ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2024 February 27; 16(2): 260-634

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGS* as 2.0; IF without journal self cites: 1.9; 5-year IF: 2.2; Journal Citation Indicator: 0.52; Ranking: 113 among 212 journals in surgery; Quartile category: Q3; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Zi-Hang Xu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
February 27, 2024

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INSTRUCTIONS TO AUTHORS
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STEPS FOR SUBMITTING MANUSCRIPTS
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ONLINE SUBMISSION
https://www.f6publishing.com

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E-mail: office@baishideng.com https://www.wjgnet.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2024 February 27; 16(2): 463-470

DOI: 10.4240/wjgs.v16.i2.463

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Immune function status of postoperative patients with colon cancer for predicting liver metastasis

Le Xiong, Fang-Chen Liu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bhosale PB, South Korea

Received: December 12, 2023
Peer-review started: December 12, 2023
First decision: January 2, 2024
Revised: January 4, 2024
Accepted: January 30, 2024
Article in press: January 30, 2024
Published online: February 27, 2024

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Abstract

BACKGROUND

Colon cancer (CC) has a high incidence rate. Radical resection is the main treatment method for CC; however, liver metastasis (LM) often occurs post-surgery. The liver contains both innate and adaptive immune cells that monitor and remove abnormal cells and pathogens. Before LM, tumor cells secrete cytokines and exosomes to adjust the immune microenvironment of the liver, thus forming an inhibitory immune microenvironment for colonization by circulating tumor cells. This indicates that the immune state of patients with CC plays a crucial role in the occurrence and progression of LM.

AIM

To observe and analyze the relationship between immune status and expression of tumor factors in patients with LM of CC, and to provide a scientific intervention method for promoting the patient prognosis.

METHODS

A retrospective analysis was performed. The baseline data of 100 patients with CC and 100 patients with CC who suffered from postoperative LM and were admitted to our hospital from May 2021 to May 2023 were included in the non-occurrence and occurrence groups, respectively. The immune status of the patients and the expression of tumor factor-related indicators in the two groups were compared, and the predictive value of the indicators for postoperative LM in patients with CC was analyzed.

RESULTS

Compared with the non-occurrence group, the expression of serum carcinoembryonic antigen (CEA), CA19-9, CA242, CA72-4 and CA50 in patients in the

occurrence group were significantly higher, while the expression of CD3+, CD4+, CD8+, natural killer (NK) and CD4+/CD25 in patients in the occurrence group were significantly lower ($P < 0.05$). No significant difference was observed in other baseline data between groups ($P > 0.05$). Multivariate logistic regression model analysis revealed that the expressions of CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 were associated with the LM in patients with CC. High expressions of serum CEA, CA19-9, CA242, CA72-4 and CA50, and low expressions of CD3+, CD4+, CD8+, NK, and CD4+/CD25 in patients with CC were risk factors for LM (OR > 1, $P < 0.05$). The receiver operating characteristic curve showed that the area under curve for CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 in the prediction of LM in patients with CC were all > 0.80, with a high predictive value.

CONCLUSION
The expression of tumor factors and immune state-related indices in patients with CC is closely associated with the occurrence of LM.

Key Words: Colon cancer; Liver metastases; Immune status; Tumor factors; Predicted value

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Core Tip: Postoperative liver metastasis (LM) in patients with colon cancer (CC) leads to a poor prognosis; therefore, monitoring the risk factors that affect postoperative LM in patients with CC is crucial to improving their prognosis. The anti-tumor immune system of the body includes cellular immunity mediated by T cells and their subsets. An imbalance in the proportion of these cells or abnormalities in their function lead to a disordered immune system and a variety of immune-mediated diseases. Therefore, a correlation between postoperative LM and immune function may occur in patients with CC.

