ORIGINAL RESEARCH

The Predictive Value of CA-125 and Hb for Ocular Metastasis in Hepatocellular Carcinoma Patients

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Objective: To explore the risk factors of ocular metastasis (OM) in patients with hepatocellular carcinoma (HCC) by analyzing the demographic characteristics and serum markers.

Methods: From July 2002 to December 2012, 1064 HCC patients were included in our study. The chi-squared test and Student's t-test were used to assess the difference between OM and any other metastasis (NOM). Receiver operating curve (ROC) was used to analyze the diagnostic value of serum biomarkers in HCC patients with OM.

Results: The incidence of OM in HCC patients was 1.88% in our research. There are no significant differences in age, gender, or histopathology in the OM group and the group without any metastasis. Binary logistic regression analysis presented that compared with the patients without cancer metastasis, carbohydrate antigen 125 (CA-125) and hemoglobin (Hb) were risk factors in hepatocellular carcinoma patients with OM ($P < 0.05$). The ROC curve analysis showed that the areas under the CA-125, Hb, and CA125+Hb curves were 0.877, 0.554, and 0.431, and the cutoff values of CA-125 and Hb each were 115.78 u/mL and 120.50 g/L.

Conclusion: Our data suggest that CA-125 and Hb are risk indicators in hepatocellular carcinoma patients with OM, and that CA-125 +Hb has potentially greater utility in diagnosing hepatocellular carcinoma.

Keywords: hepatocellular carcinoma, ocular metastases, CA-125, Hb, risk factors

Article Summary

1. We found that CA-125 and Hb are risk indicators in HCC patients with OM.
2. The study indicated that CA-125+Hb has potentially greater utility in diagnosing HCC.

Introduction

Cancer liver is the fourth common malignant tumor seen in clinical practice, with the characteristics of high malignancy, rapid progression, strong invasiveness, poor prognosis, and high mortality, bring patients with decreased survival and quality of life.[1] Hepatocellular carcinoma (HCC) is currently the most common type of primary HCC.[2] Studies have shown that HCC metastasizes mainly rely on blood spread, with lung and bone metastases accounting for 76% and 11% of metastases. And following HCC metastasis to the brain, patients often experience significant nausea and headache. The mortality rate of primary HCC is about 54% worldwide nowadays,[3] and accurate diagnosis at the early clinical stage is thought to greatly improve treatment efficacy and survival of patients. However, the high metastasis and recurrence rates of primary HCC (mainly HCC) after surgery are the primary factors affecting patients' prognosis.[4] Therefore, an in-depth study of HCC metastasizing mechanisms is essential for clinical prevention and treatment. Metastasis of liver tumors to the eye has not been reported in detail in the current literature; however, according to some studies, HCC with

ocular metastasis (OM) can cause a series of ocular symptoms, which may seriously affect the physical and mental quality of cancer patients. Therefore, early detection, diagnosis, and treatment is crucial for HCC patients with OM. Currently, clinical studies have found that some reliable predictors of immune checkpoint inhibitors response, such as PD-L1 and TMB, may help predict that HCC patients will benefit more from immunotherapy.[40–42]

In this study, we used tumor serological markers to assess factors associated with the early diagnosis of HCC with OM. Tumor serological markers are less invasive than biopsy, relatively inexpensive, reusable, and easy to screen and follow-up. Tumor markers are molecules that indicate the presence of tumor cells. These markers are produced by tumors, and a tumor may have a variety of markers. Targeted detection of tumor-associated markers in serum can facilitate the early detection and timely treatment of malignant tumors. Tumor markers are produced by tumors and accumulate in other tissues and bodily fluids.[5] The detection of tumor markers in human blood, bodily fluids, or tissue cells can aid in diagnosing the presence, pathogenesis, and prognosis of tumors. Currently, numerous serum tumor markers have been found to be associated with HCC. For example, Ma et al[6] found that CEA, CA-125, and CYFRA21-1 levels are high in lung cancer and can be used for the diagnosis of this disease. Previous studies have also shown that these markers are associated with poor prognosis in non-small cell lung cancer.[7] Cancer embryonic antigen (CEA) is significantly elevated in 70% of patients with definitive diagnosis of colorectal cancer (CRC)[8] and in 75% of patients with metastatic eye tumors,[9] while concentrations of lipid biomarkers, such as triglycerides and HDL-C, have been shown to correlate with the incidence of breast and colorectal cancers.[10] In addition, tumor markers may be potentially useful for predicting tumor metastasis. Studies have reported that elevated levels of apolipoprotein are strongly correlated with the development of tumors. Studies have demonstrated that specific apolipoproteins affect tumor growth by modulating immune cell function.[11] The levels of apolipoproteins are used to assess the prognosis of patients with HCC and colorectal cancer.[12,13]

