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CYFRA21-1/TG ratio as an accurate risk factor to predict eye metastasis in nasopharyngeal carcinoma

A STROBE-compliant article

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Abstract

Nasopharyngeal carcinoma (NPC) has a distinctive geographical distribution in China, especially southern China. There are several risk factors for NPC, such as Epstein-Barr virus, genetics, and environmental exposures. Although the incidence of eye metastasis (EM) is lower than metastasis in other body parts, it often indicates poor prognosis.

We assessed several serum biomarkers for their ability to predict EM in NPC. Patients with NPC were selected (n = 963), and were separated into two groups, EM and no eye metastasis. Ten factors were analyzed in both groups including triglyceride (TG), high-density lipoprotein, low-density lipoprotein, alkaline phosphatase, alpha fetoprotein, carbohydrate antigen-199, cancer antigen-153, apolipoproteins AI, apolipoprotein B, and cytokeratin fragment 19 (CYFRA21-1). Independent *t* tests, binary logistic regression, and receiver operating characteristic curves were used to assess the data.

The EM group had significantly higher CYFRA21-1 and lower TG compared with the no eye metastasis group. Areas under the curve for CYFRA21-1, TG and CYFRA21-1/TG were 0.966, 0.771, and 0.976, respectively. The corresponding cut-off values were 12.12 ng/ml, 0.41 mmol/L, and 13.5. The sensitivity and specificity of CYFRA21-1/TG were 100% and 92.2%, respectively.

The increased ratio of CYFRA21-1 to TG can be an accurate method to detect EM in patients with NPC.

Abbreviations: AUC = area under the curve, CYFRA21-1 = cytokeratin fragment 19, EM = eye metastasis, NEM = non-eye metastasis, NPC = nasopharyngeal carcinoma, ROC = receiver operating characteristic, TG = triglyceride.

Keywords: cytokeratin fragment 19, eye metastasis, primary nasopharyngeal carcinoma, risk factor, triglyceride

1. Introduction

Nasopharyngeal carcinoma (NPC) is a multifactorial, complex disease that originates from the surface epithelium. Most cases of NPC are squamous cell carcinoma.[1] Based on differentiation, NPC can be divided into 3 histological categories: keratinizing, non-keratinizing, and undifferentiated.[2] NPC affects individuals throughout the world, but prevalence rates are especially high in southeast Asia, Greenland, and southern China.[3] In Taiwan, the incidence of NPC is 5.4 cases per 100,000 people.[4]

Due to the abundant blood supply and lymphatic drainage circulation, there are significant differences between NPC and other head and neck tumors, which increases the risk of NPC metastasis to farther distances than in the case of other head and neck tumors.[5,6] The major distal metastasis sites are the bone, lung, liver, and lymph nodes.[7] However, metastasis to the eye is relatively rare. On the basis of existing detection and diagnosis methods, patients with NPC have a 1- and 5-year survival rates of 92% and 70%, respectively, and 20% to 25% of survivors will eventually develop metastatic disease.[8]

NPC has a satisfactory response to radiation therapy; however, if there is distal metastasis and a higher degree of malignancy, a combination of chemotherapy and radiotherapy is required to improve the long-term survival rate. Even with sufficient treatment, almost all metastasis will develop within 3 years. Tumor metastasis becomes the primary determinant of NPC mortality.[6]

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SJP and CFW contributed equally to this work.

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Epstein-Barr virus has been closely associated with NPC, and viral DNA in blood circulation is a highly sensitive and specific marker for detecting NPC.[9,10] Regrettably, many cases are asymptomatic, some patients are not diagnosed with NPC until the advanced stage, thus has a lower survival rate. The 5-year survival rate for stage IV is only 60%,[11] and these patients may not respond to treatment and have a higher incidence of regional recurrence.[3] Meanwhile, there are molecular markers used to predict metastasis, probably because of their low sensitivity and specificity.[11] It is therefore urgent to identify molecular markers with high specificity and sensitivity, which are immediate and convenient for detection of metastasis. In the present study, we collected data from patients with NPC eye metastasis (EM) and evaluated the blood concentrations of 10 potential factors to clarify their predictive values for detecting EM. We also combined them with triglyceride (TG) and cytokeratin fragment 19 (CYFRA21-1) to obtain the best prediction accuracy.

