




ORIGINAL RESEARCH

Risk factors and their diagnostic values for ocular metastases in invasive ductal carcinoma

Rong-Bin Liang¹ | Kang Yu¹ | Jie-Li Wu² | Jia-Xiang Liu¹  | Qi Lin¹  | Biao Li¹ | Yu-Qing Zhang¹ | Qian-Min Ge¹ | Qiu-Yu Li¹ | Hui-Ye Shu¹ | Yi Shao¹ 

¹Department of Ophthalmology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

²Department of Ophthalmology, Xiang'an Hospital of Xiamen University, Fujian Provincial Key Laboratory of Ophthalmology and Visual Science, Eye Institute of Xiamen University, Xiamen University School of Medicine, Xiamen, Fujian Province, China

Correspondence

Yi Shao, Department of Ophthalmology, The First Affiliated Hospital of Nanchang University, No 17, Yongwaizheng Street, DongHu District, Nanchang, Jiangxi 330006, People's Republic of China. Email: freebee99@163.com

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Abstract

Invasive ductal carcinoma (IDC) is a major type of breast cancer. Ocular metastasis (OM) in IDC is rarely seen, but patients with OM often have a poor prognosis. Furthermore, OM is difficult to detect in the early stages by common imaging examinations. In the present study, we tried to figure out the risk factors of OM in IDC and evaluate their diagnostic values for early detection. There were 1192 IDC patients who were divided into two groups according to ocular metastasis involved in this study. Clinical parameters of those patients were used to detect differences. The binary logistic regression test was then used to determine the risk factors of OM in IDC. Furthermore, ROC curves of both single and combined risk factors were established to examine their diagnostic values. The incidence of axillary lymph node metastases was significantly higher in the OM group ($p = 0.002$). Higher carbohydrate antigen 153 (CA153), lower apolipoprotein A1 (ApoA1), and hemoglobin (Hb) were risk factors for OM in IDC ($p < 0.001$, $p < 0.001$, $p = 0.038$, respectively). In the single risk factor ROC analysis, cutoff values of CA153, ApoA1, and Hb were 43.3 u/mL (CI: 0.966–0.984, $p < 0.001$), 1.11 g/L (CI: 0.923–0.951, $p < 0.001$), and 112 g/L (CI: 0.815–0.857, $p < 0.001$), respectively. Among the ROC curves of combined risk factors, CA153+ApoA1+Hb had the best accuracy, with the sensitivity and specificity of 89.47% and 99.32%, respectively (CI: 0.964–0.983, $p < 0.001$). CA153, ApoA1, and Hb are risk factors for OM in IDC. In clinical practice, the three parameters could be used as predictive factors for the early detection of OM.

KEYWORDS

diagnostic value, HIF-1, invasive ductal cancer, ocular metastasis, risk factors

Rong-Bin Liang, Kang Yu and Jie-Li Wu authors contributed equally to this work.

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1 | INTRODUCTION

Breast cancer has become common cancer in female and invasive ductal carcinoma (IDC), a major type of it, accounts for approximately 72% of all breast cancer.^{1,2} IDC originates from ductal epithelium and is formed when tumor cells penetrate the basement membrane of normal mammary ducts or acini and invade the breast stroma. Because of its invasive characteristic, IDC is prone to metastasis through either the lymphatic pathway or blood circulation pathway. Moreover, breast cancer is the main cause of ocular metastasis (OM).³ Though not common, OM can present a series of severe symptoms such as foreign body sensation, ocular pain, visual field defects, and even blindness. In clinical practice, however, physicians often focus on the primary tumor, failing to notice the potential signs of OM at an early stage. When OM progresses to an advanced stage, ophthalmectomy is often needed as chemotherapy drugs are not easy to reach the eyes, which always means disasters for patients.

Although there are abundantly available treatment options such as surgery, chemotherapy, radiotherapy, and targeted therapy, OM patients always have a poor outcome because of the particularity of the metastatic site.

The detection methods which are commonly used include ocular ultrasound, fundus photography, fundus angiography, magnetic resonance imaging (MRI), and computed tomography (CT). However, when OM is detected, the disease has always developed into an advanced stage. Hence, it is imperative to diagnose early OM in patients with IDC to take effective measures in time.