However, it is unclear whether there is a difference in the tumor markers themselves between HCC patients with and without OM. In this study, we collected the medical records of HCC patients admitted to our hospital, and retrospectively analyzed the diagnostic value of common HCC markers. We mainly tested the serum markers in HCC patients, and compared the levels of these markers between patients with and without metastasis. The factors increasing the risk of OM of HCC were identified. Our results provide a powerful medical basis of testing targets for assessing the presence of OM in HCC patients.

Materials and Methods

Study Design
All participants joined voluntarily and were informed of the study design, and all participating patients provided written informed consent and the study was performed in accordance with the tenets of the Declaration of Helsinki and its amendments. The study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of Nanchang University. The patients in this study were diagnosed with HCC from July 2002 to December 2012 based on pathological sections obtained by surgical resection or biopsy. Examine of computed tomography (CT) and magnetic resonance imaging (MRI) were used to determine whether OM occurred in patients with HCC. Exclusion criteria included patients with secondary HCC, primary ocular malignancy and benign ocular tumors.

Patient and Public Involvement Statement
The patients were not involved.

Data Collection
We collected clinical data, including age, gender, treatment, pathological type, and the presence time of OM, from clinical medical records of patients with HCC. Additionally, the levels of several tumor markers, including blood calcium concentration, hemoglobin (Hb), alkaline phosphatase (ALP), ferritin (FER), carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and cytokeratin fragment 19 (CYFRA21-1), were assessed by analyzing serum from patients. The levels of CA-125, CA-153, CA-199, CA724, serum lipids (eg, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol), Lp (a), ApoA1, and ApoB were also assessed.

ROC Curve

Receiver operating characteristic (ROC) curves was used to assess the diagnostic value of the abnormalities (abnormal ReHo values) detected by ReHo method in specific brain regions. The brain region or ReHo method has diagnostic significance when the related area under the ROC curve (AUC) is greater than 0.5.

Hematoxylin-Eosin (HE) and Immunohistochemistry (IHC) Staining

Hematoxylin-eosin (H&E) staining of eyelids and Hepatocyte IHC of eyeballs were performed in the 4-um-thick sections of HCC samples.

Statistical Analyses

We performed the *t*-test and chi-squared test to compare age and gender characteristics to avoid affecting the experimental results. Differences in the levels of tumor markers between the OM group and group with other metastases were also analyzed by the independent *t*-test. The binary logistic regression model was then applied to identify the independent risk factors for OM. A receiver operating characteristic (ROC) curve was constructed, and the area under the curve (AUC) was calculated. $P < 0.05$ indicated statistical significance of differences. All statistical analyses were performed using SPSS 21.0 software (SPSS, IBM, USA) and Excel 2010 software. Continuous data are displayed as the means ± standard deviations (SD). The statistical method is similar to the related article we reported earlier.[14]

Result

Demographics and Clinical Characteristics

1064 primary HCC patients were enrolled in this study, including 20 OM cases and 1044 NOM cases. The mean ages of OM patients and NOM patients were 51.78±13.95 and 51.92±13.65 years, respectively. The most common histopathological types were HCC and cholangiocarcinoma. According to the chi-squared test and the non-parametric summary test, there was no significant difference in gender, age, and location of other metastases between the OM group and the NOM group ($P > 0.05$) (Table 1, Figure 1).

