

Apolipoprotein A1 and B as risk factors for development of intraocular metastasis in patients with breast cancer

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Objective: Breast cancer is the most common primary lesion resulting in intraocular metastasis (IOM). In this study, we investigated the differences between breast cancer patients with and without IOM, and clarified the risk factors for IOM in patients with breast cancer.

Methods: A total of 2,381 patients with breast cancer were included in this study from January 2005 to December 2017. The chi-square test and Student's *t*-test were applied to evaluate differences between the IOM and non-IOM (NIOM) groups. Risk factors were calculated using binary logistic regression analysis. Receiver operating curve (ROC) analysis was used to assess the diagnostic value of IOM in patients with breast cancer.

Results: The IOM incidence in patients with breast cancer was 1.35%. No significant differences were detected in age, gender, menopausal status, or histopathology between the IOM and NIOM groups. The IOM group had more axillary lymph node metastases, lower ApoA1 and higher ApoB, compared with the NIOM group. Binary logistic regression indicated that ApoA1 and ApoB were risk factors for IOM in breast cancer patients (P -values < 0.001 and P -values = 0.005, respectively). ROC curve analysis revealed area under the curve values for ApoA1 and ApoB of 0.871 and 0.633, using cutoff values of 1.165 and 0.835 g/L, respectively. The sensitivity and specificity values for ApoA1 were 0.813 and 0.849, respectively, while those for ApoB were 0.813 and 0.481.

Conclusion: Our data indicate that ApoA1 and ApoB are risk factors for IOM in patients with breast cancer and that ApoA1 is more reliable than ApoB at distinguishing IOM from NIOM in patients with breast cancer.

Keywords: breast cancer, intraocular metastases, apolipoprotein A1, apolipoprotein B

Introduction

Breast cancer has become the most common malignant tumor in women¹ and, as a multifactorial disease, is closely associated with both genetic and environmental factors.^{2,3} Due to their specific molecular characteristics and clinical subtypes, breast cancers are highly malignant tumors prone to forming metastases in distant organs, including lung, bone, liver, and brain.⁴⁻⁷

Although the eye is an uncommon site of metastasis, ocular metastases are closely associated with breast cancer, which accounts for the largest proportion among all primary tumors known to develop ocular metastases.⁸ Moreover, intraocular metastasis (IOM) represents an advanced stage of breast cancer and can cause a series of clinical symptoms, including ocular pain, foreign body sensation, blurred vision, and visual

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field defects, severely affecting the quality of the patient's life.⁹ Consequently, early detection, diagnosis, and treatment of IOM is of great consequence in patients with breast cancer.

Currently, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound diagnosis (UD) are the techniques frequently used for the diagnosis of breast cancer;^{10–12} however, they have clear limitations, including high economic costs and exposure to heavy doses of radiation, caused by repeated use. To improve predictions, it is important to develop methods that are both convenient and reliable. Serum tests are ideal, as they are repeatable, low-cost, and non-invasive. Previous studies have reported that expression of programmed death 1 and the neutrophil-to-lymphocyte ratio in peripheral blood could be diagnostic and prognostic indicators, respectively, in breast cancer.^{13,14}

Blood lipids and relevant proteins have long been of interest because of their close relationship with cardiovascular diseases; however, recent studies have also reported strong correlations of these factors with the development of cancer. Several animal experiments have demonstrated that specific apolipoproteins can affect tumor growth via modulation of immune cell function.¹⁵ Moreover, levels of some apolipoproteins are also used to assess prognosis in several cancers;^{16,17} however, the predictive values of blood lipids and relevant apolipoproteins for IOM in patients with breast cancer are unknown.

In this retrospective study, we aimed to investigate the association between blood lipid-relevant parameters and IOM, and to determine the risk factors for IOM in patients with breast cancer.

