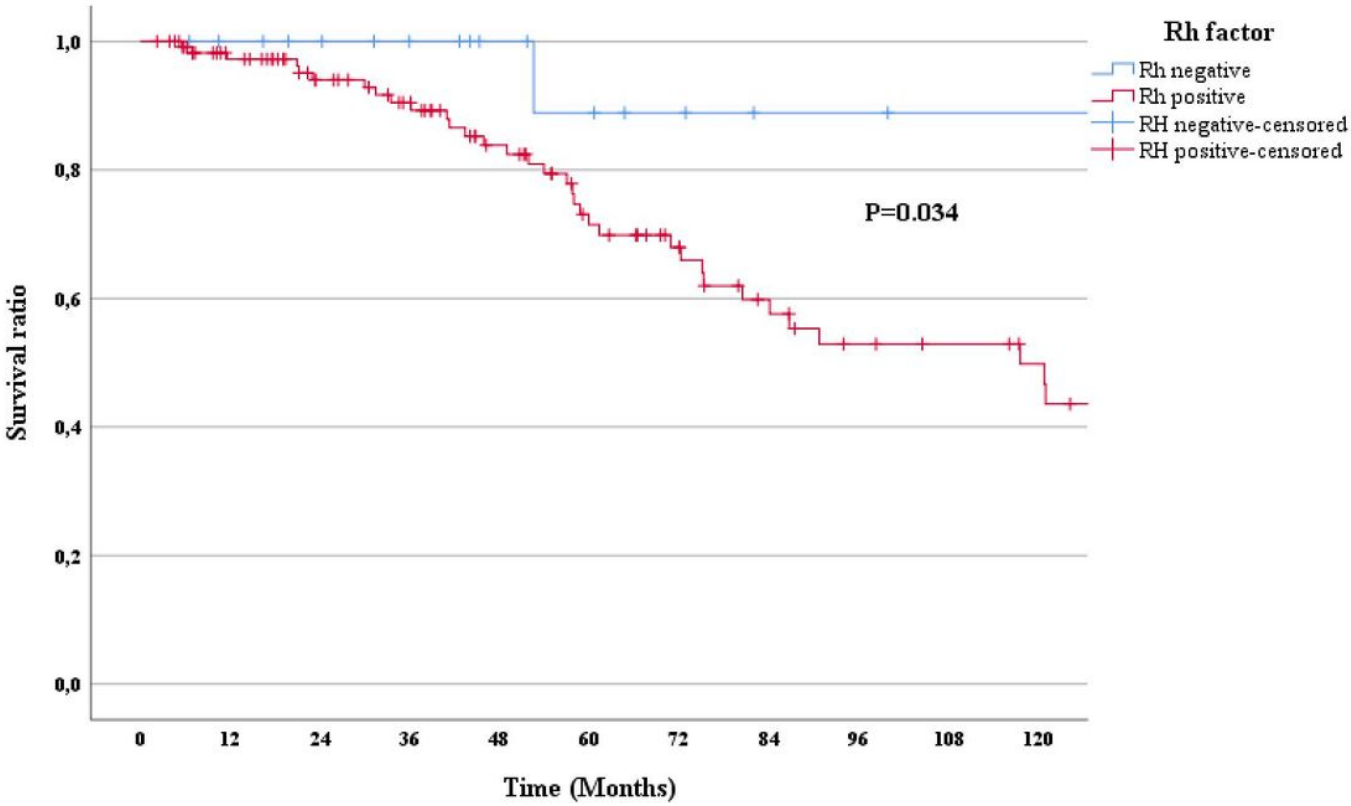


Figure 2

Kaplan-Meier survival curves for Rh factors

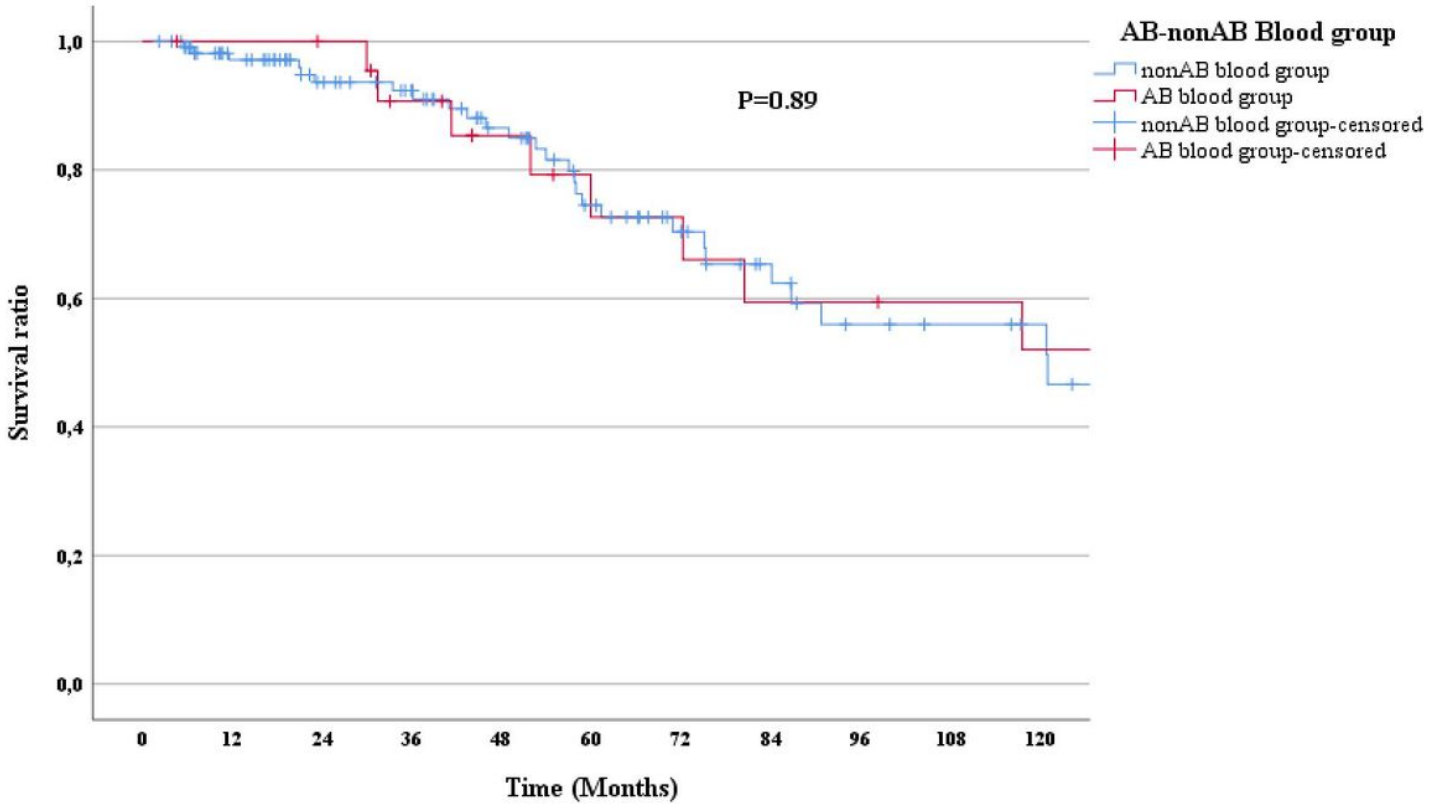


Figure 3