Differences in Clinical Features and Risk Factors Between Patients with and without Ocular Metastasis

By comparing the clinical data of OM and NOM patients, we found that CA-125 was significantly elevated and Hb concentration was decreased in the OM patients compared with that in the NOM group ($P < 0.05$). There were no significant differences in serum levels of CEA, CA-724, CA-199, CA-153, FER, ALP, TC, TG, HDL, LDL, ApoA1, ApoB, Lp (a), or serum calcium ($P > 0.05$; Table 2) between the two groups. The results of the binary logistic regression modeling showed that the high levels of CA125 and Hb could be used as independent risk factors for the prediction of HCC metastasis (Tables 2 and 3).

Table 1 The Clinical Characteristics of HCC Patients

Patient Characteristics	OM Group (n=20)	NOM Group (n=1044)	P value
Gender			
Male	17(85.0)	950(90.9)	0.354
Female	3(15.0)	94(9.001)	
Age, years			
Mean	51.78±13.95	51.92±13.65	0.697

Notes: Chi-squared test and Student's *t*-test were used. $P < 0.05$ indicated statistical significance.
Abbreviations: OM, ocular metastasis; NOM, non-ocular metastasis; HCC, hepatocellular carcinoma.
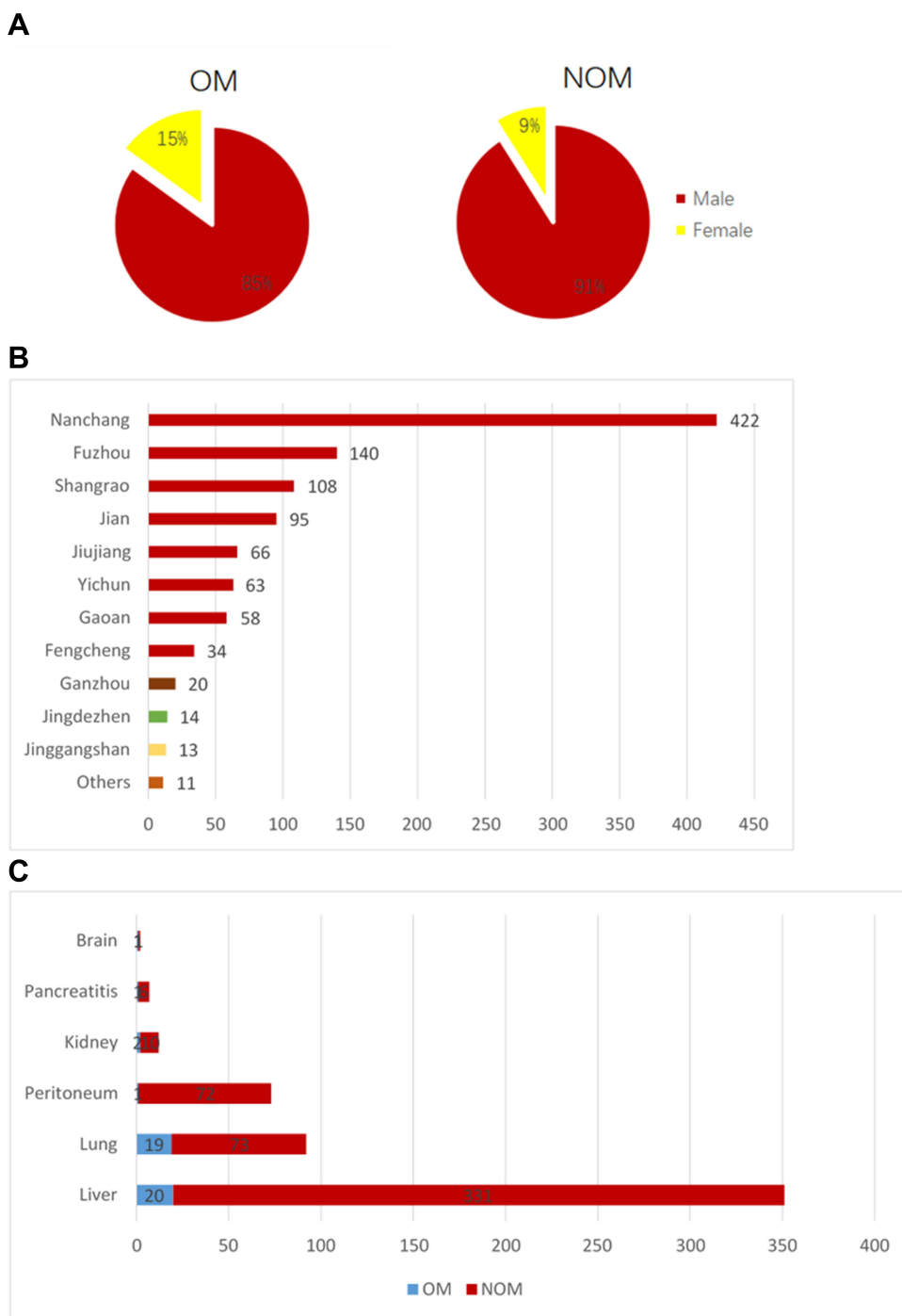
A