Citation: Xiong L, Liu FC. Immune function status of postoperative patients with colon cancer for predicting liver metastasis. *World J Gastrointest Surg* 2024; 16(2): 463-470
URL: https://www.wjgnet.com/1948-9366/full/v16/i2/463.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i2.463

INTRODUCTION

The incidence of colon cancer (CC) is high in China, and the liver is the main organ involved in CC metastasis. A previous report showed that approximately 20% and 25% of patients with CC develop simultaneous liver metastasis (LM) and LM after radical surgery, respectively. Some important factors may lead to a poor prognosis and an increased risk of LM in patients with CC. Therefore, exploring these factors is important for guiding advanced intervention and promoting patient prognosis[1-3]. The microenvironment before tumor metastasis is favorable for tumor cell colonization at a distance, and its formation is completely determined by the interaction between the primary lesion and the metastatic organ. Macrophages, hepatocytes, and neutrophils in the liver have significant tumor-promoting functions during cancer cell metastasis. Tumor cells in the primary lesion interfere with the liver microenvironment through many pathways, such as the portal vein system, in the early stage, resulting in an environment conducive to tumor cell colonization and growth[4,5]. The liver contains congenital and adaptive immune cells that monitor and eliminate abnormal cells and pathogens. The innate immune system of the liver includes natural killer (NK) cells, monocytes, and liver macrophages, which maintain the balance between immune activation and tolerance. Before LM, tumor cells secrete cytokines and exosomes to regulate the liver immune microenvironment, thereby forming an inhibitory immune microenvironment for colonization by circulating tumor cells. Notably, the immune state of CC patients plays a crucial role in the occurrence and progression of LM[6-8]. The clinical studies on the relationship between immune state-related factors and LM in patients with CC are limited. Therefore, this study focused on the immune state of patients with LM of CC and the related expression of tumor factors and analyzed their relationship with the occurrence of LM of CC to provide a scientific intervention to promote the patient prognosis.

MATERIALS AND METHODS

General data

Baseline data of 100 patients with CC who were admitted to our hospital from May 2021 to May 2023 were included in the non-occurrence group using retrospective analysis. This group included 58 males and 42 females with an age range of 42 to 70 years, with an average of 62.25 ± 3.75 years. The baseline data of 100 patients with CC with postoperative LM treated in the same period were included in the occurrence group. This group included 61 males and 39 females with an age range of 40 to 73 years, with an average of 63.02 ± 3.88 years.

Inclusion and exclusion criteria

Inclusion criteria: The diagnosis of CC was performed by referring to the Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer (2020 edition)[9] and confirmed using a case puncture or surgical pathology examination. LM of CC was based on relevant evidence in the China guideline for diagnosis and comprehensive treatment of colorectal liver metastases (version 2023)[10] and was confirmed based on clinical signs, manifestations, imaging, and pathological examination. Clinical manifestations included changes in stool traits, changes in defecation habits, abdominal discomfort or pain, and palpable masses. Additionally, CT scan and B-type ultrasound imaging analyses were performed. Pathological diagnosis for LM of CC was confirmed through a case puncture or surgical pathology. All operations related to CC were successfully performed in our hospital. The baseline data and laboratory tests of the patients were properly preserved.

Exclusion criteria: Patients with other site metastases, liver and kidney failure, CC recurrence, other intestinal diseases, mental history or antipsychotic medication (resulting in decreased compliance), or LM before surgery were excluded.

Methods

Baseline data collection method: The baseline data of the patients, including sex, age, and tumor stage, were analyzed.

Detection methods of laboratory indicators: Collecting five milliliters of fasting peripheral venous blood of each patient, and serum was collected after high-speed centrifugation. Immune-related factors, including NK cells, CD3+, CD4+, CD8+, and CD4+/CD25 in the serum, were detected using Agilent flow cytometers (NovoCyte Quanteon). Tumor factors, including serum carcinoembryonic antigen (CEA), CA242, CA72-4, CA19-9, and CA50 levels, were detected using chemiluminescence kits (Abbott, China).

Statistical analyses

Statistical analyses were performed using SPSS 24.0 software. All measurement data were subjected to the Shapiro–Wilk normality test. Data conforming to a normal distribution were expressed as mean ± SD, and comparisons between groups were performed using an independent sample *t* test. The countable data were expressed as % using the χ^2 test. Logistic regression analysis was used to observe the correlation between each indicator and patients with LM of CC. The receiver operating characteristic (ROC) curve of the patients was drawn, and the value of the main indicators for predicting LM in patients with CC after surgery was tested. The area under curve (AUC) ≤ 0.50 represented no predictive value, 0.50 < AUC ≤ 0.70 represented low predictive value, 0.70 < AUC ≤ 0.90 represented medium predictive value, and AUC >0.90 represented high predictive value. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of baseline data and laboratory indicators

Compared with the non-occurrence group, the expression of serum CEA, CA19-9, CA242, CA72-4 and CA50 in patients in the occurrence group were significantly higher, while the expression of CD3+, CD4+, CD8+, NK and CD4+/CD25 in patients in the occurrence group were significantly lower ($P < 0.05$). No significant difference was observed in other baseline data between the groups ($P > 0.05$; Table 1).

