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Elevated Risk of Breast Cancer in Blood Type a Female Individuals in Hubei Province, China

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Abstract: The relationship between the ABO blood group and the risk of female breast cancer remains a subject of ongoing debate, with differing conclusions likely attributable to variations in ethnicity and region of study populations. To elucidate the correlation between breast cancer risk and the ABO blood group in Hubei Province, China, we conducted a comprehensive analysis involving 4,060 female breast cancer patients, 10,522 breast mastitis patients, and 1621 patients who progressed from mastitis to breast cancer, all admitted to "Hubei Provincial Cancer Hospital" between 2017 and 2024. The distribution of both ABO blood groups and CA153 levels among these patients was examined. Our results show that women with blood group A have a significantly higher risk of mastitis and breast cancer, with the highest risk for progression from mastitis to cancer. In contrast, women with blood group O demonstrated the lowest incidence of mastitis, breast cancer, and progression from mastitis to breast cancer. Notably, CA153 levels were more likely to normalize in women with blood group A as treatment progressed. These results suggest that women with blood group A in Hubei Province face a heightened risk of breast cancer but experience the best treatment outcomes, whereas those with blood group O have a lower risk yet may encounter greater treatment challenges. Our findings provide more evidence for the correlation between the ABO blood group and breast cancer risk in the Han Chinese population; meanwhile, we propose the concept of setting different CA153 thresholds according to the ABO blood group.

Keywords: Breast Cancer; ABO Blood Group; CA153; Mastitis.

1. Introduction

The ABO gene located in the 9q34 region of the chromosome encodes a specific glycosyltransferase that catalyzes the addition of specific sugar molecules to the oligosaccharide chain of the H antigen, thereby forming the ABO antigen [1]. This antigenic system was first identified on erythrocytes by Carl Landsteiner in 1900. Subsequent studies on monoclonal have demonstrated that ABO antigens are also widely distributed on various cell surfaces, in body fluids and secretions. Consequently, the ABO antigen system is classified as a "tissue blood group system" and participates in the occurrence and development of various diseases [2-7].

Studies have demonstrated a significant association between ABO blood group and cancer risk. People with blood type A exhibit an elevated risk for oral, nasopharyngeal, digestive, ductal, and female genital cancers. Those with blood groups AB and B are at increased risk for digestive, pancreatic, and female genital cancers. However, individuals with blood group O show a decreased risk for gastric and pancreatic cancers [8-12]. With the deepening of research on the relationship between ABO blood type and cancer risk, two principal hypotheses have emerged to elucidate how different blood groups may influence cancer occurrence and progression. The first hypothesis is that binding A antigens to immunoglobulin M (IgM) molecules in the host may trigger elevated expression of anti-A/Tn cross-reactive immunoglobulins. This expression activates T cells and natural killer cells, causing these immune cells to mistakenly attack normal cells expressing either the A antigen. This inappropriate mobilization of immune resources may diminish the host's ability to clear cancer-associated pathogens and malignant cells, thereby fostering cancer development [13]. Another hypothesis suggests that blood-type antigens may regulate inflammatory responses by modulating circulating adhesion molecules associated with inflammation, such as tumor necrosis factor-alpha, Soluble intercellular adhesion molecule-1 (sICAM-1), thereby affecting the occurrence of malignant tumors [14]. For example, in non-O blood cancer patients, a decrease in soluble sICAM-1 levels and an increase in vascular blood disease factor (VWF) levels have been observed [15-17]. The decrease in soluble ICAM-1 content may enhance the ability of cancer cells to attach to endothelial cells, leading to cancer cell metastasis [18]; The increase in VWF content promotes platelet adhesion and aggregation at the site of inflammation, enhances vascular permeability, and thus improves the metastatic ability of cancer cells [19]. In cancer patients with type A or B blood, a decrease in tumor necrosis factor - α (TNF - α) levels has been observed [20]. TNF - α, as a key mediator of cell apoptosis, can act as an angiogenic factor at low levels, promoting the development of cancer [21].

Breast cancer is a heterogeneous malignant tumor that has a greater impact on women's health, and its risk is also significantly associated with ABO blood group. However, the conclusions from different studies are quite different. For example, the risk of breast cancer in Greece with type A blood is high [22], and the risk of breast cancer in Iceland and Morocco, individuals with type B blood is high [23,24]. These findings suggest that the risk of breast cancer varies considerably by race and ethnicity among people with different blood types. In addition, even in the same country, there are significant differences in the risk of breast cancer among people in different regions. For example, in Jilin, China, people with blood type O have a higher risk of breast cancer, while people with blood type A have a lower risk of

breast cancer. In Xinjiang, the risk of breast cancer is higher among people with type A blood, while the risk of breast cancer is lower among people with type B blood [25,26]. To sum up, the association between breast cancer risk and ABO blood group is affected by race and region.