Materials and methods

Study design

This study was conducted in accordance with the Declaration of Helsinki and approved by the medical research ethics committee of the First Affiliated Hospital of Nanchang University. All the methods used in this study were conducted under the relevant guidelines and regulations. A series of consecutive patients diagnosed with breast cancer at our hospital between January 2005 and December 2017 were included in this study. The diagnosis was made based on pathological specimens obtained by surgical resection or biopsy. IOM diagnosis was by CT and MRI. Patients with primary ocular malignant tumors, ocular benign tumors, and secondary breast cancer were excluded from the study. All participants were given details of the study design and provided signed informed consent.

Data collection

Clinical data relevant to this study were collected retrospectively from patient medical records, including: age, sex, menopausal status, histopathological subtype, total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and lipoprotein A (Lp(A)). All clinical parameters were collected at the time of initial diagnosis of breast cancer. Blood lipids were tested after fasting for at least 12 h.

Measurement of ApoA1 and ApoB levels

ApoA1 and ApoB were tested using the immune turbidimetric method. ApoA1 in reagents (Ruiyuan Biotechnology, Ningbo, Zhejiang) bound to specific antibodies in serum to form antigen-antibody complexes, resulting in turbidity, levels of which were directly proportional to those of ApoA1 in serum. Absorbance was measured and the ApoA1 content in the serum calculated, with reference to a calibration curve. ApoB was tested using the same method.

Statistical analysis

The Student's *t*-test and Chi-square test were used to evaluate whether differences in clinical features between IOM and NIOM patients were significant. Then, binary logistic regression models were established to identify independent risk factors for ocular metastasis. Receiver operating characteristics (ROC) curves were constructed and areas under the curve (AUC) values calculated, to estimate the accuracy of variables for prediction of IOM. *P*-values < 0.05 was considered statistically significant. FDR correction was used to select significant features. All the statistical analyses were conducted using SPSS17.0 (SPSS, IBM Corp, USA) and Excel 2010 (Excel, Microsoft Corp, USA) software. Continuous data are displayed as means ± standard deviation.

Results

Demographic and clinical characteristics

A total of 2,381 patients (7 men and 2,374 women) were recruited to this study, of which 32 were IOM and 2,349 NIOM cases. Average ages of IOM and NIOM patients were 46.59±7.78 and 48.21±10.41 years, respectively. Among women, 1,444 were premenopausal and 937 postmenopausal. Regarding histopathological subtype, invasive ductal carcinoma accounted for the largest proportion of tumors

Table 1 The clinical characteristics of patients with breast cancer

	IOM group, n (%)	NIOM group, n (%)	Total numbers of patients, n (%)	P-value
Age (years)^a	46.59±7.78	48.21±10.41	48.19±10.38	0.26
<50	17 (53.1)	1,385 (59.0)	1,402 (58.9)	
≥50	15 (46.9)	964 (41.0)	979 (41.1)	
Gender^b				0.91
Woman	32 (100)	2,342 (99.7)	2,374 (99.7)	
Man	0 (0)	7 (0.3)	7 (0.3)	
Menopausal status^b				0.37
Premenopausal	22 (68.8)	1,422 (60.5)	1,444 (60.6)	
Postmenopausal	10 (31.2)	927 (39.5)	937 (39.4)	
Histopathology^b				0.48
Invasive ductal carcinoma	21 (65.6)	1,384 (58.9)	1,405 (59.0)	
Other types	11 (34.4)	965 (41.1)	976 (41.0)	
Axillary lymph node metastases^b				<0.001
0	4 (12.5)	902 (38.4)	906 (38.1)	
1–4	7 (21.9)	698 (29.7)	705 (29.6)	
>4	16 (50.0)	480 (20.4)	496 (20.8)	
Unknown	5 (15.6)	269 (11.5)	284 (11.5)	

Notes: ^aStudent's t-test was used. ^bChi-square test was used. P-values<0.05 represented statistical significant.

Abbreviations: IOM, intraocular metastases; NIOM, non-intraocular metastases.

