• Clinical Research •

# Predictive value of CA-153, CA-125 and Apo A for ocular metastasis in menopausal female patients with breast cancer

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## Abstract

● **AIM:** To establish a meaningful standard for diagnosing ocular metastasis (OM) in menopausal breast cancer (BC) women, and explore the relationship between CA-153, CA-125, apolipoprotein A, and OM.

● **METHODS:** A total of 1362 menopausal female BC patients with OM volunteered to take part in this study between July 2012 and July 2022. Women with BC who are menopausal were found to have an OM incidence of 1.6%. Furthermore, CA-153, CA-125, and apolipoprotein A (Apo A) all contributed to OM in women with BC who are postmenopausal according to binary logistic regression. Receiver operating curve (ROC) analysis was used to assess the diagnostic value of OM in patients with BC.

● **RESULTS:** Both CA-153 and CA-153+CA-125 showed a higher sensitivity of 95.45%, whereas CA-153+Apo A illustrated the highest specificity of 99.02%. Moreover, CA-153 and CA-153+CA-125 had higher areas under the curve (AUC) of 0.973.

● **CONCLUSION:** The data indicate that the serum concentrations of CA-153 exhibited the most significant predictors of the diagnosis of OM in menopausal women with BC. The current study researches the utility of risk factors in predicting of OM in menopausal BC women and put forward the latest suggestions on their clinical application.

● **KEYWORDS:** menopausal female patients; breast cancer; ocular metastasis; CA-125; CA-153; apolipoprotein A
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## INTRODUCTION

Breast cancer (BC) is now the most prevalent form of malignant tumor in women[1]. In 2018, 32.4% of women were diagnosed with BC, according to data from the World Cancer Research Fund International[2]. Furthermore, 31% of all tumors in women worldwide are BC, which are the most common malignant tumors in women. It is characterized by high recurrence rate, high mortality rate, and unfavorable prognoses[3]. Also, this disease affected 1.7 million women worldwide in 2012, making it a global priority[4]. Therefore, it is no exaggeration to say that there are probably more studies on BC than any other malignant tumor.

During menopause, ovary function ceases, reproductive hormone production ceases, and fertility is irreversibly lost, which is a natural part of aging reproductive organs[5]. Menopause is an important transition in the reproductive life cycle of women, as it signals the end of fertility[6]. Menopause is also an important determinant of future BC risk[7]. Ovarian degeneration and estrogen reduction are closely related to menopause and are considered to be risk factors for BC[8].

However, much evidence also shows that the external influence factors of BC are lack of physical exercise[9], high-fat diet[10], mutagenic and carcinogenic compounds in food[11], and drinking[12]. Heredity also can increase BC predisposition[13]. Excessive drinking has been linked to BC risk in previous studies, but whether light drinking has adverse effects on the human body is still unclear[14]. Based on the review of Scoccianti *et al*[14], we selected drinking more than 15 g per day as one criterion and divided the sample into two groups, to compare the relationship between drinking and ocular metastasis (OM) in BC and assess the histopathological features caused by drinking.

In addition, after several years from the occurrence of primary BC, the probability of distant metastasis of patients is higher than that of local recurrence[15]. And any part of the body can be affected by BC, including the eyes (only 3%–10% of cases)[16]. In the study of Demirci *et al*[17], all BC patients with OM, regardless of their treatment history, had a poor systemic prognosis, with survival rates of 65% after one year and 24% after five years, with survival rates of 65% at 1-year follow-up and 24% at 5-year follow-up. This shows that early diagnosis can bring early treatment which can significantly improve the prognosis of patients with distant metastasis[15]. Although diagnostic imaging examination (*e.g.*, magnetic resonance imaging, ultrasonography, mammography, and other scientific and effective imaging methods) may contribute to reduced morbidity and mortality[1], they are either expensive or need a high level of technical support. Thus, in the current study, we adopted a simple, inexpensive, routine hematological examination to establish a universally accepted diagnostic standard for BC by detecting biomarkers in the serum.

Tumor markers exist in the blood tissue of patients and are substances synthesized and released by tumor cells during the occurrence and development of tumors. The more vigorously the tumor grows, the higher the number of corresponding markers, which can also be a type of substance produced by other tissues or cells. The elevation of tumor markers may indicate the occurrence of a tumor or the recurrence and metastasis of a previous tumor. The normal reference range for tumor markers is the normal range calculated by epidemiological investigations and statistics for most healthy individuals[18]. Their presence or quantity changes can indicate the nature of the tumor, in order to understand its tissue development, cell differentiation, and cell function, and to assist in the diagnosis, classification, prognosis, and treatment guidance of tumors. In addition, some benign diseases such as inflammation, liver and kidney dysfunction, skin diseases, endometriosis, *etc*. may be accompanied by abnormal elevation of tumor markers. Normal physiological changes such as pregnancy and menstruation can affect some tumor markers. In addition, unhealthy lifestyle habits such as drinking alcohol, smoking, and staying up late may also lead to abnormal tumor markers[19].