Hematological indices of patients sometimes can reflect the progress of their diseases earlier than imaging examination. The method of analyzing clinical features and hematological indices of patients has already been used to evaluate the possibility of distant metastases.⁴⁻⁷ As the method is non-invasive and repeatable, it is useful in clinical practice to identify distant metastases in an early stage.

In this retrospective study, we tried to find out risk factors and their diagnostic values for OM in IDC through analyzing the clinical features and hematological indices of IDC patients.

2 | MATERIALS AND METHODS

2.1 | Data collection

A total of 1192 patients with IDC were involved in this retrospective study. The samples were collected from the year 2008 to 2017 in the medical records systems. The inclusion criteria were as follows: (i) Patients were diagnosed with primary breast cancer at The First Affiliated Hospital of Nanchang University. (ii) Ophthalmic examinations in OM

patients indicated intraocular space-occupying lesions. (iii) The pathological diagnosis of IDC was confirmed by the Pathology Department of The First Affiliated Hospital of Nanchang University. In addition, patients with metastatic breast cancer or primary ocular malignant tumor were excluded from the study. Imaging data and pathological results of patients are shown in Figure 1.

The clinical parameters of the patients were compiled from their medical records including age, menopausal status, axillary lymph node metastases (ALNM), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), lipoprotein A (LipA), alkaline phosphatase (ALP), calcium (Ca) carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 153 (CA153), and carbohydrate antigen 199 (CA199). Continuous data were presented as mean \pm standard deviation. This study meets the requirements of the declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University.

2.2 | Study design

All patients were divided into two groups: the OM group and the non-ocular metastasis (NOM) group. The diagnoses of IDC and OM were achieved by biopsy. The clinical features of the patients between the OM and NOM groups were compared to find out the differences. Significant features were evaluated through binary logistic regression to figure out the risk factors of OM in IDC patients. The receiver operating characteristic (ROC) curves were then established to assess the diagnostic accuracy of the risk factors in clinical practice.

2.3 | Statistical analysis

First, the chi-squared test was used to detect differences in age, menopausal status, and ALNM. The normality test was then performed to determine the normal distribution of the data. As the data did not obey the normal distribution, clinical parameters between the two groups were compared using the rank-sum test. Binary logistic regression was used to determine the risk factors for OM in patients with IDC. ROC curves of a single risk factor were established to evaluate the predictive accuracy. ROC curves of combined risk factors were also established to determine the best method of diagnosing OM in IDC patients. The ROC curves of combined factors were established in the following steps: (i) The binary logistic regression analysis was firstly made using the combined factors as covariates and using the status (whether developing OM) as dependent variables. (ii) Then obtain the prediction probabilities of each sample and put them in the