The Han ethnic group constitutes 91.1% of China's total population and 95.2% of Hubei Province's population. We used patients with breast diseases in the Hubei Cancer Hospital as our study subjects, hoping to reveal the correlation between ABO blood groups and breast cancer risk in the Han ethnic group population, so as to optimize the diagnosis and treatment process for Han Chinese breast cancer patients.

2. Materials and Methods

This study included patients diagnosed with breast disease at the 'Hubei Provincial Cancer Hospital' from 2017 to 2024. Clinical and histopathological data were collected anonymously, including patients' age at diagnosis, gender, disease type, blood group, and glycan antigen 153 (CA153) test value. The study data focused on ABO blood group, gender, disease type, and CA153 test values.

To investigate the relationship between blood group and breast cancer risk, we used to process the collected data using RStudio software (version 4.4.2). Breast cancer cases were identified by screening for entries labeled "breast cancer" or "breast malignancy" in the "Diagnosis" column, Mastitis cases were obtained by screening the data for inflammatory breast disease in the 'Diagnosis' column. For the risk analysis of mastitis progressing to breast cancer, we combined the data in the 'Diagnosis' and 'Date of test' columns to extract records of those who progressed to breast cancer after the initial diagnosis of mastitis. To assess the trend of CA153 changes in patients with different blood groups during the course of treatment, We analyzed the CA153 data by treatment duration in four time periods: 0 to 4 months, 4 to 8 months, 8 to 12 months, and 12 to 24 months.

3. Results

3.1. The Proportion of People with Different Blood Groups Suffering from Breast Cancer

(1)The distribution of ABO blood types among women in Hubei Province is as follows: 31.51% for blood type A, 8.28% for blood type AB, 24.79% for blood type B, and 35.42% for blood type O [27]. Our study included 4060 patients with breast cancer. Among these, 1,353 (33.33%) were classified as blood type A, 383 (9.43%) as blood type AB, 1,029 (25.34%) as blood type B, and 1,295 (31.90%) as blood type O. A one-sample proportions test was conducted for each blood type, and the significance of differences in proportions is illustrated in Figure 1.

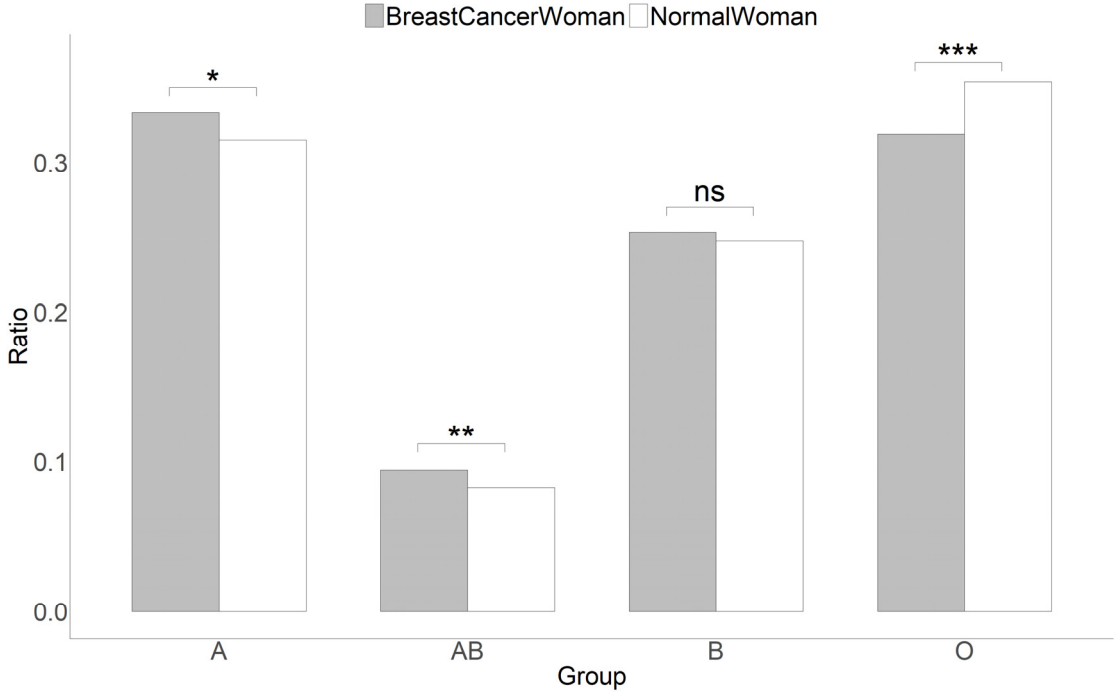


Fig 1. ABO Blood Type Distribution Differences Between Breast Cancer Patients and Normal Women