Abnormal elevation of CA153 is commonly seen in breast malignant tumors, and mild abnormalities are occasionally observed in benign diseases such as breast adenomas[20]. The positive rate of CA153 in BC patients was significantly higher than that in healthy people. The level of CA153 in BC patients is closely related to the treatment effect. Detection of CA153 can be used to monitor the treatment effect of BC patients and determine whether there is metastasis after surgery. When there is metastasis, the positive rate of CA153 is as high as 60% to 80%[21]. Abnormal increase of CA125 is common in gynecological malignancies, such as BC, ovarian cancer, endometrial cancer, cervical cancer, fallopian tube cancer, *etc*. It may also be slightly increased in some gynecological benign diseases[22]. Apolipoprotein A (Apo A) is a special type of lipoprotein, and abnormal elevation is mainly caused by genetic factors. Patients with high lipoprotein A often have more than one family member with similar blood lipid abnormalities[23]. Although the lipid composition of Apo A is similar to low-density lipoprotein (LDL), the concentration of Lipoprotein a (LPA) is not affected by gender, age, weight, and cholesterol lowering drugs, making it difficult to adjust for abnormally elevated levels of this lipoprotein. Previous studies have found that the level of apolipoprotein A in the blood of patients with diagnosed BC is significantly higher than that of benign breast tumors and healthy controls (physical examination population), suggesting that there may be a certain relationship between lipoprotein a and the occurrence of BC[24].

In the our study, a correlation was also examined between serum biomarker levels CA-153, CA-125, and Apo A, and OM in menopausal BC patients in the Jiangxi Province. We aimed to establish a meaningful standard for diagnosing OM in menopausal BC women, and explore the relationship between CA-153, CA-125, Apo A, and OM.

## PARTICIPANTS AND METHODS

**Ethical Approval** The First Affiliated Hospital of Nanchang University's medical research ethics committee, Nanchang, Jiangxi Province, China approved the study. All participants in the study gave informed consent. All procedure was carried out in compliance with the principles outlined in the Declaration of Helsinki.

**Study Design** In this retrospective study, between July 2012 and July 2022, a total of 1362 menopausal women with BC were evaluated and subdivided into OM and non-ocular metastasis (NOM) groups. The OM were assessed through ophthalmic B-type ultrasound, fundus photography, indocyanine green angiography (ICGA) and fundus fluorescein angiography (FFA; Figure 1). The diagnosis of

OM was validated through the application of both computed tomography (CT) and magnetic resonance imaging (MRI). Inclusion criteria of OM: 1) BC patients with OM; 2) heart function is normal, kidney function is normal, and imaging can be performed; 3) no metal implants, MRI can be performed. Exclusion criteria: 1) presence of primary malignant and benign ocular tumors; 2) presence of comorbidities; 3) presence of other metastatic cancers; 4) mental illness. Inclusion criteria of NOM: 1) patients with BC; 2) heart function is normal, kidney function is normal, and imaging can be performed; 3) no metal implants, MRI can be performed. Exclusion criteria: 1) presence of comorbidities; 2) metastasis to other organs or lymph nodes; 3) mental illness. All medical records were up-to-date and basic demographic and clinical data were collected in a timely manner.

**Data Collection** Diagnostic records of patients were analyzed to determine serum levels of relevant biomarkers (*e.g.*, age, histopathological types, and drinking habits). Several biomarkers were then compared between the two groups, which contained calcium, alkaline phosphatase (ALP), total cholesterol, CA-153, CA-125, CA-199, carcinoembryonic antigen (CEA), triglyceride (TG), LDL, high density lipoprotein (HDL), Apo A, Apo B, lipoprotein(a) [Lp(a)], and hemoglobin (HB). All medical records were obtained during the initial diagnosis of BC, biomarkers were tested by the Laboratory Department of our hospital, the test sample was the patient's blood.

**Statistical Analysis** The differences in histopathological type and age between the OM and NOM groups were evaluated using Chi-squared tests and Student's *t*-tests. An investigation of single OM risk factors was conducted using binary logistic regression models. Receiver operating characteristic (ROC) curves showed the differences in sensitivities, specificities, and areas under the curve (AUCs) of CA-125, CA-153, and Apo A. OM diagnosis accuracy was evaluated by the AUCs in menopausal patients with BC. $P<0.05$ was considered statistically significant. Statistical analysis was carried out through Microsoft Office Excel 2016 (Microsoft Corp, USA), SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA), and MedCalc 18.6.0 statistical software (MedCalc, Ostend, Belgium). Continuous data were represented as mean±standard deviation (SD).

## RESULTS

**Demographics and Clinical Characteristics** The analysis was conducted on 22 individuals with OM and 1340 individuals with NOM. Demographic data are presented in Table 1. Figure 2 shows typical images of the hematoxylin-eosin (HE) and Immunohistochemistry (IHC) staining of specimens from the OM portion of BC. The average age of the OM and NOM groups was 54.0±3.0 and 59.5±2.5y, respectively (all ages of menopausal patients with BC>45y). No significant differences ($P>0.05$) were observed in the histopathological types between the OM and NOM groups (Table 1). Furthermore, Table 2 shows that no notable histopathological type ($P>0.05$) had been observed in most menopausal patients with BC and OM. No significant differences ($P>0.05$) in histopathological types were observed between the drinking and non-drinking groups (Table 1). Radical surgery was used on all patients. Tables 1 and 2 shows the details of all menopausal women with BC. Figure 3 shows the proportion of drinkers and non-drinkers in two groups.