(59.0%). In the IOM group, 71.9% of patients had developed axillary lymph node metastases, while in the NIOM group the proportion was 50.1%. The detailed clinical characteristics of the patients are presented in Table 1 and Figure 1.

Evaluation of clinical features as risk factors for IOM

There were no differences in the levels of TC, TG, HDL, LDL and Lp(A) between IOM and NIOM patients; however, levels of ApoA1 were lower (1.01 mmol/L) in the IOM group than those in the NIOM group (1.49 mmol/L). Moreover, ApoB levels were higher (0.91 g/L) in the IOM group than the NIOM group (0.86 g/L) (Table 2). Further analysis using a binary logistic regression model showed that ApoA1 and ApoB levels were independent risk factors for IOM (Table 3).

Cut-off, AUC, sensitivity, and specificity values of ApoA1 and ApoB for diagnosis of intraocular metastasis

As shown in Figure 2 and Table 4, the AUC value for ApoA1 was 0.871, while its sensitivity and specificity for prediction of IOM were 0.813 and 0.849, respectively. The AUC value for ApoB was 0.633, with sensitivity and specificity values of 0.813 and 0.481, respectively. These data

were based on cut-off values of 1.165 g/L and 0.835 g/L for ApoA1 and ApoB, respectively. All of these results were statistically significant.

Discussion

The incidence of breast cancer is currently rising rapidly; however, the survival times of patients with breast cancer are also increasing, which can be attributed to the use of mammography for early tumor detection, adjuvant chemotherapy, hormonal therapy, and targeted therapies.^{18–21}

Nevertheless, many patients with breast cancer still develop distant metastases. The incidence of IOM among patients with breast cancer reported by different studies varies from 5% to 30%.^{22,23} Moreover, IOM represents a marker of poor prognosis in various types of cancer. In 1959, Garrett reported a 79-year-old man with IOM from seminoma.²⁴ To date, IOM has been reported in patients with malignant melanoma,²⁵ non-small cell lung cancer,²⁶ esophageal carcinoma,²⁷ head and neck cancer,²⁸ gastric adenocarcinoma,²⁹ renal cell carcinoma,³⁰ choriocarcinoma,³¹ and colorectal cancer³² (Table 5). Unfortunately, IOM is difficult to detect at an early stage; hence, it is essential to improve rates of early diagnosis. Since apolipoproteins are reported to influence tumor metabolism,¹⁵ and tests on lipids and relevant apolipoproteins are repeatable, low-cost, and do not expose patients to

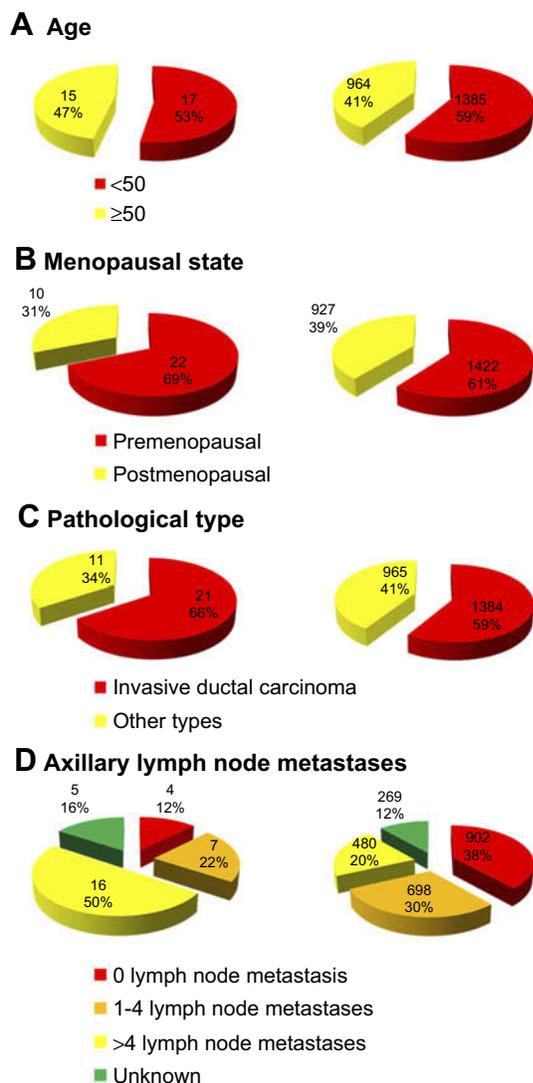


Figure 1 Clinical features of breast cancer patients with and without IOM.