Logistic regression analysis of the relationship between immunity-related indicators, tumor-related indicators, and LM of CC

The levels of serum CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 in patients with CC were considered the covariates, and LM was considered the dependent variable (1 = occurred and 0 = not occurred). A multivariate logistic regression model analysis showed that the expression of CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 was associated with LM in patients with CC. High expressions of serum CEA, CA19-9, CA242, CA72-4 and CA50, and low expressions of CD3+, CD4+, CD8+, NK, and CD4+/CD25 in patients with CC were risk factors for LM (OR > 1, $P < 0.05$; Table 2).

Analysis of immune-related and tumor-related indicators in predicting the correlation between LM and CC

The levels of serum CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 in patients with CC were considered test variables, and LM was considered the state variable (1 = occurred, 0 = not occurred). Further, ROC curves were drawn (Figure 1). The results indicated that the AUC of CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 for predicting LM in patients with CC were all >0.80, with a high prediction value (Table 3).

DISCUSSION

Cellular carcinogenesis is a dynamic process. During different periods, different stimulation and agonist factors work together or in sequence to induce disease and accelerate disease progression. Notably, the immune state of the body is also one of the stimulation factors. The anti-tumor immune system mainly involves cellular immunity mediated by T cells and their subsets. An imbalance in the proportion of these cells or abnormalities in their function lead to a disordered

Table 1 Comparison of baseline data and laboratory indicators of patients between the two groups

Data		Occurrence group (*n* = 100)	Non-occurrence group (*n* = 100)	Statistical values	*P* value
Sex	Male	61 (61.00)	58 (58.00)	$\chi^2 = 0.187$	0.666
	Female	39 (39.00)	42 (42.00)		
Age		63.02 ± 3.88 (49-71)	62.25 ± 3.75 (53-71)	$t = 1.427$	0.155
Tumor site	Right hemicolon	40 (40.00)	45 (45.00)	$\chi^2 = 0.512$	0.475
	Left hemicolon	60 (60.00)	55 (55.00)		
Tumor typing	Infiltration type	22 (22.00)	30 (30.00)	$\chi^2 = 0.189$	0.389
	Ulcer type	35 (35.00)	30 (30.00)		
	Uplift type	45 (45.00)	40 (40.00)		
CEA (μg/L)		8.95 ± 1.30	5.25 ± 1.52	$t = 18.499$	< 0.001
CA19-9 (IU/mL)		42.25 ± 8.25	22.56 ± 4.58	$t = 20.867$	< 0.001
CA242 (U/mL)		142.25 ± 20.52	85.65 ± 15.05	$t = 17.055$	< 0.001
CA72-4 (U/mL)		55.85 ± 10.58	23.25 ± 5.28	$t = 27.570$	< 0.001
CA50 (U/mL)		42.25 ± 6.25	32.15 ± 4.20	$t = 13.413$	< 0.001
CD3+ (%)		53.45 ± 5.52	67.50 ± 8.40	$t = 13.978$	< 0.001
CD4+ (%)		26.58 ± 3.45	37.35 ± 4.10	$t = 20.100$	< 0.001
CD8+ (%)		24.52 ± 4.10	33.02 ± 6.50	$t = 11.060$	< 0.001
NK (%)		31.25 ± 3.85	45.20 ± 5.15	$t = 21.695$	< 0.001
CD4+/CD25 (%)		5.10 ± 2.15	9.52 ± 3.56	$t = 10.628$	< 0.001

CEA: Carcinoembryonic antigen; NK: Natural killer.