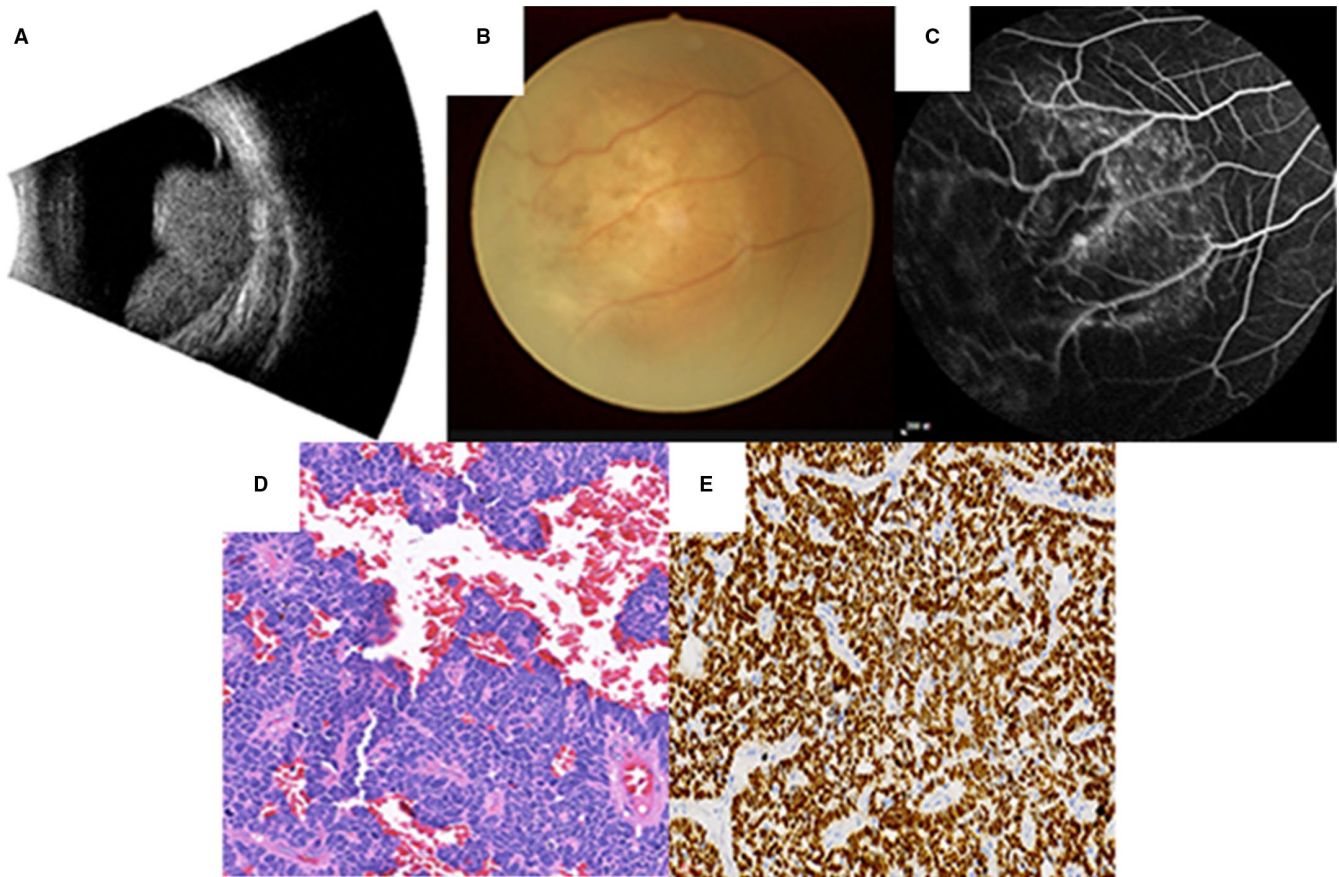


FIGURE 1 Imaging and pathological data of OM in IDC patients. (A) Ultrasound examination of ocular (right eye). Hypoechoic mass with an irregular shape could be seen in the posterior pole of the right eye. Echo attenuated behind the mass and infiltration could be seen around the mass. (B) Fundus photography (right eye). Under the retina, yellow nodular flat bulges with unclear boundaries could be seen. (C) Fundus angiography (right eye). Fluorescence leakage and low fluorescence in the lesion could be seen. Blood vessels were visualized in the field of vision. (D) Hematoxylin-eosin staining of the right ocular tumor, X200. Infiltration of cancer cells arranged in cords and nests with hyperchromatic nuclei could be seen in the tissue. Cellular atypia was obvious.

ROC analysis as the values of the specific test (Using the combined factors to detect OM was defined as a test). The SPSS 17.0 (SPSS, IBM Corp, USA) software was used to process the data.

3 | RESULTS

3.1 | Demography and clinical features

There were a total of 1192 patients with IDC (19 with OM, 1173 without OM). In the OM group, the mean age was 44.79 ± 7.91 years, whereas the age in the NOM group was 48.06 ± 10.32 years. In the OM group, 15 patients were premenopausal and 4 were postmenopausal, while in the NOM group, 732 patients were premenopausal and 441 were postmenopausal ($p = 0.139$). There were 728 patients with ALNM (16 OMs vs 712 NOMs) and 464 patients without ALNM (3 OMs vs 461 NOMs) ($p = 0.001$) (Table 1). There were no differences in age and menopausal status. However,

the incidence of OM rates showed an increasing trend with increasing number of lymph node metastasis.