Notes: IOM on the left sides, NIOM on the right sides. **(A)** The age between IOM and NIOM, **(B)** the menopausal state between IOM and NIOM, **(C)** the pathological type between IOM and NIOM, **(D)** the axillary lymph node metastases between IOM and NIOM.

Abbreviations: IOM, intraocular metastases; NIOM, non-intraocular metastases.

radiation risks, we investigated lipid-relevant parameters as potential predictors of IOM, by comparing blood their levels among breast cancer patients with and without IOM.

The incidence of IOM in patients with breast cancer in this study was 1.35%, which is lower than the rates reported by Nelson et al and Kreusel et al^{22,23}. This may be attributable to the fact that CT and MRI were not widely used in the past, because of their high cost, hence many patients with breast cancer and IOM did not choose to undergo these examinations, resulting in a lower reported incidence of IOM. Moreover, patients in the IOM group had more axillary lymph nodes metastases, revealing that IOM is associated with advanced stage breast cancer. Additionally, we identified ApoA1 and ApoB as risk factors for IOM in patients with breast cancer.

ApoA1, an essential component of high density lipoprotein (HDL), plays indispensable roles in transporting peripheral lipids to the liver and preventing extrahepatic cells from absorbing excessive lipid.³³ Recently, ApoA1 has attracted increasing attention in ophthalmology, as levels of this factor are closely related to dry eye, diabetic retinopathy, age-related macular degeneration, and other eye diseases.^{34–36} More importantly, ApoA1 has an anti-tumor function. In an animal experiment conducted by Zamaniandaryoush et al¹⁵ mice expressing a human ApoA1 transgene had increased numbers of M1 macrophages, an anti-tumor phenotype, which reduced tumor burden and metastasis. In contrast, ApoA1-deficient (A1KO) mice exhibited enhanced tumor growth and reduced survival, while injecting human ApoA1 into A1KO mice significantly reduced tumor growth and metastasis. Researchers also found that ApoA1 did not directly influence the tumor, rather it promoted the anti-tumor functions of macrophages by altering their phenotypes from M2 to M1. Moreover, a correlation between

Table 2 The differences of clinical lipids-relevant parameters between patients with and without IOM

Clinical features	IOM group	NIOM group	t	P-value
TC (mmol/L)	4.43±0.75	4.56±0.93	-0.999	0.325
TG (mmol/L)	1.31±0.70	1.36±0.86	-0.405	0.688
HDL (mmol/L)	1.34±0.49	1.36±0.35	-0.345	0.731
LDL (mmol/L)	2.59±0.61	2.72±0.77	-1.138	0.263
ApoA1 (g/L)	1.01±0.32	1.49±0.49	-8.019	<0.001
ApoB (g/L)	0.97±0.24	0.86±0.23	2.369	0.024
Lp(a) (mg/L)	210.50±156.19	211.20±221.96	-0.024	0.981

Abbreviations: TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp(a), lipoprotein a; IOM, intraocular metastases.

Table 3 The binary logistic regression results

Factors	B	OR	OR (95% CI)	P-value
TC	-0.165	0.848	0.572–1.257	0.412
TG	-0.076	0.927	0.596–1.442	0.737
HDL	-0.180	0.835	0.300–2.322	0.730
LDL	-0.229	0.796	0.490–1.292	0.355
ApoA1	-7.107	0.001	0.000–0.006	<0.001
ApoB	1.630	5.106	1.359–19.178	0.016
Lp(a)	0.000	1.000	0.998–1.002	0.986

Note: P-values<0.05 represented statistical significant.