OM

NOM

- Male
- Female

B

City	Value
Nanchang	422
Fuzhou	140
Shangrao	108
Jian	95
Jiujiang	66
Yichun	63
Gaoan	58
Fengcheng	34
Ganzhou	20
Jingdezhen	14
Jinggangshan	13
Others	11

C

■ OM ■ NOM

Figure 1 The demographic characteristics of the included cases (**A** and **B**) and different types of cancer with ocular metastases (**C**).

CA-125 and Hb as Diagnostic Markers

Figure 2 shows CA-125 and Hb as single factors in the ROC curve and as a combination for predicting OM in HCC patients. Table 4 shows that their cutoff values were 115.78 u/mL and 120.50 g/L, respectively. The AUC of CA-125 had higher accuracy, and its sensitivity in our study was as high as 90%, making it the best diagnostic marker of OM. The specificity of Hb detection for OM was low, at 53.5%. After the combined analysis of CA-125 with Hb data, CA-125 and Hb were found to have high sensitivity and relatively low specificity, and the AUC was 0.431. All results were

Table 2 Differences in Tumor Markers Between HCC Patients with and without OM

Tumor Markers	OM Group	NOM Group	t	P value
CEA (ng/mL)	11.29±26.81	518.46±12,112.28	1.426	0.941
CA-125 (u/mL)	499.41±356.26	116.43±244.63	15.975	<0.001
CA-199 (u/mL)	191.34±300.31	214.96±3879.47	1.839	0.840
CA-153 (u/mL)	18.47±13.04	19.29±21.08	27.832	0.510
CA-724 (u/mL)	7.81±9.30	6.74±5.52	33.569	0.332
FER (mmol/L)	230.84±248.97	250.37±177.25	45.386	0.836
ALP (mmol/L)	207.5±90.88	149.73±131.45	36.439	0.394
TG (mmol/L)	4.74±1.85	6.05±12.76	13.376	0.754
TC (mmol/L)	1.88±1.38	1.40±1.07	12.530	0.477
HDL (mmol/L)	1.57±1.30	1.47±1.04	15.051	0.320
LDL (mmol/L)	2.91±1.97	2.50±1.28	37.552	0.481
ApoA (g/L)	1.64±0.47	1.54±0.42	40.284	0.519
ApoB (g/L)	1.01±0.59	1.07±0.80	2.887	0.472
Lp (a) (mg/L)	148.2±182.73	225.42±251.00	29.695	0.154
Serum calcium (g/L)	10.24±36.19	2.15±0.27	8.541	0.511
Hb (g/L)	116.15±36.32	118.63±22.82	163.484	0.026

Notes: Independent-samples *t*-test was performed. P < 0.05 indicates statistical significance.
Abbreviations: HCC, hepatocellular carcinoma; OM, ocular metastases; NOM, non-ocular metastases; CEA, carcinoembryonic antigen; CA-125, carbohydrate antigen 125; CA-199, carbohydrate antigen 199; CA-153, carbohydrate antigen 153; CA-724, carbohydrate antigen 724; FER, ferritin; ALP, alkaline phosphatase; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA, apolipoproteinA; ApoB, apolipoproteinB; Lp, lipoprotein; Hb, hemoglobin.