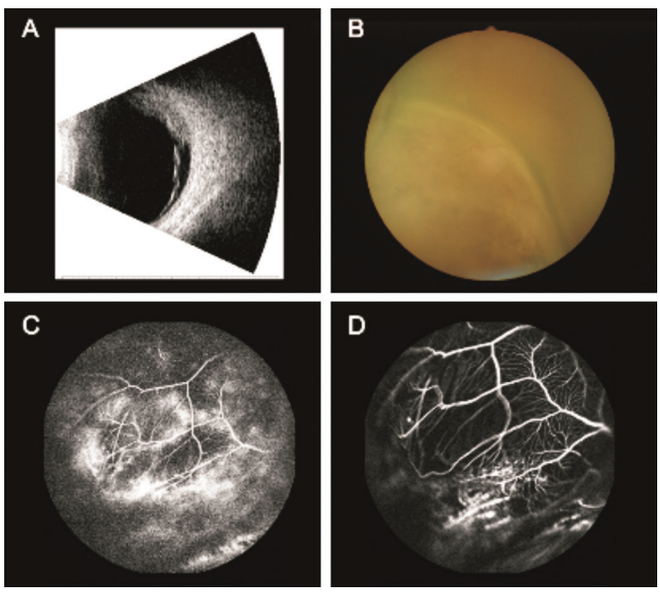


**Figure 1 An example of breast cancer patients with OM** A: Ophthalmic B-type ultrasound; B: Fundus photography; C: Fundus fluorescein angiography; D: Indocyanine green angiography. OM: Ocular metastasis.

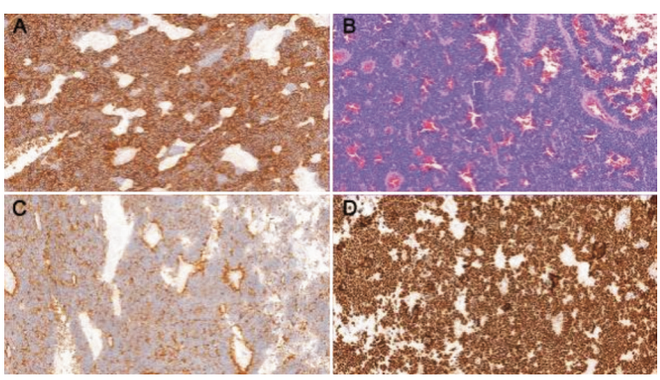


**Figure 2 The HE and IHC staining images of OM in breast cancer patients** A: CD56; B: HE; C: SYN; D: TTF-1. HE: Hematoxylin-eosin staining; IHC: Immunohistochemistry; OM: Ocular metastasis; SYN: Synaptophysin; TTF: Thyroid transcription factor.

**Clinical Data and Risk Factors Related to Ocular Metastasis** The analysis of serum biomarker data acquired from patient records revealed that the concentrations of CA-125, CA-153, TG, HDL, Apo B, and Lp(a) in the NOM group were significantly lower than those in the OM group

**Table 1 Clinical characteristics of menopausal female patients with breast cancer** *n* (%)

| Patient characteristics | OM group[a] (*n*=22) | NOM group (*n*=1340) | *P* |
|---|---|---|---|
| Mean age[c] | 54.0±3.0 | 59.5±2.5 | <0.001[c] |
| Histopathological type | | | 0.898 |
| Ductal carcinoma | 1 (4.5) | 55 (4.1) | |
| Invasive ductal carcinoma | 13 (59.1) | 746 (55.7) | |
| Lobular carcinoma | 0 | 36 (2.7) | |
| Squamous cell carcinoma | 0 | 2 (0.1) | |
| Adenocarcinoma | 0 | 54 (4.0) | |
| Others | 8 (36.4) | 447 (33.4) | |

[a]Ocular metastasis including intraocular metastasis and eyelid metastasis; [b]Chi-squared test, [c]Student's *t*-test for comparison between the OM and NOM groups. *P*<0.05 denoted statistical significance. OM: Ocular metastasis; NOM: Non-ocular metastasis.

**Table 2 Histopathological types of menopausal female patients with breast cancer with drinking or non-drinking** *n* (%)

| Histopathological type | Drinking (*n*=296) | Non-drinking (*n*=1066) | *P*[a] |
|---|---|---|---|
| Ductal carcinoma | 15 (5.1) | 41 (3.8) | 0.611 |
| Invasive ductal carcinoma | 157 (53.1) | 602 (56.6) | |
| Lobular carcinoma | 9 (3.0) | 27 (2.5) | |
| Squamous cell carcinoma | 0 | 2 (0.2) | |
| Adenocarcinoma | 9 (3.0) | 45 (4.2) | |
| Others | 106 (35.8) | 349 (32.7) | |

[a]Chi-square test was used for comparison between OM group and NOM group. *P*<0.05 represented statistically significant.