(2)Figure 1 shows that the proportion of breast cancer patients with blood group A is significantly higher than the control population ($p=1.28\times10^{-2}$). The proportion of breast cancer patients with blood group AB is very significantly higher than the control population ($p=7.65\times10^{-3}$). The proportion of breast cancer patients with blood group O is highly significantly lower than the control population ($p=2.68\times10^{-6}$). The proportion of breast cancer patients with blood group B is not significantly different from the control population ($p=4.13\times10^{-1}$). Therefore, the above statistics imply that people with blood groups A and AB have a higher risk of breast cancer, and people with blood group O have a lower risk of breast cancer, in the Hubei region of China.

3.2. The Proportion of People with Different Blood Groups Suffering from Mastitis

(1)To investigate the association between ABO blood groups and mastitis risk, we collected ABO blood type data from 10,522 patients diagnosed with mastitis. Among these patients, there were 3,537 cases of blood type A (33.62%), 929 cases of blood type AB (8.83%), 2,646 cases of blood type B (25.14%), and 3,410 cases of blood type O (32.41%). A one-sample proportions test was conducted separately for each blood group, and the significance of the differences in

proportions is presented in Figure 2.

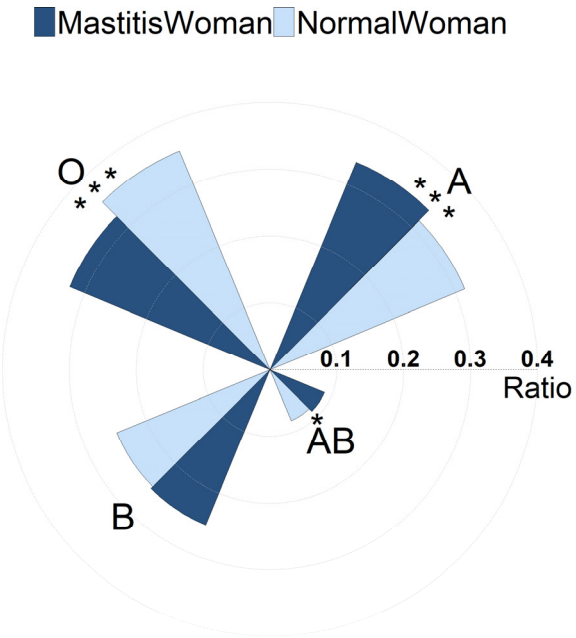


Fig 2. Differences in ABO Blood Type Distribution Between Mastitis Patients and Normal Women

(2)Figure 2 illustrates that the proportion of mastitis patients with blood group A is highly significantly higher than that of the control population ($p = 3.34 \times 10^{-6}$). The proportion of mastitis patients with blood group AB is significantly higher than that of the control population ($p = 4.10 \times 10^{-2}$). However, the proportion of mastitis patients with blood group O is highly significantly lower than that of the control population ($p = 1.05 \times 10^{-10}$). The proportion of mastitis patients with blood group B is not significantly different from the control population ($p = 3.96 \times 10^{-1}$). These findings suggest that the risk of mastitis is higher in individuals with blood groups A and AB, while it is lower in those with blood group O in Hubei Province, China.