3.2 | Risk factors of OM in patients with IDC

Rank sum test was used and significant differences were found in the levels of CEA, CA125, CA153, Hb, ALP, TC, LDL, and ApoA1 (Table 2). The result of binary logistic regression showed that IDC patients with higher level of CA153, lower level of ApoA1 and Hb were more easily to develop OM. (Table 3).

3.3 | ROC curve analysis for a single risk factor

ROC curves were constructed for a single risk factor to evaluate their predictive values in clinical practice (Figure 2).

TABLE 1 Clinical features of patients with invasive ductal carcinoma.

	OM	NOM	χ^2 value	<i>P</i> value
Age (years)	44.79 ± 7.91	48.06 ± 10.32	1.134	0.649
<25	0	5		
25–65	19	1108		
>65	0	60		
Menopausal status (n)				
Premenopausal	15	732	2.187	0.139
Postmenopausal	4	441		
Axillary lymph node metastases (n)				
0	3	461	12.204	0.002
1–4	4	417		
>4	12	295		
ER				
Positive	12	741	0.621	0.733
Negative	6	403		
Unknown	1	29		
PR				
Positive	10	650	0.618	0.734
Negative	9	494		
Unknown	0	29		
HER2				
Positive	8	553	0.844	0.656
Negative	11	588		
Unknown	0	32		
T classification				
T1	1	107	17.957	0.001
T2	15	748		
T3	1	72		
T4	2	13		
Unknown	0	233		
Clinical stages				
I	0	73	20.275	0.001
II	7	637		
III	10	219		
IV	2	35		
Unknown	0	209		

Notes: *p* < 0.05 represented statistical significance. T1: tumor size ≤20 mm; T2: 20 mm < tumor size ≤50 mm; T3: tumor size >50 mm; T4: tumor invaded chest wall or skin. T-classification and clinical stages were in line with the 2018 edition of the 8th AJCC TNM breast cancer staging.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor-2, T classification, tumor size classification; NOM, non-ocular metastases; OM, ocular metastases; PR, progesterone receptor.

The AUC of CA153 was 0.977 (95% CI: 0.966–0.984) and the cutoff value of CA153 was 43.3 u/mL, which means that IDC patients with CA153 levels higher than 43.3 u/mL are more likely to have OM. The sensitivity and specificity of CA153 were 94.74% and 96.68%, respectively. The AUC of ApoA1 was 0.938 (95% CI: 0.923–0.951) and the sensitivity

and specificity were 84.21% and 94.88%, respectively. IDC Patients with their ApoA1 levels lower than 1.11 g/L are more likely to have OM. For Hb, the AUC was 0.837 (95% CI: 0.815–0.857) and the cutoff value was 112 g/L, with a sensitivity and specificity of 78.95% and 77.92%, respectively. To sum up, CA153 level higher than 43.3u/mL, ApoA1 level

Clinical features	OM group	NOM group	Z value	<i>p</i> value
CEA (ng/mL)	20.17 ± 46.97	4.70 ± 27.91	-3.539	<0.001
CA125 (u/mL)	78.84 ± 136.58	18.50 ± 40.52	-4.786	<0.001
CA153 (u/mL)	143.26 ± 131.55	17.20 ± 23.85	-7.135	<0.001
CA199 (u/mL)	25.06 ± 48.18	17.12 ± 19.53	-1.272	0.203
Hb (g/L)	99.89 ± 16.48	120.96 ± 13.43	-5.044	<0.001
ALP (u/L)	110.95 ± 75.01	65.75 ± 30.26	-3.563	<0.001
Ca (mmol/L)	2.32 ± 0.43	2.44 ± 0.58	-0.259	0.796
TC (mmol/L)	4.24 ± 0.99	5.40 ± 1.93	-2.993	0.003
TG (mmol/L)	1.55 ± 0.51	2.23 ± 1.91	-0.796	0.426
HDL (mmol/L)	2.93 ± 3.22	2.16 ± 1.72	-0.236	0.813
LDL (mmol/L)	1.84 ± 0.68	3.46 ± 1.81	-5.279	<0.001
ApoA1 (g/L)	0.90 ± 0.32	1.75 ± 0.78	-6.564	<0.001
ApoB (g/L)	1.10 ± 0.36	1.50 ± 1.26	-0.231	0.817
LipA (mg/L)	140.05 ± 30.44	185.11 ± 203.38	-0.739	0.46

Notes: Mann-Whitney test was used. *p* < 0.05 represented statistical significance.