(*P*<0.05). Conversely, the NOM group exhibited elevated levels of ALP, calcium, total cholesterol, LDL, Apo A, and HB (*P*<0.05). CEA concentrations in the two groups did not differ significantly (*P*>0.05). The results of these analyses are presented in Tables 3 and 4. Moreover, CA-153, CA-125, and Apo A were identified as independent risk factors which associated with OM in an analysis of binary logistic regression (Table 5). In medicine, cutoff values[25] are positive judgment values, diagnostic thresholds for diseases, or reference values that affect medical behavior. The criteria for selecting appropriate cutoff values come from the optimal solution of diagnostic or decision-making performance. Generally speaking, the examination results themselves are only objective quantitative indicators, and cutoff values can help diagnose positive examination results and clarify the physiological/pathological value of the detection indicators[26]. Sensitivity, also known as true positive rate or detection rate, reflects the ability of a test to detect patients. The higher the sensitivity, the lower the missed diagnosis rate[27]. Specificity, also known as true negative rate, the higher the specificity, the lower the misdiagnosis rate[28]. The AUC reflects the value of

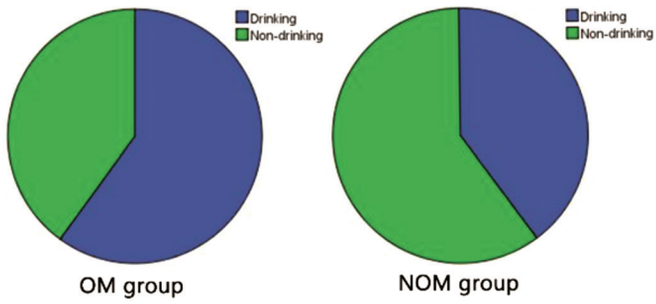


**Figure 3 The drinking and non-drinking proportion of menopausal female breast cancer patients with OM or NOM** OM: ocular metastasis; NOM: Non-ocular metastasis.

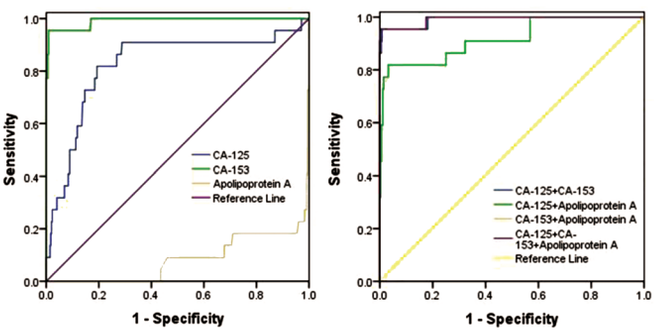


**Figure 4 ROC curves of single risk factors and the combinations of risk factors for detecting OM in menopausal female patients with breast cancer** ROC curves of CA-125, CA-153 and apolipoprotein A as single risk factor and the combination of CA-125, CA-153 and apolipoprotein A to detected OM in menopausal female patients with breast cancer. ROC: Receiver operating characteristic; AUC: Area under curve; OM: Ocular metastasis.

the diagnostic test[29]. The larger the area and the closer it is to 1.0, the higher the accuracy of the diagnosis; The closer it is to 0.5, the lower the accuracy of the diagnosis; When it is equal to 0.5, there is no diagnostic value. AUC=0.5-0.7, low accuracy; AUC=0.7-0.9, with certain accuracy; AUC>0.9, high accuracy[30]. Table 6 shows some risk factors for BC metastases[31-43].

**Performance of CA-125, CA-153, and Apo A in Diagnosing OM** It can be seen in Table 5 that CA-153, CA-125, and Apo A exhibit critical values of 19.30 U/mL, 61.35 U/mL, and 1.12 g/L, respectively. The AUC of CA-153 as a single risk factor yielded the highest value of 0.973. We later examined these risk factors both pairwise and as a whole. Figure 4 illustrates the ROC curves for CA-153, CA-125, and Apo A as single factors as well as their combinations. We found that CA-153 showed the highest AUC values with relatively high sensitivity and specificity, which were 0.973, 95.45%, and 97.38%, respectively. Among the indicators under investigation, there was the greatest sensitivity in CA-153 and CA-153+CA-125 (95.45%), whereas CA-153+Apo A showed the highest specificity (99.02%). There was statistical significance to all of these findings (*P*<0.05).