3.3. The Proportion of Mastitis Progressing to Breast Cancer in Different Blood Groups

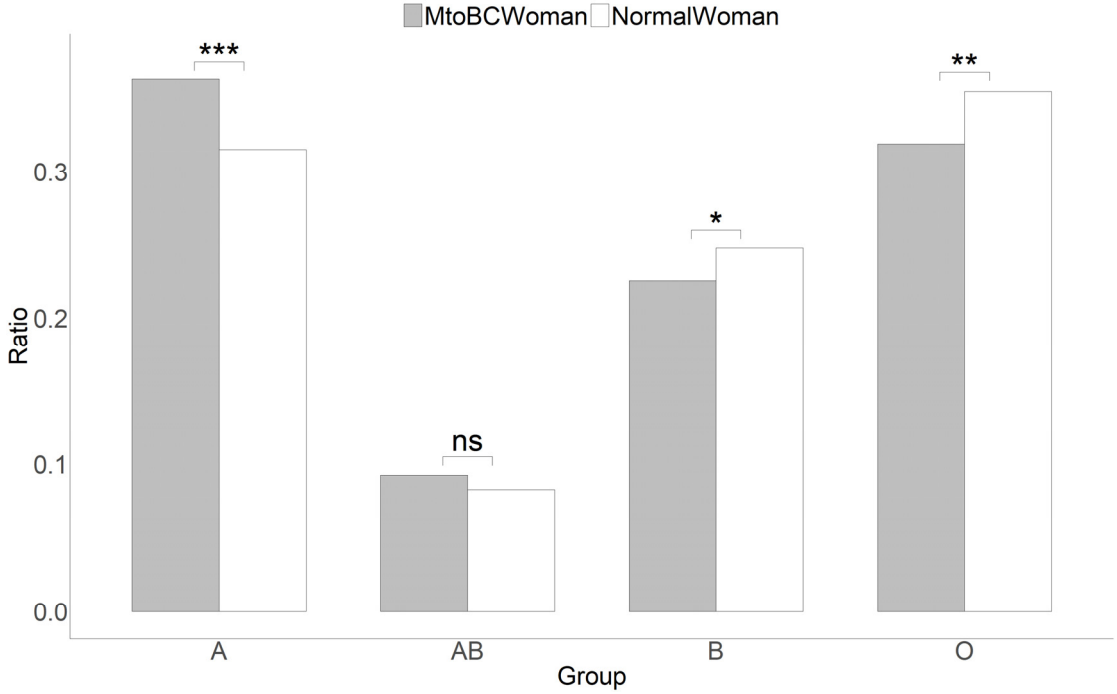


Fig 3. Differences in ABO blood group distribution between patients with mastitis developing breast cancer and normal women

(1)Analysis of Figures 1 and 2 reveals that A and AB blood groups have a higher risk of mastitis and breast cancer. Conversely, individuals with blood group O demonstrate a lower risk for both mastitis and breast cancer. We conducted further analysis to assess whether the progression from mastitis to breast cancer differs across blood types and collected ABO blood group data of 1621 patients who developed from mastitis to cancer. Among these patients, 589 (36.34%) were classified as blood group A, 150 (9.25%) as blood group AB, 365 (22.52%) as blood group B and 517

(31.89%) as blood group O. A one-sample proportions test was conducted for each blood type, with the significance of the differences in proportions illustrated in Figure 3.

(2)Figure 3 indicates that the proportion of patients with blood group A who developed breast cancer from mastitis is highly significantly higher than that of the control population ($p = 2.89 \times 10^{-5}$). In contrast, the proportion of patients with blood group B who progressed to breast cancer from mastitis is significantly lower than that of the control population ($p = 3.41 \times 10^{-2}$). Similarly, patients with blood group O demonstrate a very significantly lower rate of breast cancer progression from mastitis compared to controls ($p = 2.99 \times 10^{-3}$). There was no significant difference in the proportion of patients with blood group AB who developed breast cancer from mastitis relative to the control population ($p = 1.55 \times 10^{-1}$).

These findings suggest that patients with blood group A face the highest risk of developing breast cancer from mastitis, while those with blood group O exhibit the lowest risk. Therefore, women with blood type A in the Hubei region need to pay special attention to monitoring breast inflammation.

3.4. Differences in CA153 Indices During Breast Cancer Treatment in People with Different Blood Groups

(1) CA153 is a glycoprotein whose antigenic determinant cluster is partially composed of glycans and peptides. It is generally accepted that a normal CA153 level should be less than 24 U/mL. However, levels of CA153 often remain below this threshold in the early stages of breast cancer, which limits its utility in early adjuvant diagnosis. However, studies have demonstrated that serum CA153 levels tend to increase as breast cancer progresses, highlighting its clinical significance in prognostic assessment. To investigate the differences in CA153 levels during the treatment of breast cancer patients with varying blood types, we plotted the CA153 density curve.