2. Patients and methods

2.1. Ethics statement

This study was supported by the Medical Research Ethics Committee of the First Affiliated Hospital of Nanchang University. All subjects signed informed consent forms and agreed to participate in this research. All procedures of this study were conducted in accordance with the Declaration of Helsinki. The IRB approval number is cdyfy2016011.

2.2. Patients

Included patients were all diagnosed with primary NPC (n = 963) between 2002 and 2016. Patients were admitted to the hospital without previous treatment such as surgery or chemotherapy. Patients with primary eye cancer were excluded. Pathological examination of specimens extracted by surgical resection or biopsy was performed to detect primary NPC. Secondary metastasis were diagnosed by computed tomography and magnetic resonance imaging.

2.3. Study design

Clinical data including age, sex, and site of metastasis were collected from the participants' medical records. Ten tumor markers were investigated, as follows: TG, HDL (high-density lipoprotein), LDL (low-density lipoprotein), ALP (alkaline phosphatase), AFP (alpha fetoprotein), CA199 (carbohydrate antigen-199), CA153 (cancer antigen-153), ApoAI (apolipoprotein AI), ApoB (apolipoprotein B), and CYFRA21-1.

Table 1

The clinical characteristics in eye metastasis and non-eye metastasis groups.

Characteristics	EM (n = 23)	NEM (n = 940)	*P* value
Gender			
Male	16	680	
Female	7	260	
Mean age*	52.5 ± 9.4	50.6 ± 11.7	.214

* Independent *t* test was performed. $P < .05$ revealed significant difference.
EM = eye metastasis, NEM = non-eye metastasis.

2.4. Statistical analyses

Differences in age, sex, and tumor marker expression levels between the EM and non-EM (NEM) groups were evaluated by independent *t* tests. Binary logistic regression was performed to investigate independent risk factors for EM. Receiver operating characteristic (ROC) curves were also plotted, and area under the curve (AUC) values were calculated. The cut-off values, sensitivity, and specificity of risk factors were analyzed. Differences were considered significant at $P < .05$. All data were analyzed using SPSS 22.0 (IBM, USA) and Excel 2010 software.

3. Results

3.1. Demographic and clinical characteristics

The total number of patients with NPC was 963, 23 in the EM group and 940 in the NEM group. Most participants were male (72.3%), and the mean ages were 52.5 ± 9.4 and 50.6 ± 11.7 years in the EM and NEM groups, respectively ($P > .05$, *t*-test). More details are shown in Table 1 and Figures 1–3. The most common metastasis in the NEM group was to the cervical lymph nodes.

3.2. Risk factors for EM in patients with NPC

To determine whether the 10 tumor markers can be used to discriminate EM from other types of metastasis, we compared their expression levels between the EM and NEM groups. Table 2 shows that TG was significantly decreased and CYFRA21-1 was markedly increased in the EM group compared with the NEM

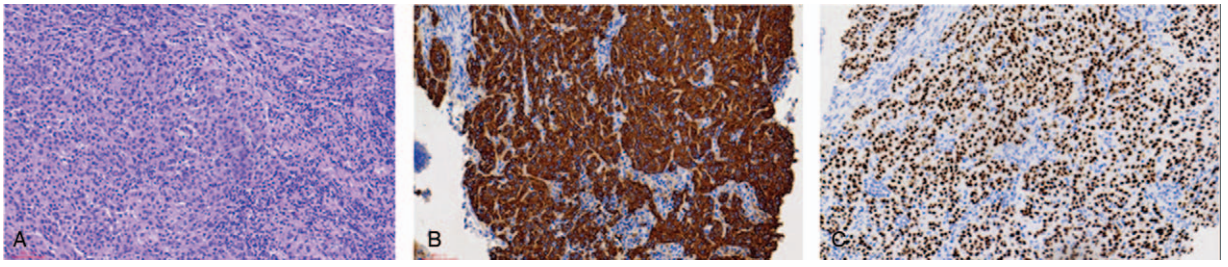


Figure 1. The hematoxylin-eosin staining and Immunohistochemistry images from nasopharyngeal carcinoma patients with eye metastasis. A. Nasopharyngeal carcinoma (HE × 200) B. P40(+)(SP × 200) C. CK(+)(SP × 200). The tissue was collected from eye metastasis site of nasopharyngeal carcinoma. HE = hematoxylin-eosin, SP = streptavidin-perosidase.