Abbreviations: ALP, alkaline phosphatase; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Ca, Calcium; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LipA, lipoprotein a; NOM, non-ocular metastases; OM, ocular metastases; TC, total cholesterol; TG, triglyceride.

TABLE 3 Binary logistic regression results.

Factors	B	Exp(B)	95% CI	<i>p</i> value
CA153 (u/mL)	0.022	1.022	1.010–1.034	<0.001
ApoA1 (g/L)	-8.169	0.000	0.000–0.011	<0.001
Hb (g/L)	-0.046	0.955	0.915–0.998	0.038

Notes: The forward-LR method was used in the binary logistic regression analysis. *p* < 0.05 represented statistical significance.

Abbreviations: ApoA1, apolipoprotein A1; B, coefficient of regression, CI, confidence interval; CA153, carbohydrate antigen 153; Hb, hemoglobin.

lower than 1.11g/L and Hb level less than 112g/L were three-single risk factors for IDC patients to develop OM. Among the three single risk factors, CA153 level higher than 43.3u/mL had the best predictive accuracy (Table 4).

3.4 | ROC curve analysis for combined risk factors

To look for the best diagnostic method, ROC curves of the combined risk factors were established (Figure 3). The AUC of CA153+Hb was 0.97 (95% CI: 0.959–0.979) and the sensitivity and specificity were 89.47% and 93.78%, respectively. For ApoA1+Hb, the AUC was 0.954 (95% CI: 0.940–0.965) and the ROC curve showed a higher specificity of 98.55%,

TABLE 2 Differences of clinical parameters between two groups.

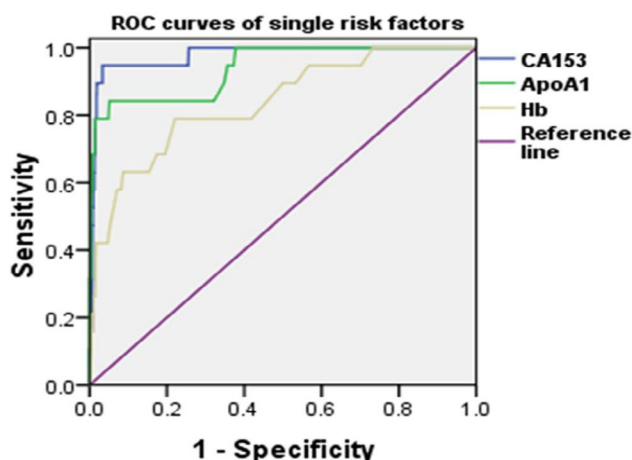


FIGURE 2 ROC curves of single risk factors for OM in IDC. ROC curves of CA153, ApoA1, and Hb are shown in the figure. Abbreviations: ROC, receiver operating characteristic; OM, ocular metastases; IDC, invasive ductal carcinoma; CA153, carbohydrate antigen 153; ApoA1, apolipoprotein A1; Hb, hemoglobin.

but lower sensitivity of 84.21%. For CA153+ApoA1, the AUC was 0.968(95% CI: 0.957–0.977) and the sensitivity and specificity were 89.47% and 97.78%, respectively, which were the highest among all the combined two factors. The combination of all three risk factors had the best predictive value, with the sensitivity of 89.47% and the specificity of 97.78%, and the AUC of 0.975 (95% CI: 0.964–0.983) (Table 4).

TABLE 4 ROC analysis of risk factors for predicting OM in IDC.