Kaplan-Meier survival curves for A and nonA blood groups

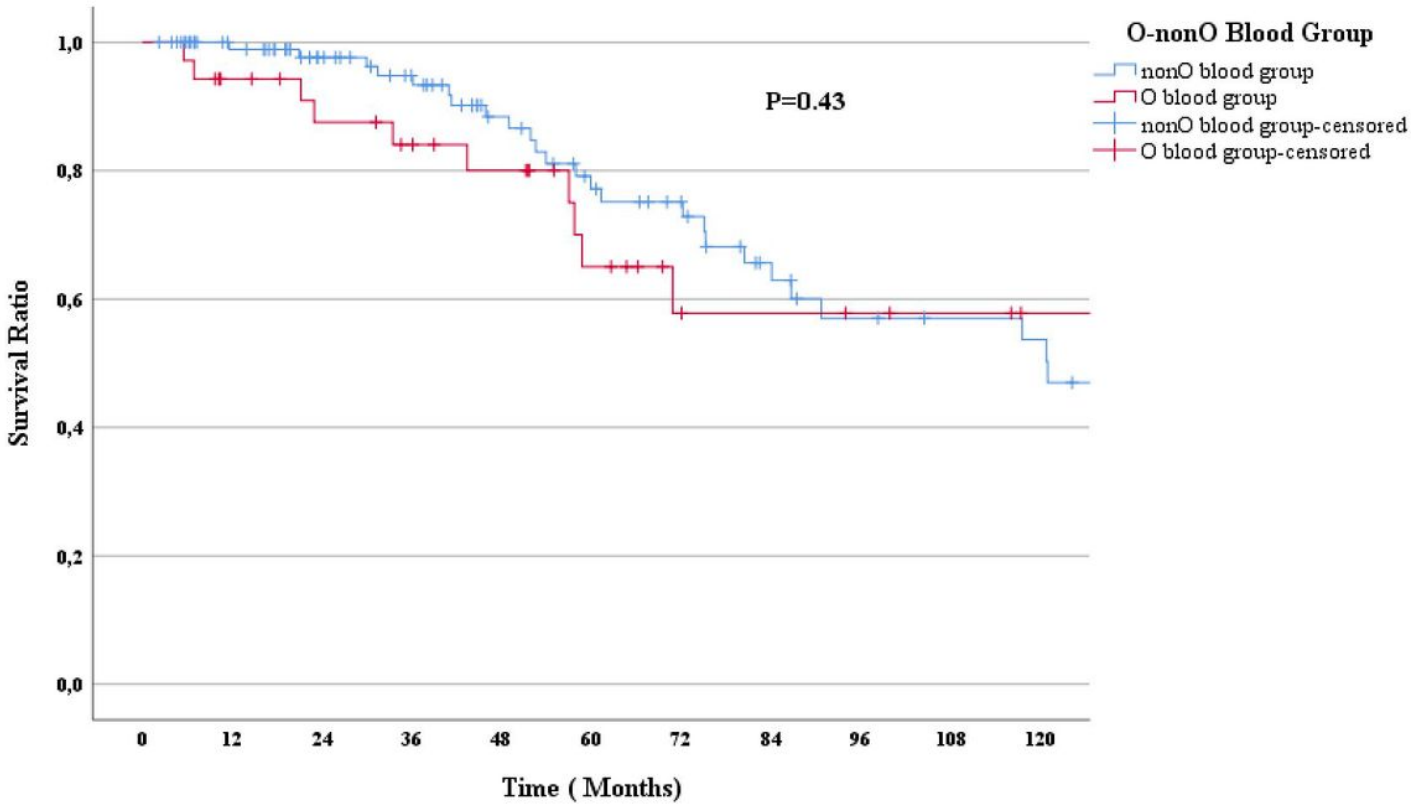


Figure 4

Kaplan-Meier survival curves for O and nonO blood groups