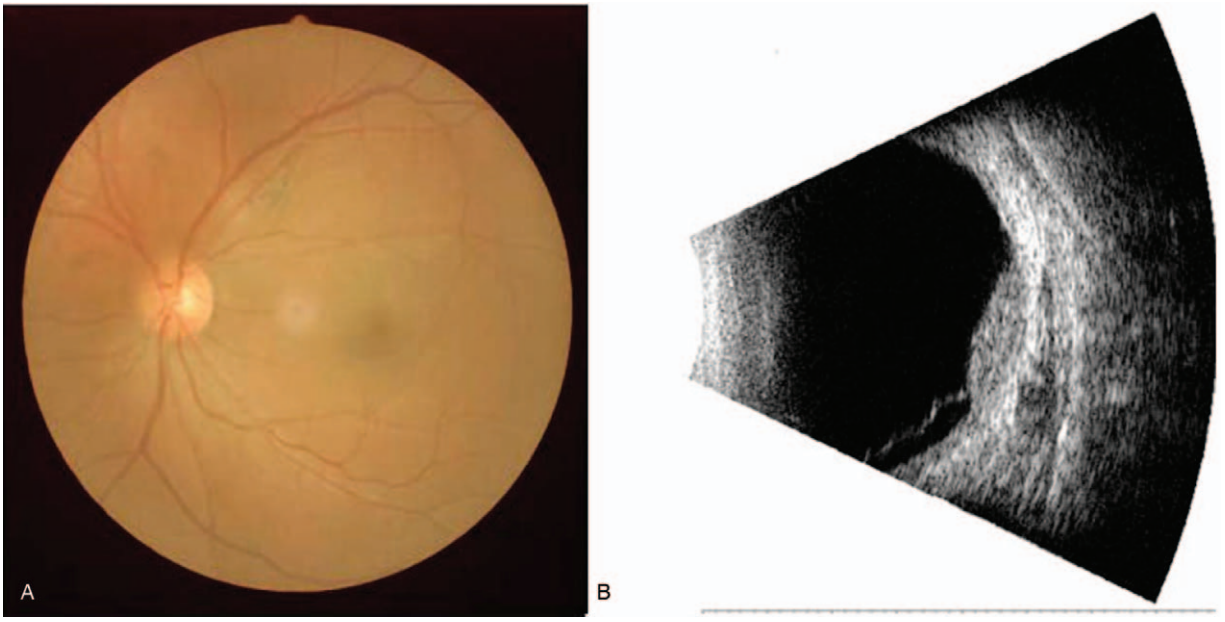
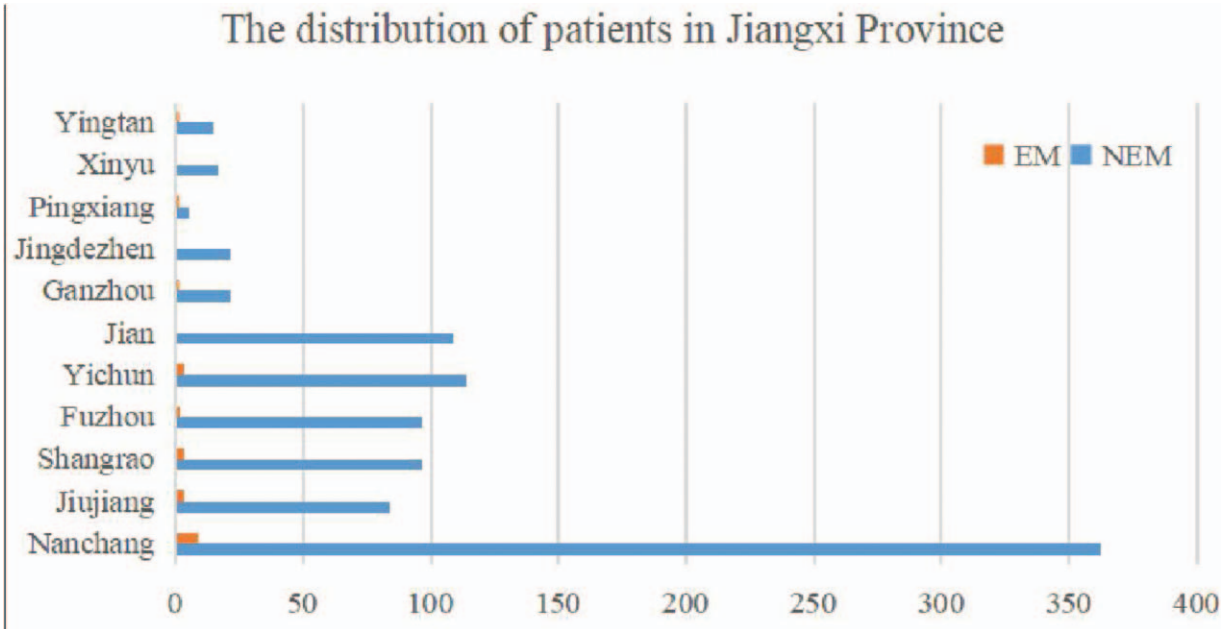