	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	CI	<i>p</i>
CA153 (u/mL)	43.3	94.74	96.68	0.977	0.966–0.984	<0.001
ApoA1 (g/L)	1.11	84.21	94.88	0.938	0.923–0.951	<0.001
Hb (g/L)	112	78.95	77.92	0.837	0.815–0.857	<0.001
CA153+Hb	-	89.47	93.78	0.97	0.959–0.979	<0.001
ApoA1+Hb	-	84.21	98.55	0.954	0.940–0.965	<0.001
CA153+ApoA1	-	89.47	97.78	0.968	0.957–0.977	<0.001
CA153+ApoA1+Hb	-	89.47	99.32	0.975	0.964–0.983	<0.001

Notes: *p* < 0.05 represented statistical significance.

Abbreviations: ApoA1, apolipoprotein A1; AUC, area under the curve; CI, confidence interval; CA153, carbohydrate antigen 153; Hb, hemoglobin; ROC, receiver operating characteristic.

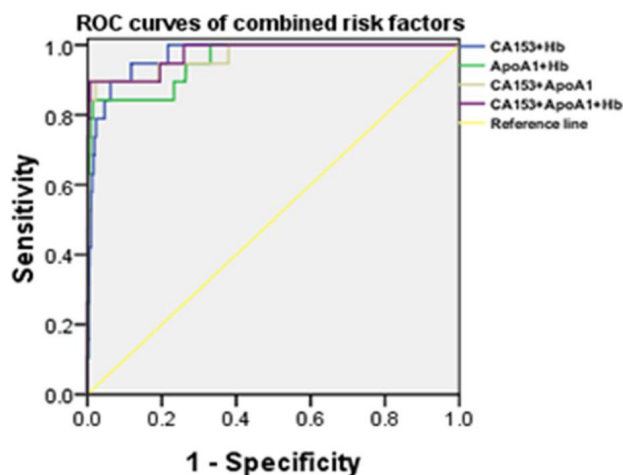


FIGURE 3 ROC curves of combined risk factors for OM in IDC. ROC curves of CA153+Hb, ApoA1+Hb, CA153+ApoA1, and CA153+ApoA1+Hb are shown in the figure. Abbreviations: ROC, receiver operating characteristic; OM, ocular metastases; IDC, invasive ductal carcinoma; CA153, carbohydrate antigen 153; ApoA1, apolipoprotein A1; Hb, hemoglobin.

4 | DISCUSSION

Breast cancer has become the most common cancer in women. It is a heterogeneous disease with different clinical

characteristics in different subtypes.⁸

IDC is the major type of invasive nonspecific cancer, where cancer cells can easily enter the vein via the lymphatic route, or directly enter the blood circulation leading to distant metastasis.

OM is caused by hematogenous metastasis of tumor. Choroid is the most common site in an ocular where OM occurs, for the blood supply of choroid is supported by a plurality of large ciliary posterior short arteries in the posterior part of the eyeball, and there is extensive anastomotic communication between the choroidal vessels. As the blood flow of choroid is rich, it is prone to develop metastasis.

Although CT and MRI are common techniques to detect distant metastasis, they have the disadvantages of high expenditure and high radiation doses.

Recently, serum parameters and clinical features of patients have been widely applied to evaluate the possibility of metastases. Risk factors obtained by the statistical analysis were useful to predict distant metastases in clinical practice. Studies of risk factors for various metastases are summarized in Table 5.^{5,6,9-12}

In the present retrospective study, we explored the risk factors for OM in 1192 patients with IDC and analyzed their diagnostic values. As patients in the OM group were more likely to have other metastases and their diseases were also in advanced stages, they often had poor prognosis. Axillary

TABLE 5 Summary literatures.