Abbreviations: TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp (a), lipoprotein a.

ApoA1 and patient prognosis has been reported for several cancers, including colorectal cancer, gastric cancer, hepatocellular carcinoma, ovarian cancer, and renal cancer.^{16,17,37–39} Patients with lower levels of ApoA1 and higher levels of circulating tumor cells had elevated recurrence rates and shorter survival times. These data suggest that ApoA1 has an important role in inhibiting tumor growth and invasion. To date, many studies have demonstrated that decreased ApoA1 levels are closely associated with the occurrence and development of breast cancer. His et al⁴⁰ reported that low serum ApoA1 levels are a high-risk factor for breast cancer, while Lane et al⁴¹ demonstrated that women with decreased levels of ApoA1 are more likely to develop early recurrence of breast cancer. These studies suggest that low ApoA1 levels are related to the occurrence and recurrence of breast cancer. However,

Martin et al⁴² reached the controversial conclusion that levels of serum ApoA1 are positively correlated with the risk of breast cancer, based on data from a nested case-control study of 4,690 women who had high mammographic density.

Overall, we hypothesized that levels of ApoA1 are related to IOM in breast cancer patients and we explored this correlation in our retrospective study. The results of our study demonstrate that low ApoA1 levels were associated with IOM of breast cancer, consistent with previous findings. The cut-off value was 1.165 g/L in our study, where patients with breast cancer whose ApoA1 levels were <1.165 g/L were more likely to develop IOM. Moreover, the AUC of the ROC curve showed a relatively high accuracy for distinguishing patients with breast cancer with IOM from those without, revealing the excellent diagnostic value of ApoA1 for prediction of IOM.

ApoB is a type of apolipoprotein present on the surface of LDLs. Unlike ApoA1, the function of ApoB is transporting lipids to cells within the human body.⁴³ ApoB levels are positively correlated with the risk of cardiovascular diseases. As the blood vessels of the eye are dense and tiny, and can easily be covered by lipids, there is also a relationship between ApoB and ophthalmological diseases. Levels of ApoB are associated with elevated intraocular pressure, lens opacity, retinopathy, and primary open angle glaucoma.^{44–47} Apart from its essential role in lipid transport, ApoB is also associated with cancer genome mutations. Apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) participates in ApoB

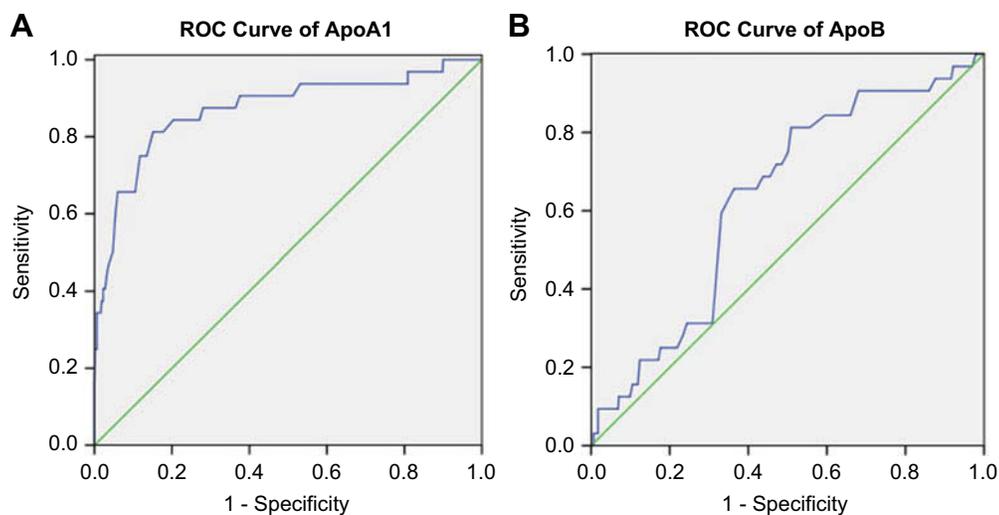


Figure 2 The ROC curves of risk factors for detecting IOM in breast cancer.