Figure 2. Example of patients with eye metastasis seen on fundus camera and eye B ultrasonic.



	Nanchang	Jiujiang	Shangrao	Fuzhou	Yichun	Jian	Ganzhou	Jingdezhen	Pingxiang	Xinyu	Yingtan
NEM	362 (38.5%)	84 (8.9%)	96 (10.2%)	96 (10.2%)	114 (12.1%)	109 (11.6%)	21 (2.2%)	21 (2.2%)	5 (0.5%)	17 (1.8%)	15 (1.6%)
EM	9 (39.1%)	3 (13.0%)	3 (13.0%)	2 (8.7%)	3 (13.0%)	0	1 (4.3%)	0	1 (4.3%)	0	1 (4.3%)

Figure 3. The distribution of patients in Jiangxi Province. There are 11 cities in Jiangxi Province including Nanchang, Jiujiang, Shangrao, Fuzhou, Yichun, Jian, Ganzhou, Jingdezhen, Pingxiang, Xinyu and Yingtan. EM = eye metastasis, NEM = non-eye metastasis.

Table 2

Comparison of tumor makers between eye metastasis and non-eye metastasis group.

Tumor marker	EM	NEM	*P* value
TG (mmol/L)	0.8 ± 0.2	1.5 ± 1.1	<.0001
HDL (mmol/L)	1.2 ± 0.5	1.3 ± 0.5	.444
LDL (mmol/L)	11.0 ± 40.8	3.2 ± 10.9	.366
ALP (U/L)	73.3 ± 19.3	84.6 ± 50.8	.287
AFP (ng/ml)	2.0 ± 2.4	1.8 ± 1.1	.657
CA199 (U/ml)	10.8 ± 29.3	5.4 ± 7.7	.387
CA153 (U/ml)	15.5 ± 10.0	14.6 ± 15.4	.786
ApoAI (g/L)	1.7 ± 0.4	1.7 ± 0.9	.901
ApoB (g/L)	1.3 ± 1.3	1.1 ± 0.8	.393
CYFRA21-1 (ng/ml)	34.1 ± 16.6	6.6 ± 12.6	<.0001

Independent *t* test was performed. $P < .05$ revealed statistical significance.
AFP = alpha fetoprotein, ALP = alkaline phosphatase, ApoAI = apolipoprotein AI, ApoB = apolipoprotein B, CA153 = cancer antigen-153, CA199 = carbohydrate antigen-199, CYFRA 21-1 = cytokeratin fragment 19, EM = eye metastasis, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NEM = non-eye metastasis, TG = triglyceride.

group ($P < .05$); however, other markers were not significantly different between the two groups ($P > .05$). The binary logistic regression results indicated that TG and CYFRA21-1 could be considered independent factors to predict EM in patients with NPC ($P < .0001$, Table 3).

3.3. Assessment of the predictive value of CYFRA21-1/TG

To analyze the predictive value of the CYFRA21-1/TG ratio, ROC curves were generated (Figs. 4 and 5). The cut-off values for TG and CYFRA21-1 were 0.41 mmol/L and 12.2 ng/ml, respectively, with AUC values of 0.771 and 0.966. Calculating the ratio of these 2 factors indicated that the sensitivity and specificity were 100% and 92.2%, respectively, and the AUC was 0.976. The results are shown in Table 4. These analyses showed that the CYFRA21-1 to TG ratio may be useful for predicting EM in patients with NPC.