Table 3 Risk Factors for OM in HCC Patients

Factors	B	Exp(B)	OR (95% CI)	P
CA-125 (u/mL)	0.005	1.005	1.003–1.007	<0.001
Hb (g/L)	0.030	1.030	1.004–1.058	0.026

Notes: Binary logistic analysis was applied. P < 0.05 indicates statistical significance.
Abbreviations: HCC, hepatocellular carcinoma; B, coefficient of regression; OR, odds ratio; CI, confidence interval; CA-125, carbohydrate antigen 125; OM, ocular metastases.

statistically significant (P < 0.05; Figure 2, Table 4). And some eye examination results of a HCC patients with OM (Figure 3). In addition, Hematoxylin-eosin (HE) staining and Immunohistochemical staining (IHC) are shown in Figure 4.

Discussion

At present, many studies have reported many cases of OM of clinical malignant tumors (Table 5). For various types of malignant tumors, OM often indicates a poor prognosis, and patients will suffer vision decline, ocular pain and a series of other problems that seriously affect the quality of life of patients.

Metastatic HCC, also known as secondary HCC, occurs as a result of advanced malignant tumors. HCC is more prone to metastasis than other types of HCC. Studies have shown that the incidence of metastatic HCC in China is 1.2-fold higher than that of primary HCC, while the ratio in Europe and the United States is 20-fold higher than that of primary HCC. Treatment efficacy in metastatic HCC directly improves the quality of life and survival of patients; however, the treatment of this cancer is very challenging. With the development of tumor diagnosis and treatment technology though, increasingly more clinicians are facing the troublesome treatment of metastatic HCC. Although there are many treatment methods for metastatic HCC, the prognosis of this disease is currently not satisfactory. Generally, patients will die within one year after diagnosis of liver metastasis, and patients with multiple liver metastases are more likely to die within two to three years. The removal of as much of the primary lesion as possible and adoption of comprehensive surgery-based treatment may enable the disease to be alleviated to the maximum extent, the quality of life of patients be improved, and
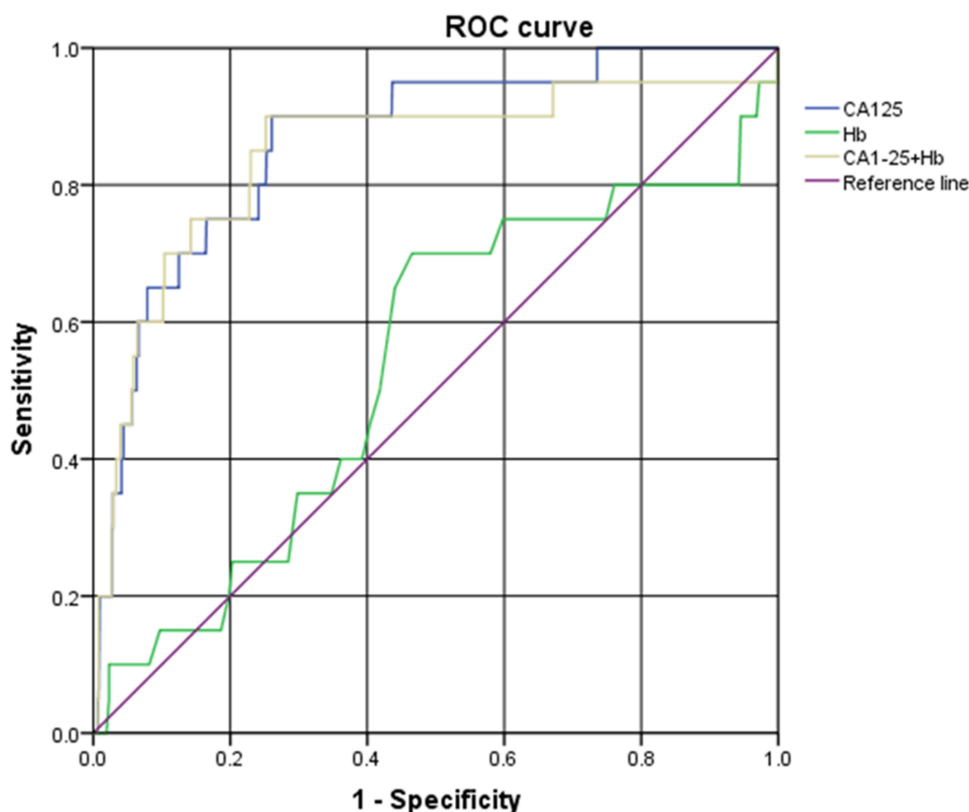
Figure 2 ROC curve shows CA-125 and Hb as single factors and as a combination for predicting OM in HCC patients.