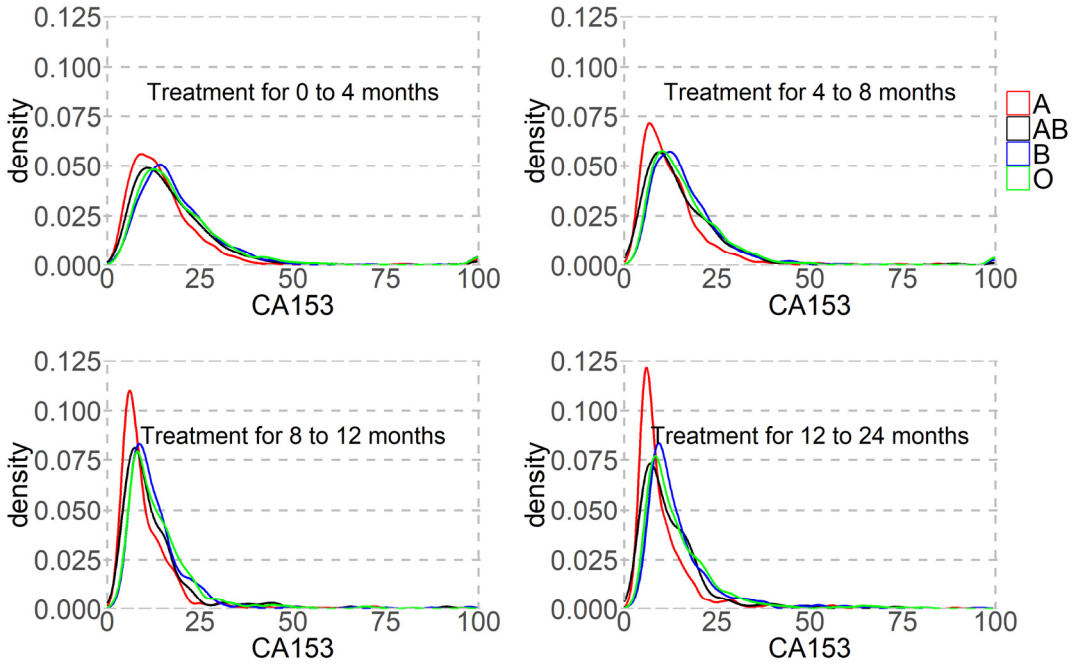


Fig 4. Changes of CA153 in Breast Cancer Patients with Different Blood Types

(2)Figure 4 illustrates the changes in CA153 levels across different treatment intervals in breast cancer patients. Notably, the proportion of blood type A patients with CA153 levels below 24 U/mL gradually increased over the two-year period, suggesting enhanced responsiveness to current therapeutic agents and favorable treatment outcomes in this subgroup. Among non-A blood group patients, a gradual increase in the proportion of individuals with CA153 levels below 24 U/mL was observed during the first year, indicating positive treatment responses. However, the absence of significant changes in the second year suggests a plateau in therapeutic efficacy, potentially necessitating alternative treatment strategies beyond the first year.

4. Discussion

Extensive research has shown that blood group antigens are associated with the development and progression of a wide range of organ malignancies and hematological malignancies. However, the association between the ABO blood group and breast cancer risk remains contentious. Some studies have shown that there is no significant correlation between the ABO blood group and the risk of breast cancer [28,29]. However, other studies have found a significant correlation, and the conclusions of these studies vary considerably, with some studies pointing to a higher risk in people with blood group A, while others have shown a higher risk in people with blood group B [22-24]. Our study found that individuals with blood type AB in Hubei Province, China, have the highest risk of breast cancer, followed by those with blood type A, who have an elevated risk. Conversely, individuals with blood type O have a lower risk, while those with blood type B exhibit no significant difference in risk. These phenomena imply to us that there are large differences in the risk of breast cancer among people with ABO blood groups in different races, or the same race in different environments. Research has demonstrated that A, B, and H blood group antigens can specifically bind to certain pathogens, thereby facilitating their colonization or invasion and assisting these pathogens in evading immune clearance mechanisms, Contributing to an

increased risk of specific diseases in individuals with certain blood types [30,31]. Another aspect, blood group antigens may function as 'pseudo-receptors,' obstructing pathogen binding to actual receptors, interfering with the colonization or invasion of these pathogens, thereby reducing the susceptibility of individuals with certain blood types to specific diseases [31]. But the glycosyltransferases associated with the ABO blood group antigens in humans include alpha 1-3-N-acetylgalactosaminyltransferase (which is responsible for the formation of the A antigen) and alpha 1-3-galactosyltransferase (which is responsible for the formation of the B antigen). The number of alleles encoding these two enzymes exceeds 100, resulting in variations in the expression levels of these glycosyltransferases across different populations [31]. For example, the expression of glycosyltransferases for the synthesis of B antigens is weak in East Asian populations, whereas the expression of glycosyltransferases for the synthesis of A antigens is weak in Caucasian populations [31,32].This results in the number of antigens being affected by race even for the same blood type. Therefore, when investigating the relationship between ABO blood groups and disease susceptibility, it is crucial to consider the distribution of alleles linked to these glycosyltransferases across diverse populations and geographical regions.