4. Discussion

Eye anatomical structure is closely related to the nose and paranasal sinuses, which is associated with corresponding clinical symptoms during the process of invasion and metastasis of NPC. EM of NPC can lead to orbital bone destruction and ophthalmic nerve invasion that can result in the extraocular muscle movement disorders, as well as retinal invasion that can cause vision impairment or loss, diplopia, and other problems.[12] EM is rare because of the lack of the lymphatic vessels in the eyes and orbits.[13] In our department, only 2.3% of patients with NPC had EM.

Table 3

The binary logistic regression model between eye metastasis and non-eye metastasis group.

Tumor marker	B	Exp(B)	*P* value
TG	−2.742	0.064	.001
CYFRA21-1	0.049	1.051	<.0001

The binary logistic analysis was performed. $P < .05$ means significant difference.
B = coefficient of regression, CYFRA 21-1 = cytokeratin fragment 19, TG = triglyceride.

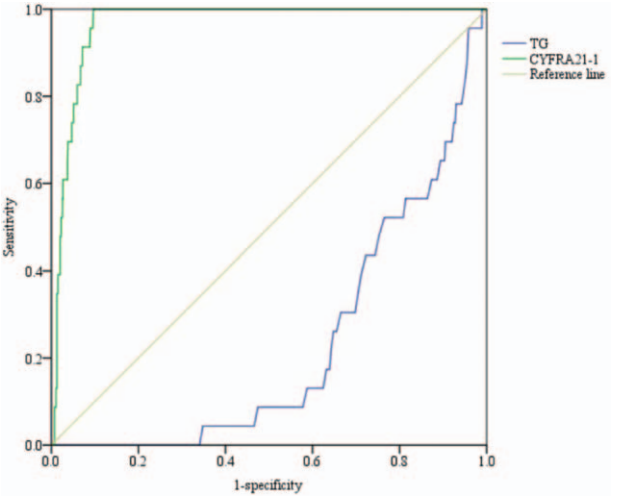


Figure 4. The receiver operating characteristic curves of different markers to predict eye metastasis in primary nasopharyngeal carcinoma. TG and CYFRA21-1 were performed as single factor of detecting EM in ROC curves. The line of CYFRA21-1 above reference line revealed the increased level in EM group, compared with NEM group. Additionally, the line of TG below reference line indicated less expression in EM group than that in NEM group. TG = triglyceride, EM = eye metastasis, ROC = receiver operating characteristic, CYFRA 21-1 = cytokeratin fragment 19.

EM has been reported in various cancers including lung,[14] pancreatic,[15] gastric,[16] pheochromocytoma,[17] upper gastrointestinal tract carcinoma,[18] neuroendocrine neoplasms,[19] breast,[20] renal carcinoma,[21] colorectal,[22] prostate,[23] and thyroid carcinoma[24] (Table 5).

Previous studies of risk factors[25–31] for lymphatic metastasis and distant metastases of primary NPC are shown in Table 6.

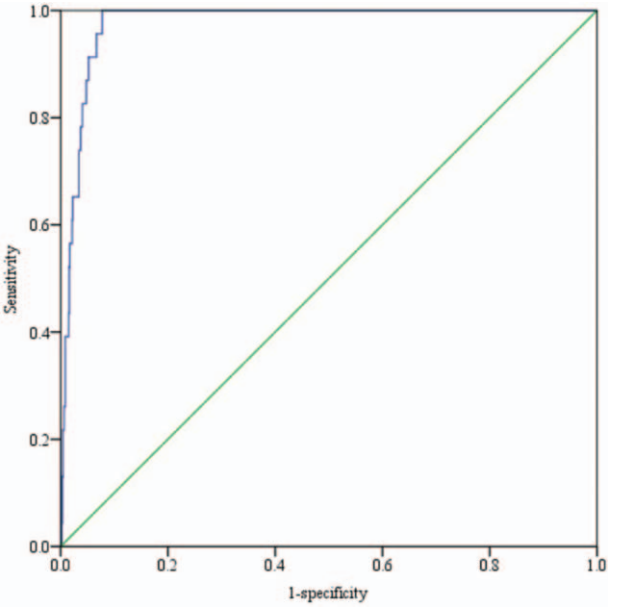


Figure 5. The receiver operating characteristic curve of cytokeratin fragment 19 to triglyceride ratio for diagnosing eye metastasis in primary nasopharyngeal carcinoma.