**Table 3 Differences in the concentration of various tumor biomarkers between menopausal female breast cancer patients with and without OM**

| Tumor biomarkers | OM group | NOM group | *t*-test | *P* |
|---|---|---|---|---|
| ALP (U/L) | 107.50±46.50 | 123.00±64.00 | -8.390 | <0.001 |
| Calcium (mmol/L) | 2.12±0.00 | 2.21±0.18 | -4.929 | <0.001 |
| Total cholesterol (mmol/L) | 3.68±0.64 | 4.49±0.86 | -17.733 | <0.001 |
| CEA (ng/mL) | 1.92±0.36 | 14.99±12.36 | -0.796 | 0.426 |
| CA-125 (U/mL) | 18.50±2.50 | 9.90±0.07 | -12.601 | <0.001 |
| CA-199 (U/mL) | 9.44±2.87 | 14.90±3.81 | -2.893 | 0.004 |
| CA-153 (U/mL) | 75.55±56.46 | 35.69±21.82 | 53.182 | <0.001 |
| TG (mmol/L) | 2.19±0.23 | 1.12±0.41 | -27.917 | <0.001 |
| HDL (mmol/L) | 1.73±1.03 | 1.27±0.13 | 18.545 | <0.001 |
| LDL (mmol/L) | 1.18±0.35 | 2.89±0.82 | -40.514 | <0.001 |
| Apolipoprotein A (g/L) | 1.22±0.28 | 1.59±0.19 | -79.998 | <0.001 |
| Apolipoprotein B (g/L) | 1.16±0.48 | 0.75±0.12 | -7.320 | <0.001 |
| Lipoprotein-a (mg/L) | 159.50±26.50 | 146.00±100.00 | -10.342 | <0.001 |
| HB (g/L) | 101.50±1.50 | 119.50±12.50 | -36.093 | <0.001 |

Independent sample *t*-test. *P*<0.05 denoted statistical significance. OM: Ocular metastasis; NOM: Non-ocular metastasis; ALP: Alkaline phosphatase; CEA: Carcinoembryonic antigen; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HB: Hemoglobin.

**Table 4 Risk factors of OM in menopausal female patients with breast cancer**

| Factors | *B* | Exp(*B*) | OR (95%CI) | *P* |
|---|---|---|---|---|
| ALP (U/L) | -0.002 | 0.998 | -38.042- -23.633 | <0.001 |
| Calcium (mmol/L) | -1.610 | 0.200 | -0.313- -0.135 | <0.001 |
| Total cholesterol (mmol/L) | -0.466 | 0.627 | -1.981- -1.586 | <0.001 |
| CA-125 (U/mL) | <0.001 | 1.000 | -661.751- -483.600 | <0.001 |
| CA-153 (U/mL) | 0.011 | 1.011 | 61.819-66.550 | <0.001 |
| TG (mmol/L) | -1.203 | 0.300 | -2.584- -2.245 | <0.001 |
| HDL (mmol/L) | 0.128 | 1.136 | 1.117-1.381 | <0.001 |
| LDL (mmol/L) | -2.549 | 0.078 | -2.609- -2.368 | <0.001 |
| Apolipoprotein A (g/L) | -8.591 | <0.001 | -0.915- -0.871 | <0.001 |
| Apolipoprotein B (g/L) | -0.237 | 0.789 | -0.282 - -0.163 | <0.001 |
| Lipoprotein-a (mg/L) | -0.002 | 0.998 | -81.122- -55.271 | <0.001 |
| HB (g/L) | -0.045 | 0.956 | -15.643- -14.032 | <0.001 |

Binary logistic regression analysis. *P*<0.05 denoted statistical significance. *B*: Coefficient of regression; OR: Odds ratio; CI: Confidence interval; OM: Ocular metastasis; ALP: Alkaline phosphatase; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HB: Hemoglobin.

## DISCUSSION

In both developed and less-developed countries, BC is the most prevalent type of cancer among women[44]. However, the epidemiological features of BC differ in developing countries from those in western countries[45]. More than 6 million women worldwide live with a diagnosis of BC[6]. The incidence of BC continues to be extremely high. However, overall BC mortality has shown a rapid decline by 39% per year from 1989 to 2015[46].

Menopause can increase the incidence of BC by influencing estrogen levels. Based on the studies of Wang *et al*[47] and Ekwueme *et al*[48], we selected menopausal individuals with BC, who were older than 45 years old. Moreover, the World Cancer Research Fund International and American Cancer Society recommend limiting alcohol consumption and changing lifestyles to reduce the risk of BC by 25% to 30% in spite of their controversial recommendations[44], even though these recommendations are controversial. In the study of Scoccianti *et al*[49], the intake of alcoholic beverages has been linked to the incidence of female BC, exhibiting a linear dose-response relationship. The impact of excessive alcohol consumption has been acknowledged for a long time, and even moderate drinking is linked to a higher risk of BC[49]. However, in the study of the Collaborative Group on Hormonal Factors

**Table 5 Cut-off value, sensitivity, specificity, and AUC of single risk factors for the prediction of OM in menopausal female breast cancer patients**

| Factor | Cut-off value | Sensitivity (%) | Specificity (%) | AUC | *P* |
|---|---|---|---|---|---|
| CA-125 | 19.30 | 81.82 | 79.70 | 0.808 | <0.001 |
| CA-153 | 61.35 | 95.45 | 97.38 | 0.973 | <0.001 |
| Apolipoprotein A | 1.12 | 77.27 | 95.67 | 0.896 | <0.001 |
| CA-125 +CA-153 | - | 95.45 | 96.84 | 0.973 | <0.001 |
| CA-125+apolipoprotein A | - | 77.27 | 95.34 | 0.896 | <0.001 |
| CA-153 +apolipoprotein A | - | 81.82 | 99.02 | 0.927 | <0.001 |
| CA-125+CA-153 +apolipoprotein A | - | 81.82 | 98.87 | 0.918 | <0.001 |

Sensitivity and specificity were acquired at the cut-off value. *P*<0.05 denoted statistical significance. AUC: Area under the curve.