Author	Year	Primary cancer	Metastasis	Risk factors
Cao et al ⁵	2012	Breast cancer	Liver	LDH+GGT+CA153
Zhou et al ¹¹	2017	Lung cancer	Bone	CA125+ALP
Chen et al ⁶	2017	Breast cancer	Bone	ALMN+CA153+ALP+Hb
Chen et al ⁹	2017	Renal cell cancer	Bone	ALP+Ca+Hb
Huang et al ¹⁰	2017	Bladder cancer	Bone	Ca+ALP+Hb
Zhu et al ¹²	2019	Colorectal cancer	Eye	HDL

Abbreviations: ALMN, axillary lymph node metastases; ALP, alkaline phosphatase; Ca, calcium; CA153, carbohydrate antigen 153, CA125, carbohydrate antigen 125; GGT, γ -glutamyltransferase; Hb, hemoglobin; HDL, high-density lipoprotein; LDH, lactate dehydrogenase.

lymph node metastasis is more common in patients with poor prognosis, which might explain the fact where more axillary lymph node metastases were seen in the OM group compared with the NOM group. In addition, through various analyses, CA153, ApoA1, and Hb were found to be the risk factors for OM in IDC patients.

4.1 | CA153

CA153, as a breast cancer-related antigen, is derived from the mammary epithelial surface. Elevated CA153 could be seen in 30%-50% of breast cancer patients. However, its positive rate was only 20%-30% in patients with early breast cancer. In spite of this, it is valuable in detecting distant metastases in breast cancer patients, especially when the disease cannot be evaluated by radiological procedures.¹³ The specificity and sensitivity of CA153 in predicting bone metastasis were 76.62% and 86.97%, respectively.⁶ In liver metastasis, they were 52.0% and 80.8%, respectively.⁵ In the present retrospective study, CA153 showed a high sensitivity (94.74%) in diagnosing OM in IDC patients. In addition, the cutoff value of CA153 was 43.3 u/mL, indicating that patients with IDC with a level of CA153 higher than 43.3 u/mL were more prone to develop OM.

4.2 | ApoA1

ApoA1, as the main structural protein of HDL, participates in the reverse transport of cholesterol. Previous studies have shown that ApoA1 levels are associated with cardiovascular diseases.¹⁴ In addition, it has anti-tumor functions. An experiment showed that the injection of ApoA1 into mice could effectively inhibit tumor growth and metastasis.¹⁵ Moreover, ApoA1 was found to have an effective immunomodulatory role in the tumor microenvironment, for it can change tumor-associated macrophages from pre-tumor M2 to anti-tumor M1 phenotype.¹⁵

Studies have also shown decreased ApoA1 levels in patients with malignant tumors. For instance, ApoA1 levels were decreased in children with acute lymphoblastic leukemia and returned to normal after therapy.¹⁶ Investigations also suggested that people with low levels of ApoA1 are more likely to have lung cancer and colorectal carcinoma.^{17,18} As it exerts anti-tumor effects, ApoA1 has been used to diagnose and evaluate the prognosis of tumors. Farias-Eisner et al.¹⁹ reported that ApoA1 combined with prealbumin and transferrin has a sensitivity of 71% in diagnosing endometrial cancer. Tuft et al.²⁰ found that patients with ovarian serous adenocarcinoma have longer overall survival when higher levels of ApoA1 mRNA are detected in their chest and abdominal dropsy before chemotherapy. In the present retrospective study, IDC patients with ApoA1 lower than 1.11 g/L

were prone to develop OM. It can be used to diagnose OM in patients with IDC, with a sensitivity of 84.21% and specificity of 94.88%.

4.3 | Hemoglobin

Hb is a special protein in red blood cells, whose main function is to transport oxygen and carbon dioxide. Cancer patients are prone to have relatively low Hb levels due to tumor-related hemorrhage, surgery, chemoradiotherapy, etc. With the decreasing of Hb, the oxygen partial pressure of tumor tissue also decreased significantly,²¹ which would cause hypoxia in tumor tissue. Hypoxia will increase the genetic instability of tumor cells and cause genomic changes,²² which will enhance tumor adaptability and give birth to some invasive tumor cells, leading to tumor progression and distant metastasis. Moreover, the high expression of hypoxia-inducible factor-1 α (HIF-1 α), a crucial transcription factor, will cause angiogenesis of tumor tissue and accelerate tumor infiltration,²³ which could easily lead to OM. In addition, hypoxia will also cause alterations of PI3 K/AKT/mTOR, MAPK, and NF- κ B pathways,²⁴⁻²⁶ thus promoting tumor metastasis. Hence, Hb level is closely related to the prognosis of cancer patients.