Table 4

The cutoff value, sensitivity, specificity and area under the curve of triglyceride, cytokeratin fragment 19 and cytokeratin fragment 19/ triglyceride in detecting the eye metastasis in metastatic nasopharyngeal carcinoma.

Tumor maker	Cutoff value	sensitivity	specificity	AUC	*P* value
TG (mmol/L)	0.41	100%	1.1%	0.771	<.0001
CYFRA21-1 (ng/ml)	12.185	100%	90.3%	0.966	<.0001
CYFRA21-1/TG	13.5	100%	92.2%	0.976	<.0001

The sensitivity and specificity were calculated at the point of Youden index. $P < .05$ indicates statistical significance.
AUC = area under the curve, CYFRA 21-1 = cytokeratin fragment 19, TG = triglyceride.

It is extremely important to identify accurate methods to detect EM in patients with NPC. Due to its undifferentiated or poorly differentiated nature, NPC is highly malignant and may not be diagnosed until the advanced stage. Additionally, EMs in NPC are usually small, and the infiltrating type cannot be detected by conventional imaging techniques unless there is a considerable degree of bone destruction and significant changes in structure density. Therefore, patients with ocular symptoms caused by advanced NPC would be extremely difficult to identify with computed tomography.[32] Since we do not fully understand the molecular mechanisms of metastasis and invasion, our treatment approach to NPC is more conservative. NPC treatment is still dominated by radiotherapy. A large accumulative amount of radiation is needed to achieve satisfactory therapeutic effects due to the deep anatomical location of the tumor.[33] However, the tumor is also near the eyes, and radiation can harm ocular structure and function. For patients with NPC, eye discomfort due to EM is indistinguishable from eye problems induced by radiation. As a result, effective biological markers with high specificity and sensitivity would be helpful to determine whether the ocular symptoms were caused by radiation or NPC EM. Depending on the etiology, patients can be treated with appropriate methods to alleviate pain and prolong survival time.

Serological markers have many advantages including minimal invasiveness and convenient acquisition. Although scientists have been aware of a number of serological markers associated with metastasis and prognosis, there are no specific serological markers for EM of NPC. In this study, TG and CYFRA21-1 were found to be useful markers.

Table 5

Studies of eye metastasis from different cancers.

Author	Year	Disease with EM
Xu et al[14]	2017	Lung cancer
Shield et al[15]	2018	Pancreatic cancer
Goto et al[16]	2019	Gastric cancer
Rider et al[17]	2019	Pheochromocytoma
Siddiqui et al[18]	2019	Upper gastrointestinal tract carcinoma
Kamieniarz et al[19]	2019	Neuroendocrine neoplasm
Welch et al[20]	2019	Breast cancer
Chumdermpadetsuk et al[21]	2019	Renal carcinoma
Min et al[22]	2020	Colorectal cancer
Pastore et al[23]	2020	Prostate cancer
Chacón González et al[24]	2020	Thyroid carcinoma

The table summed up studies on EM from different types of cancer.
EM = eye metastasis.

Table 6

The risk factors of metastases of primary nasopharyngeal carcinoma.

Author	Year	Metastatic sites	Risk factors
Chen et al[25]	2011	Distant metastasis	RNV
Zhao et al[26]	2012	Distant metastasis	LMP1
Cai et al[27]	2014	Distant metastasis	MIP-3α, cystatin A
Zheng et al[28]	2014	Lymphatic metastasis	p-Mnk1, p-eIF4E
Tang et al [29]	2016	Distant metastasis	LDL-C
Hu et al[30]	2017	Lymphatic metastasis	VEGFR2 rs2071559
Chen et al[31]	2019	Distant metastasis	EGFR

The table summed up studies on risk factors of metastases from primary NPC.
EGFR = epidermal growth factor receptor, LDL-C = low-density lipoprotein cholesterol, LMP1 = latent membrane protein, MIP-3α = macrophage inflammatory protein-3α, NPC = nasopharyngeal carcinoma, p-eIF4E = the phosphorylation of eukaryotic translation initiation factor 4E, p-Mnk1 = the phosphorylation of MAP kinase-interacting kinases, RNV = retropharyngeal nodal volume, VEGFR = vascular endothelial growth factor receptor.