the survival time to be prolonged. Studies have shown that tumor size, degree of cell differentiation, whether the tumor breaks through the capsule, whether it is accompanied by peripheral micro-metastasis, and whether there is portal vein tumor thrombus are significantly correlated with the metastasis and recurrence of HCC. Wayne et al[24] found that regardless of the presence of liver cirrhosis, large tumor size and portal vein tumor thrombus were the main factors associated with recurrence after HCC surgery. The analysis of hematogenous metastasis in the context of HCC metastasis and identification of the most frequent sites of metastasis are crucial for early clinical diagnosis of this disease as well as to guide the choice of clinical treatment strategies and aid prognosis. Studies have shown that men are more likely to develop HCC than women. Some studies reported that the rate of intravascular metastasis in male HCC patients was significantly higher than that in female patients, indicating that the former is prone to intravascular metastasis. Furthermore, the rate of intravascular metastasis among elderly patients was only 25.00%, which is significantly lower than that among middle-aged and young patients, indicating that the latter are more likely to have intravascular metastasis and miss the opportunity for surgery.

Molecular biology shows that HCC has two ways of hematogenous metastasis due to the anatomical characteristics of double blood supply, together with the portal vein collection of abdominal most organs of the blood reflux and the effect

Table 4 The Cutoff Value, Sensitivity, Specificity, and AUC for Individual Risk Factors in Predicting OM in HCC Patients

Factor	Cutoff Value	Sensitivity (%)	Specificity (%)	AUC	P
CA-125 (u/mL)	115.78	90.0	73.9	0.877	< 0.001
Hb (g/L)	120.50	70.0	53.5	0.554	0.026
CA-125+Hb	95.03	100.0	6.8	0.431	0.003

Notes: Sensitivity and specificity were obtained at the cutoff value. P < 0.05 indicates statistical significance.
Abbreviations: HCC, hepatocellular carcinoma; AUC, area under the curve; OM, ocular metastasis; CA-125, carbohydrate antigen 125.
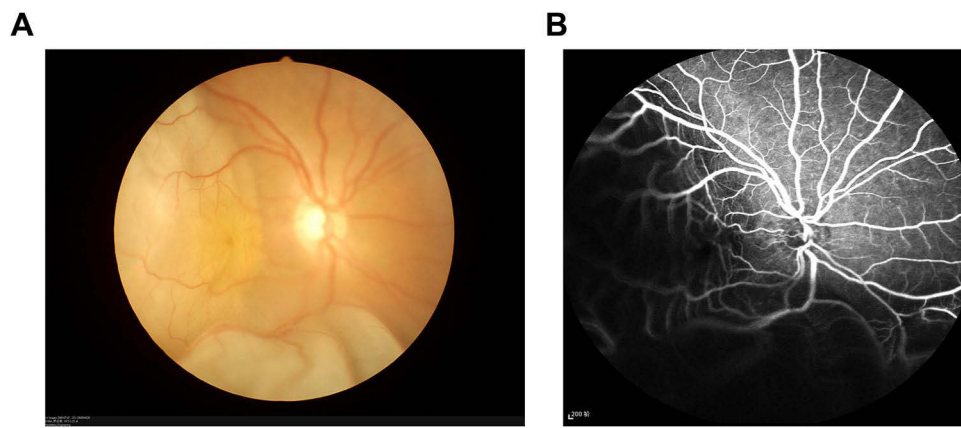
A