Currently, Hb level has been used as a prognostic factor in nasopharyngeal carcinoma, vulvar squamous cell carcinoma, advanced head and neck cancer, and early breast cancer.^{24,27-29}

In the present study, we found Hb an independent risk factor of OM in patients with IDC. IDC patients with Hb level lower than 112 g/L were more likely to develop OM. Therefore, Hb could also be used to predict OM in patients with IDC, with a sensitivity of 78.95% and specificity of 77.92%.

4.4 | Combined diagnostic values

Moreover, to obtain a better predictive method, diagnostic values of the combined risk factors were also detected. Among the two combined risk factors, CA153 and ApoA1 had the best accuracy, with the sensitivity and specificity of 89.47% and 97.78%, respectively. The best diagnostic accuracy was obtained when using three combined risk factors, CA153+ApoA1+Hb, with the sensitivity and specificity of 89.47% and 97.78, respectively.

4.5 | Axillary lymph node metastases

Lymph node metastases serve as a marker of the host response to malignant tumors, and the number of lymph node

metastases indirectly reflects the invasiveness of tumors. In the study,³⁰ it was found that compared with patients without lymph node metastases, those with four or more lymph node metastases had a worse prognosis after recurrence. However, the prognosis of patients with only one to three lymph nodes involved was not significantly different from that of patients with negative lymph node metastases, so the number of lymph nodes involved is a key determinant of the prognosis after recurrence. Bone is the most common part for distant metastases of breast cancer, whose most common extra-organ metastasis is bone metastasis. In the study of Chen et al,⁶ it was found that lymph node metastasis could be an independent risk factor of breast cancer bone metastasis, and the incidence of breast cancer bone metastasis was the highest among patients with four or more axillary lymph nodes involved. Although there is no literature reporting that axillary lymph nodes can be taken as a risk factor of ocular metastasis from breast cancer, we can speculate that the number of axillary lymph node metastases might be an important risk factor for it.

We get most information through our eyes. Ocular metastasis of breast cancer is not very common, but once the tumor metastasizes to eyes, the patient's vision will be greatly affected, which will further reduce his quality of life. Therefore, improving the cognition of clinical features and risk factors of ocular metastasis among breast cancer patients is of great significance for early diagnosis and treatment, which can help improve the long-term prognosis of patients and prevent serious consequences of ocular metastasis. A serum tumor examination has advantages including reproducibility, non-invasiveness, and a low cost, which is more convenient and quick compared with traditional CT and MRI, and it causes less harm to patients. Therefore, we analyzed the clinical characteristics of patients with ocular metastases from breast cancer and identified risk factors of ocular metastases.

4.6 | Limitations

Yet, there were also some limitations in this retrospective study. First, some patients might have other distant metastases where elevated CA153 could also be seen,³¹ which might influence the conclusion. Second, the sample size of the OM group was relatively small as it is rare to be seen in clinical practice and all participants were from the same institution, which might have some bias. Third, the statistical analysis could only demonstrate a connection between risk factors and OM in IDC patients but the specific mechanisms still need further experiments.

To sum up, we determined the risk factors for OM in IDC and analyzed their diagnostic values. In clinical practice, when CA153, ApoA1 or Hb levels of IDC patients alter beyond their cutoff values, CT, MRI, and ocular ultrasound are

advised to be performed to detect whether OM has occurred in IDC patients so that timely treatment could be made at an early stage which may improve patients' survival time and quality of life.

5 | PATIENT CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Shao Y designed the study. Ge QM, Liang RB, and Zhang YQ collected the clinical data. Fang JW and Liu JX performed statistical analyses. Fang JW, Min YL, and Li B prepared the manuscript. Lin Q and Shi WQ made the figures and tables. All authors read and approved the final manuscript.

ETHICAL STATEMENT

This study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of Nanchang University and followed the principles of the Declaration of Helsinki. Informed consents from participants were obtained.

ORCID

Jia-Xiang Liu  <https://orcid.org/0000-0002-9717-7472>

Qi Lin  <https://orcid.org/0000-0002-9742-1674>

Yi Shao  <https://orcid.org/0000-0003-1571-2433>

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