Triglyceride (TG) is stored in the lipid droplets as energy to provide ATP by lipolysis. It can form phospholipids and other complex lipids. All cells can synthesize and breakdown TG. One study showed that the expression level of intracellular lipids or the size and/or number of lipid droplets were increased in various cancer cells including breast, prostate, liver, and colon.[34] Similarly, a large-scale cohort study revealed subjects with high TG may have increased risks of rectal and breast cancer.[35] These results indicate that TG may play an important role in providing energy to sustain malignant cell growth and proliferation. Notably, we found decreased blood TG in NPC patients with EM. The occurrence of EM indicates that cancer is in an advanced stage. One possible explanation is that the cancer cells grow rapidly and deplete TG levels, but the mechanism of decreased TG in NPC patients with EM requires further investigation.

CYFRA21-1 is the fragment of cytokeratin 19 in epithelial cells, especially in the pulmonary tissue.[36] It is released into serum during the late S and G2 phases of the cell cycle.[37] When cells become cancerous, metabolism is enhanced, necrosis is accelerated, and abundant CYFRA21-1 is released into the blood.[38] Elevated concentrations of serological markers are closely associated with tumor progression and invasion.[39] CYFRA21-1 has been reported as an independent predictor for small cell lung carcinoma, with elevated serum concentration suggesting a higher risk for patients for developing advanced lung cancer.[40] It is also expressed in various malignant cancers. It was reported that combining CYFRA21-1 and CA125 can be used to detect epithelial ovarian cancer.[37] Patients with head and neck cancer with a high CYFRA21-1 level are more likely to have poor prognosis.[41] Serum CYFRA21-1 level may also be able to predict NPC.[42] Rao et al reported that increased postoperative serum CYFRA21-1 and squamous cell carcinoma antigen may be risk factors for lymph node metastasis and recurrence in patients with laryngeal carcinoma.[43] Serum CYFRA21-1 can also be a prognostic factor for breast cancer liver metastasis.[44] Our results revealed significantly increased CYFRA21-1 expression in NPC patients with EM. This indicates that the cancer had progressed into an advanced stage, which is in line with previous findings.

In this study, we divided patients with NPC into 2 groups according to the presence of EM. The results showed that serum CYFRA21-1 in patients with EM was significantly increased

compared with the NEM group, and the cut-off value was 12.12 ng/ml. Meanwhile, serum TG decreased significantly compared with that of patients without metastasis, and the cut-off value was 0.41 mmol/L. To our best knowledge, this is the first time that CYFRA21-1 and TG have been associated with EM in patients NPC. Since the direction of changes for these two indicators were opposite, we calculated the ratio to obtain more significant data. After generating the ROC curve of the ratio of these 2 markers, we found the sensitivity and specificity of CYFRA21-1/TG were 100% and 92.2%, respectively. Based on these values, we hypothesize that this ratio could be used as an independent indicator for predicting EM in patients with NPC, possibly before it is evident on imaging.

There are limitations to our study. First, since it is difficult for NPC to metastasize to eyes, we were only able to analyze a small number of cases. Secondly, all the samples in this study were diagnosed with NPC, we did not perform a comparison between these samples and healthy controls. Thirdly, this was a retrospective study. We had limited information to analyze, and the materials we obtained may also have introduces recall bias. Thus, further investigations are needed to confirm our results.

In conclusion, the ratio of serum CYFRA21-1 to TG can be a reliable measure to predict the ocular metastasis of NPC.

Author contributions

Data curation: Yajie Yu.
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Investigation: Yajie Yu, Chenyu Yu, Siyi Chen, Biao Li.
Methodology: Shengjia Peng.
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Resources: Yi Shao.
Supervision: Yi Shao.
Validation: Shengjia Peng, Chufeng Wang, Siwen Tan, Yi Shao.
Visualization: Jiaxin Peng.
Writing – original draft: Shengjia Peng, Chufeng Wang.
Writing – review & editing: Shengjia Peng.

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