B

Figure 3 Fundus camera image of HCC patients. (**A**) Retinal fundus photography. (**B**) Fundus fluorescence angiography.
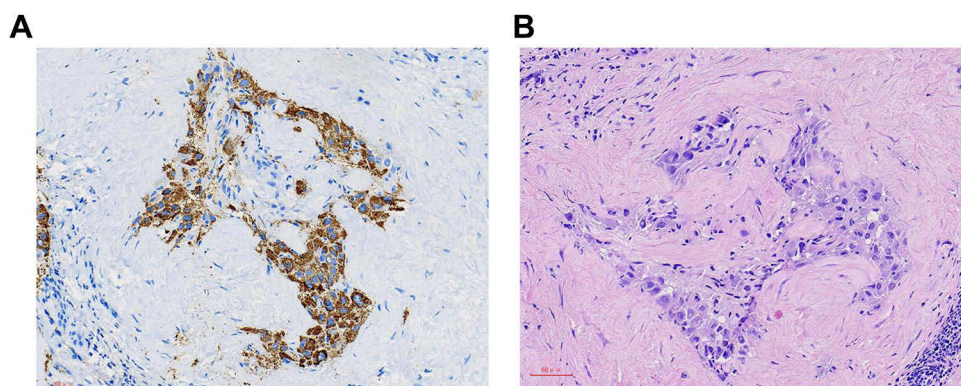
A

B

Figure 4 Pathological images of HCC patients. (**A**) Hematoxylin-eosin (HE) staining. (**B**) Hepatocyte IHC staining.

of liver itself filtration, resulting in liver metastatic tumors. As cancer metastasis involves multiple genes and mechanisms and comprises different phenotypes (such as hematopoietic metastasis and lymphatic metastasis), it is difficult to identify a single related gene that is linked to this process. Recent data suggest that many molecular changes associated with HCC metastasis, such as various serological factors, are common to solid tumors. It is possible to identify a set of related genes that may be used to make a clinically valuable prediction of a certain phenotype of HCC that may additionally serve as a preventive target. If predictors of HCC metastasis can be identified, it may be possible to provide

Table 5 Studies on the OM from Different Cancers

Author	Year	Diseases with OM
Tei, et al[14]	2014	Rectal cancer
Shah, et al[15]	2014	Lung cancer
Hazan, et al[16]	2014	Choriocarcinoma
Cristina, et al[17]	2015	Primary bone leiomyosarcoma
Mercado, et al[18]	2016	Cutaneous melanoma
Fountas, et al[19]	2017	Thyroid cancer
Essadi, et al[20]	2017	Renal cancer
Levison, et al[21]	2018	Breast cancer
Chang, et al[22]	2018	Esophageal carcinoma
Wu, et al[23]	2019	Gastric carcinoma

Notes: The table summed up studies on OM from different types of cancer.
Abbreviation: OM, ocular metastasis.

effective intervention, in a timely manner, to patients prone to postoperative metastasis to reduce the risk of metastasis. At present, many studies have analyzed the risk factors of OM such as breast cancer, lung cancer and colorectal cancer (Table 6), and there are many molecular markers related to HCC metastasis have been found, which are expected to be useful indicators for predicting postoperative recurrence and metastasis of HCC, while such related study about HCC with OM has not been reported. Our study found that CA-125+Hb has great predictive value for the diagnosis of HCC complicated with OM, which will contribute to the further evaluation of future clinical trials, and provide a basis for further research to improve the accuracy of CA-125+Hb in OM diagnosis of HCC, and contribute to the clinical application of this biomarker.

In Table 7, we list various studies on HCC metastasis demonstrating that the detection of tumor markers in the serum of patients is a reliable method for diagnosing and preventing HCC metastasis. In the traditional serological test, alpha fetoprotein (AFP) is used. As the oldest and most widely used serological marker, the limitations of AFP have been increasingly identified. Approximately 1/3 of patients are negative for AFP,[38] which limits its application in the early diagnosis of HCC and indicates the need for the development of other markers.

In this study, we analyzed the relevance between OM and HCC. We collected serum samples from patients with HCC and evaluated the change of each index. We measured the concentration of CA-125 and Hb in serum from a large number of patients as independent risk factors for patient with OM from HCC ($P < 0.001$, $P < 0.05$). We also use ROC curve to analyze oriented biomarkers. Consequently, we concluded that CA-125 and Hb are significant risk factors for patient with OM from HCC. The result of ROC curves accurately reflected the relationship between the specificity and sensitivity of the analysis method, and is the comprehensive representative of the test accuracy, using the ROC curves of these biomarkers, reliable clinical trials can be developed. Blood CA-125 levels of higher than the critical value of 115.78 U/mL and blood Hb levels higher than the critical value of 120.50 g/L indicate a higher risk of OM in patients with HCC. Accordingly, the AUC for CA-125 is the highest based on detailed diagnostic techniques (eg, CT and MRI of the eye); therefore, this marker shows high accuracy in distinguishing OM