Notes: (A) The ROC curve of ApoA1. The AUC was 0.871 (P-values<0.001; 95% CI: 0.794–0.948) (IOMs<NIOMs); (B) The ROC curve of ApoB. The AUC was 0.633 (P-values=0.011; 95% CI: 0.544–0.722) (IOMs>NIOMs).

Abbreviations: ROC, receiver operating characteristic; AUC, areas under the curve; CI, confidence interval; IOM, intraocular metastases; NIOM, non-intraocular metastases.

Table 4 The ROC results of risk factors for predicting IOM in breast cancer patients

	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95% CI	P-value
ApoA1 (g/L)	1.165	0.813	0.849	0.871	0.794–0.948	<0.001
ApoB (g/L)	0.835	0.813	0.481	0.633	0.544–0.722	0.011

Abbreviations: AUC, area under the curve; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; IOM, intraocular metastases; ROC, receiver operating characteristics.

Table 5 Studies on the IOM from different cancers

Author	Year	Diseases with IOM
Garrett et al ²⁴	1959	Seminoma
Mcdonald et al ²⁷	1997	Esophageal carcinoma
Gangadharan et al ³¹	1999	Choriocarcinoma
Pompeu et al ³⁰	2005	Renal cell carcinoma
Fang et al ²⁸	2007	Head and neck cancer
Kelmenson et al ²⁵	2011	Malignant melanoma
Sitaula et al ²⁹	2011	Gastric adenocarcinoma
Khawaja et al ³²	2015	Colorectal cancer
Niu et al ²⁶	2016	Non-small cell lung cancer

Abbreviation: IOM, intraocular metastases.

RNA editing, and abnormal expression of APOBEC can cause mutations in tumor suppressor genes and proto oncogenes.^{48–50} Although ApoB is not directly relevant to tumors, it has been used to predict cancer development and recurrence. Ma et al³⁷ reported that the ApoB/ApoA1 ratio can be used as a prognostic indicator in patients with gastric cancer (GC), where those with high ApoB/ApoA1 ratios had shorter survival times. In our study, we found that ApoB was also a risk factor for IOM in patients with breast cancer. Breast cancer patients with ApoB levels >0.835 g/L were prone to IOM; however, ROC curve analysis indicated a relatively low accuracy. Consequently, ApoB should be applied cautiously for the prediction of IOM in patients with breast cancer, and we consider ApoA1 a more reliable indicator of IOM diagnosis in these patients.

This study has some limitations. First, data were collected over a long period time and, despite our best efforts, some data were missing, and differences among individuals conducting the tests may have contributed to minor discrepancies; however, these will not have influenced the results. Second, all the records used in this experiment were from the same medical institution, which could potentially have introduced confounding factors. Experiments from additional medical institutions are expected to be conducted. Third, this study merely demonstrates correlations between altered ApoA1 and ApoB levels and IOM in patients with breast cancer; we were unable to determine whether IOM caused the changes in ApoA1 and

ApoB or vice versa. Finally, we only investigated altered levels of ApoA1 and ApoB in patients with IOM from breast cancer; hence, whether these two parameters exhibit differences associated with other distant metastases from breast cancer, and how they are altered, remain unknown.

In conclusion, this study is the first to demonstrate that ApoA1 and ApoB are risk factors for IOM in patients with breast cancer. These two parameters are potential targets for the therapy of IOM in patients with breast cancer. At present, many scientists are focused on the anti-tumor effects of chemical reagents and their mechanisms.^{51,52} We hope that our results will encourage relevant experiments investigating the potential molecular mechanisms underlying the antineoplastic effects of ApoA1 and ApoB.

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Disclosure

The authors report no conflicts of interest in this work.

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