As research into the relationship between chronic inflammation and cancer continues, there is growing evidence that chronic inflammation promotes the development and progression of cancer. However, only a few cancers, such as rectal, gastric, and hepatocellular cancers, have been confirmed to be associated with chronic inflammation, and inconsistent conclusions remain about the relationship between more cancer types and chronic inflammation [33-36]. In the present study, we identified that women with blood type A exhibited a significantly heightened risk for both breast cancer and mastitis, in contrast to women with blood type O, who displayed a markedly reduced risk for these conditions. Furthermore, our analyses revealed that patients with blood group A were at an increased risk for the progression of mastitis to breast cancer, while those with blood group O demonstrated a decreased risk for this progression. These findings suggest a significant association between mastitis and breast cancer. However, the data also indicated that women with blood group AB experienced an increased risk for both mastitis and breast cancer; but no significant difference was noted in the risk for progression of mastitis to breast cancer in this group. Meanwhile, women with blood group B did not show significant differences in the risk of mastitis and breast cancer, but they exhibited a lower risk of progression from mastitis to breast cancer. These observations partially challenge the direct association between mastitis and breast cancer. Moreover, In addition, with the intensive research on ABO blood group and cancer risk, there is a hypothesis that blood group antigens may influence the chronic inflammatory state associated with carcinogenesis, and thus tumorigenesis and spread, by modulating the expression levels of several circulating adhesion molecules associated with inflammatory responses [14]. Different blood group antigens regulate chronic inflammation to different states, while chronic inflammation can promote cancer development and progression. Consequently, when investigating the interplay between cancer and chronic inflammation, it is recommended to consider ABO blood type as one of the influencing factors.

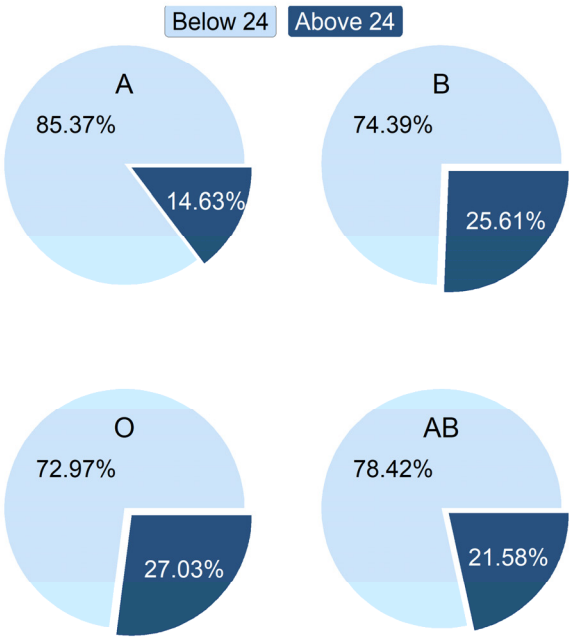


Fig 5. Distribution of Early CA153 in Patients with Breast Cancer of Different Blood Types

When the CA153 level exceeds the threshold (24 U/mL), it typically indicates the presence of breast cancer in the patient [37]. We analyzed the initial CA153 values of breast cancer patients and the results are shown in Figure 5. The results showed that the proportion of initial CA153 values exceeding the threshold was significantly lower in patients with blood type A than in patients with other blood types. However, the relatively high risk of breast cancer in the blood group A population increases the probability of missed diagnosis in blood group A patients, leading to the fact that the specificity of CA153 has not yet been fully utilized in blood group A patients. Based on this, we suggest that a relatively low CA153 threshold be reset for patients with blood group A at the time of clinical diagnosis to improve the accuracy of initial breast cancer diagnosis.

CRediT Authorship Contribution Statement

Hongbo Zhang: Formal analysis, Investigation, Writing - original draft, Writing -review & editing. **Yazhe Li:** Writing - original draft. **Shaochun Hu:** Data curation, Supervision. **Xiaoping Chen:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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