Table 6 Studies on the Risk Factors of OM from Different Cancers

Author	Year	Diseases with OM	Increased Features	Decreased Features
Lin, et al[24]	2019	Lung cancer	Calcium, ALP, AFP, CEA, CA-125, CA-199, CYFRA21-1, TPSA	HB, NSE
Liu, et al[25]	2019	Breast cancer	ApoB	TC, TG, HDL, LDL, ApoAI, Lp (a)
Zhu, et al;	2019	Colorectal	TC, HDL, CEA	TG, LDL
Min, et al[26,27]	2020	cancer		

Note: The table summed up studies on the risk factors of OM from different types of cancer.
Abbreviation: OM, ocular metastasis.

Table 7 The Risk Factors for Metastases of Primary HCC

Author	Year	Histopathological Type	Metastatic Sites	Risk Factors
Lin, et al[28]	2003	HCC	Lung	Tumor size
Ogawa, et al[29]	2004	HCC	Distant metastasis	CD44v3
Xiang, et al[30]	2009	HCC	Bone	CXCR4
Lin, et al[31]	2010	HCC	Vessel	Aurora B
HSIAO SY et al[32]	2011	HCC	Brain	ALP
Chua TC, Morris DL[33]	2012	HCC	Bone	r-GT
Morimoto, et al[34]	2014	HCC	EHM	Platelet, DCP
Wan P et al[35]	2014	HCC	Pancreas	CA-199
Chen, et al[36]	2015	Small HCC	IHM and EHM	VEGF
Lee, et al[37]	2019	HCC	EHM	AFP

Note: The table summed up studies on risk factors of metastases from primary hepatocellular carcinoma.
Abbreviations: HCC, hepatocellular carcinoma; CD44v3, CD44 variant exon 3; CXCR4, CXC motif chemokine receptor 4; DCP, des-γ-carboxyprothrombin; VEGF, vascular endothelial growth factor; AFP, alpha-fetoprotein; EHM, extrahepatic metastasis; IHM, intrahepatic metastasis.

patients from elderly lung cancer patients. To improve the accuracy of diagnosing HCC with OM, we combined the detection of CA-125 and Hb and found that the combination of CA-125+Hb showed relatively high sensitivity and specificity, and may therefore be more accurate for the prediction of OM in HCC.

There are some limitations in our study, as for the study was conducted using only data collected at our hospital, which may not represent the entire OM patient population. Further research that includes a larger sample size and multi-center study are needed to improve the rigor and credibility of these risk factors in predicting OM in elderly lung cancer patients. The metastatic stage of HCC is usually fatal.[39] Most of the patients in this study were not classified by tumor type; therefore, we could not determine the risk factors for OM based on tumor stage. However, there are few studies in this area at present, and our study fills this gap. In the future, we can collect a large number of samples from multiple clinical centers for further understanding.

Strengths and Limitations of This Study

Our results provide a powerful medical basis of testing targets for assessing the presence of OM in HCC patients.

The study was conducted using only data collected at our hospital, which may not represent the entire OM patient population. Most of the patients in this study were not classified by tumor type; therefore, we could not determine the risk factors for OM based on tumor stage.

Conclusion

In summary, the incidence of OM in the HCC patients in our study was 1.88%. The most common histopathological subtype in the present OM patients was HCC, followed by cholangiocarcinoma. Serum concentrations of CA-125 and Hb were determined to be independent risk factors for patient with OM from HCC. We also found that the combination of CA-125+Hb has great predictive value and should be further assessed in future clinical trials for the diagnosis of HCC with OM. Further in-depth studies are needed to improve the accuracy of CA-125+Hb in the diagnosis of HCC with OM to enable clinical application of this biomarker.

Data Sharing Statement

No additional data available.

Ethical Approval

All research methods were approved by the committee of the medical ethics of the First Affiliated Hospital of Nanchang University and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All subjects were explained the purpose, method, potential risks and signed an informed consent form.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Xin Xiong, Rong Rong, and Li-Ying Tang are co-first authors for this study. The authors report no conflicts of interest in this work.

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