**Table 6 Risk factors for metastases of breast cancer**

| Author | Year | Histopathological type | Metastatic sites | Risk factor |
|---|---|---|---|---|
| da Silva *et al*[31] | 2016 | Invasive ductal carcinoma | Axillary lymph node | Age |
| Zhou *et al*[32] | 2017 | Triple-negative carcinoma | Lymph node | ANXA3 |
| Li *et al*[33] | 2017 | NS | Bone | Marrow adiposity |
| Wang *et al*[34] | 2017 | Invasive carcinoma | Lymph node | ECT2 |
| Pestalozzi *et al*[35] | 2008 | HER2-positive carcinoma | CNS | Negative steroid receptor |
| Takalkar *et al*[36] | 2016 | Invasive ductal carcinoma | NS | Increasing age, low parity and obesity |
| Altundag *et al*[37] | 2007 | Invasive ductal carcinoma | CNS | Lung metastasis |
| Zhang *et al*[38] | 2013 | Invasive ductal carcinoma | Axillary lymph node | CCR5 |
| Friesenhengst *et al*[39] | 2018 | Ductal carcinoma | Lymph node | CYP19A1 |
| Salamanna *et al*[40] | 2018 | NS | Bone | Estrogen |
| Coleman[41]] | 2002 | NS | Bone | N-telopeptide and C-telopeptide |
| Lei *et al*[42] | 2017 | MBC | Axillary lymph node | PR |
| Cummings *et al*[43] | 2014 | NS | Liver | Age<49y |

ANXA3: Annexin A3; ECT2: Epithelial cell transforming sequence 2; CNS: Central nervous system; CCR5: Investigate chemotactic factor receptor 5; CYP19A1: A kind of aromatase; MBC: Mucinous breast cancer; PR: Progesterone receptor; NS: Not specific.

in BC, there was no material difference in BC based on alcohol consumption[50].

Research has shown that exposure to alcohol induces the expression of aldehyde dehydrogenase 2 (ALDH2), which stabilizes PD-L1 protein expression by physically interacting with the intracellular portion of PD-L1 and inhibiting proteasome dependent degradation mediated by the E3 ubiquitin ligase speckle type POZ protein[51]. Importantly, inhibiting ALDH2 reduces the PD-L1 protein in cells and promotes the infiltration of tumor infiltrating T cells. These findings highlight the crucial role of ALDH2 in promoting alcohol mediated tumor escape from immune surveillance and facilitating tumor progression. Epidemiological evidence suggests that excessive alcohol consumption is associated with immune suppression, thereby eliminating immune surveillance against tumor formation. According to reports, alcohol can impair the function and activation of T cells, and induce T cell apoptosis. In addition, it was found that ALDH2 can promote the stability of PD-L1 protein. Importantly, it has been demonstrated that the combination of ALDH2 inhibition and PD-1/PD-L1 checkpoint inhibitors can enhance the anti-tumor activity of effector immune cells. In summary, the research findings indicate that alcohol consumption can induce ALDH2 and subsequently upregulate PD-L1 expression, thereby sparing it from immune surveillance[52]. Researchers have found that alcohol has always had harmful effects on patients. Gastric cancer patients who drink excessively are more likely to have high levels of BRF1 expression and MPO positive inflammatory cell filtration. Alcoholics are more likely to experience abnormal range of BRCA1 in non-tumor tissues. Previous studies have found a similar association between BRF1 levels and alcohol intake in patients with BC[53] and liver cancer[54]. In addition, the tumor marker AFP is also elevated in long-term heavy drinkers[55], which may be due to the continuous repair of liver cells caused by the stimulation of alcohol on liver cells.

It is known that alcohol can cause adverse health effects due to the presence of ethanol, which is carcinogenic to humans and can cause several cancers. Studies show that even moderate consumption of alcohol (drink once a day) can cause adverse health effects due to the presence of ethanol, which is carcinogenic to humans and can lead to multiple types of

cancers (oral cavity, pharynx, larynx). Thus, based on the study of Scoccianti *et al*[14], we conducted a single-center trial at our hospital using the standard for drinking as more than 15 g per day. We concluded that drinking was associated with OM in BC.

Moreover, most cancer-associated deaths occur due to metastasis[56], distant metastases of BC usually occur several years after the primary BC[15]. In addition to distant metastases occurring in the bone, lung, and liver, BC can spread almost anywhere in the body, including the eyes (only 3%–10%)[50] and pituitary gland[57]. Intraorbital metastases of BC are rarely diagnosed, even though pathological reports suggest an incidence of up to 30%[50]. However, once OM occurs, the prognosis of BC is poor. In the study of Demirci *et al*[17], 93% of cases, in which patients presenting with visual symptoms due to uveal metastases from BC, the prognosis was unfavorable, with survival rates of 65% and 24% after one year and five years of follow-up, respectively. BC may affect the eye and orbit by metastatic neoplastic infiltration through blood and lymph; the uvea is the most common site of presentation[58]. In addition, most metastatic orbital tumors originate from the lung, followed by the breast, liver, adrenal gland, and stomach. Furthermore, OM from BC affects female patients alone[59]. Reports have also shown that adenocarcinoma of the breast can manifest as OM[60], and at other times, it is indicative of nonpalpable primary breast carcinoma[61].

Dieing *et al*[16] reported two cases of intraorbital extraocular metastases of BC. Both patients had been diagnosed with metastatic BC for several years, and both had been stable. Due to often minimal or absent symptoms, diagnosing the condition was challenging[16]. However, once diagnosed, individuals with initial BC, advanced localized conditions, or regional recurrence can achieve a cure through contemporary combined therapies, including surgery, radiation, drug therapy[14], immunotherapy[4], and targeted treatments with biological drugs[4]. Patients with metastatic disease are treated with palliative intent to alleviate symptoms and prolong survival[14]. In Germany, the five-year survival rate of BC is 87%, which shows that the chances of a complete recovery are even higher for patients with early BC[14]. Thus, the establishment of standardized diagnostic criteria for OM in BC are necessary. OM can sometimes be missed by conventional diagnostic methods, such as CT and MRI. For example, standard cerebral MRI failed to detect any cerebral or ocular tumors in the first patient of the study of Dieing *et al*[16].

Currently, better treatment decisions could be made by identifying BC biomarkers-molecules that identify precancerous cells that are likely to progress to invasive cancer[4] through advances in genomics[50]. Although treatment methods[4,62] have shown progress, simpler, convenient diagnostic methods with strong feasibility have not been established. Hematological evaluation is a routine diagnostic process for various diseases. Therefore, we were keen to identify a diagnostic indicator, based on our detection of serum biomarkers.

We found an interesting phenomenon regarding the HDL concentration in the OM group, which was higher than that in the NOM group ($P$<0.05); whereas the LDL concentration was lower ($P$<0.05). Some studies suggest that the relationship between HDL and menopause is complex, because higher HDL-C may indicate dysfunctional HDL metabolism[63], and lower LDL may be related to early atherosclerosis during menopause[64].

Table 3 shows selected risk factors and various combinations of such factors for the detection of OM in menopausal patients with BC. In the current study, our laboratory conducted an analysis of patient serum samples to quantify the concentrations of ALP, calcium, total cholesterol, CEA, CA-125, CA-199, CA-153, TG, HDL, LDL, Apo A, Apo B, Lp(a), and HB. Based on previous findings that total cholesterol, TG, Lp(a), and increased Apo B are associated with aging in women and menopause[65-66]; ALP is a risk factor for bone metastases in lung cancer[67-68]; and we selected CA-125, CA-153, and Apo A as individual risk factors because calcium and HB are susceptible to other factors ($P$<0.01, $P$<0.01, and $P$<0.01, respectively). AUC, sensitivity, and specificity for each of these biomarkers are presented in Table 5. Furthermore, CA-153 alone is effective for diagnosing OM in BC patients who have undergone menopause based on our findings. With these ROC curves as a guide, it is possible to develop reliable clinical tests. The presence of CA-125, CA-153, and Apo A concentrations higher than 19.30 U/mL, 61.35 U/mL, and 1.12 g/L represent critical blood levels for the presence of OM in BC patients who have reached menopause. Consequently, there are other diagnostic techniques that can be used (*e.g.*, CT and MRI imaging of the eye) to provide more detailed information. Another point that deserves attention is the highest specificity of the combination of CA-153+Apo A (99.02%), which was also accurate in predicting OM.

CA153 was initially discovered to be a tumor antigen that can be recognized by two monoclonal antibodies, DF3 and 115D8, simultaneously. Monoclonal antibody DF3 can recognize the core protein of mucin 1 (MUC1 or CD227), while monoclonal antibody 115D8 recognizes a portion of the polysaccharide chain on MUC1. Previous studies have shown that MUC1 can mediate the production of growth factors such as connective tissue growth factor, platelet-derived growth factor-A, and platelet-derived growth factor-B, which can promote the activation of MAPK and PI3K/Akt pathways, enhance the

proliferation and survival ability of tumor cells[69]. MUC1 can also regulate the expression, stability, and activity of hypoxia inducible factor-1 alpha (HIF-1α). HIF-1α can regulate the expression of enzymes in the glycolytic pathway, which is the preferred metabolic pathway for cancer cell proliferation. CA153, as a soluble form of MUC1, also participates in many processes of tumor occurrence and development. In addition, CA153 can reduce the interactions between cells and between cells and matrix, and decrease its adhesion. Meanwhile, overexpression of CA153 can promote the separation of tumor cells from peripheral stromal cells, normal cells, and so on. The serum CA153 level in BC was abnormally elevated, and its level was positively correlated with TNM stage, histological grade, and lymph node metastasis[70].

CA125 is a large transmembrane glycoprotein derived from the epithelial cells of the body cavity (pericardium, pleura, and peritoneum) and Mullerian tubes (fallopian tubes, endometrium, and cervical endometrium). Under normal circumstances, due to the intercellular connections and the blocking effect of the basement membrane, CA125 cannot enter the serum, so CA125 cannot be detected or has a very low concentration in normal human serum[71]. When the tissue undergoes malignant transformation, the synthesized CA125 in the cell concentrates at the edge of the cell, causing depolarization of the local cell membrane and transporting CA125 antigen; Invasive tumor cells can damage tissue structure, and the secretion of CA125 after the disruption of intercellular connections and basement membrane can be released into the bloodstream. Its functions are as follows: under physiological conditions, CA125 forms a polysaccharide rich barrier to protect epithelial cells from pathogen invasion, and under pathological conditions, CA125 can protect cancer cells from surveillance by inhibiting natural killer cells (its potential mechanism may be that the highly glycosylated tandem repeat domain of CA125 can bind to an immunosuppressive protein - galectin-1). CA125 can induce tumor cell movement by reducing the expression of calcium binding protein E and increasing epithelial mesenchymal transition; It can also enhance the invasion ability of tumor cells and promote tumor tissue invasion into the serosa by binding to mesothelin (a glycoprotein expressed by peritoneal mesothelial cells)[72].

As a clinical doctor, it is necessary to understand the appropriate items and latest developments of tumor markers. Therefore, clinical doctors need to constantly learn new knowledge and skills, and understand the latest developments in testing projects. Multidisciplinary collaboration in interpreting tumor markers, mutual understanding between clinical departments and laboratory departments, can better promote the rational application of tumor markers. In addition, it is necessary to understand the impact of the pre- and post testing stages on the application of tumor markers, such as the correlation between the results of many testing items and the physiological state of the patient at the time of blood collection: the whole blood white blood cell count of the same patient may be different in the morning and afternoon[73], the sex hormone test values may be different during the physiological period and pre physiological period[74], the antral follicle count and CA125 are related to the menstrual period[75], and the AFP of pregnant individuals may also be different from usual[76]. Compared with diagnostic methods such as imaging examination and pathological biopsy, tumor marker detection is very convenient and economical, suitable for cancer screening. However, there are numerous tumor markers, and the sensitivity or specificity of a single marker is often low, which cannot meet clinical requirements. In theory and practice, it is advocated to simultaneously measure multiple markers to improve sensitivity and specificity. In addition, tumor markers are not the only basis for tumor diagnosis. In clinical practice, it is necessary to consider other methods such as clinical symptoms and imaging examinations comprehensively. The diagnosis of tumors must be based on tissue or cellular pathology. Unlike diagnostic methods such as imaging and biopsy, due to individual differences in patients, specific clinical conditions, and other factors, the analysis of tumor markers needs to be combined with clinical conditions and compared from multiple perspectives in order to draw objective and true conclusions. Certain tumor markers can also be abnormally elevated in certain physiological conditions or benign diseases, and attention should be paid to differentiation.

Moreover, there are also limitations associated with the current research. There were several problems with the study, including the exclusive evaluation of transient data from the time of primary diagnosis, a small sample size derived from a single medical center, and the absence of tumor classification. If the research sample comes from only one center, it may result in selection bias and cannot represent a wider population or patient group, as patients in a specific center may have specific characteristics or disease spectrum. Geopolitical bias may also occur, as samples from a single center only reflect unique environmental, genetic, or lifestyle factors that may differ in other regions. In addition, large centers may have more medical resources and technology, which may affect the diagnosis, treatment, and prognosis of patients, which may not be available in small or different types of medical centers, resulting in resource limitation bias. Thus, more medical centers need to be included in the sample size in order to conduct a valid study. In addition, previous studies[77] have found that perimenopausal syndrome has an impact on tumor markers, positively correlated with AFP, CA125, CA153, but

not correlated with CEA. Menopausal status is negatively correlated with CA125. Different treatment plans may also have an impact on tumor markers. These confounding factors may lead to confounding bias. In this study, we balanced confounding factors through random allocation and ensured that cases and controls were similar in certain potential confounding factors through matching. In the future, we will further improve the research plan, limit the perimenopausal time and treatment methods of the research subjects, and use statistical models (such as regression analysis and propensity score analysis) to adjust for the influence of confounding factors, in order to reduce their impact.

In conclusion, CA-153 predicts the incidence of OM more accurately than other risk factors, as evidenced by its high sensitivity, specificity, and AUC. CA-153 shows superior predictive value, owing to its high sensitivity, specificity, and AUC, among various risk factors for OM. Menopausal women with BC who drink alcohol are at a greater risk of developing OM. The present findings need to be verified prospectively and high-quality screening, diagnosis, and treatment needs to be provided to all segments of the affected population[78].

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**Data Availability:** The datasets generated during and/or analysed during the current study are accessible *via* the PubMed.

Upon reasonable request, the corresponding author will make available the datasets generated and/or analyzed as part of this study. All the data generated or analysed during the course of this study are comprehensively contained within this published article (and its supplementary information files).

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