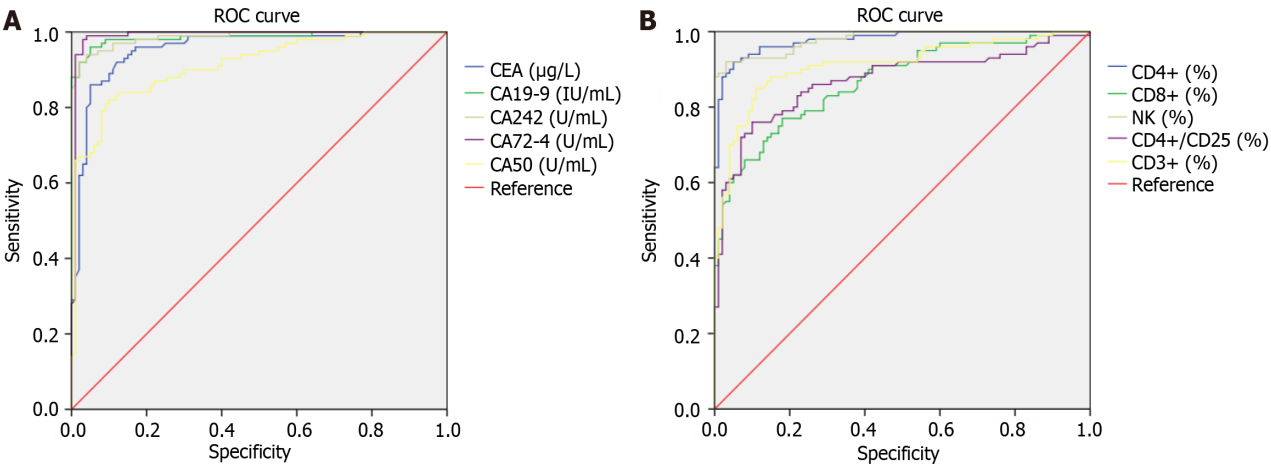

Figure 1 Receiver operating characteristic curve. A: Receiver operating characteristic (ROC) curve of tumor factor-related indices for predicting liver metastasis in patients with colon cancer; B: ROC curve of immune state-related indicators for predicting liver metastasis in patients with colon cancer. ROC: Receiver operating characteristic; CEA: Carcinoembryonic antigen; NK: Natural killer.

immune system and a variety of immune-mediated diseases[11-13]. Therefore, the immune status of patients with cachexia is critical.

Our results indicated that the levels of serum CEA, CA19-9, CA242, CA72-4 and CA50 in patients in the occurrence group were higher than those in the non-occurrence group, while the expression of CD3+, CD4+, CD8+, NK and CD4+/CD25 in patients in the occurrence group were lower than those in the non-occurrence group. A multivariate logistic regression model indicated that the expression of CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 was associated with LM in patients with CC. High expressions of serum CEA, CA19-9, CA242, CA72-4 and CA50, and low expressions of CD3+, CD4+, CD8+, NK, and CD4+/CD25 in patients with CC were risk factors for LM, indicating that these indicators can be used to predict LM in patients with CC. Tumor markers are macromolecular

Table 2 Logistic regression analysis of the relationship between immune-related indicators, tumor-related indicators, and liver metastasis in colon cancer

Variable	B	SE	Walls	*P* value	OR value	95% confidence interval	
						Upper limit	Lower limit
Constant	-14.183	2.230	40.440	< 0.001	0.000	-	-
CEA	1.953	0.299	42.755	< 0.001	7.051	3.926	12.662
CA19-9	0.483	0.081	35.206	< 0.001	1.620	1.382	1.900
CA242	0.163	0.027	37.738	< 0.001	1.177	1.117	1.240
CA72-4	0.630	0.178	12.509	< 0.001	1.878	1.324	2.662
CA50	0.367	0.051	51.721	< 0.001	1.443	1.306	1.595
CD3+	0.318	0.045	49.250	< 0.001	1.374	1.258	1.502
CD4+	0.85	0.127	40.082	< 0.001	2.236	1.743	2.869
CD8+	0.255	0.084	9.257	< 0.001	1.291	1.095	1.521
NK	0.582	0.111	27.604	< 0.001	1.790	1.440	2.224
CD4+/CD25	0.476	0.091	27.525	< 0.001	1.610	1.348	1.923

OR: Odds ratio; CEA: Carcinoembryonic antigen; NK: Natural killer.

Table 3 Efficacy analysis of the relationship between immune-related and tumor-related indicators in predicting liver metastasis in colon cancer

Indicator	AUC	95% CI for AUC	Standard error	*P* value	Cut-off value	Sensitivity	Specificity
CEA	0.956	0.927-0.984	0.014	< 0.001	4.170	0.990	0.770
CA19-9	0.986	0.972-1.000	0.007	< 0.001	21.820	0.990	0.640
CA242	0.987	0.976-1.000	0.006	< 0.001	89.915	0.990	0.420
CA72-4	0.990	0.976-1.000	0.007	< 0.001	28.625	0.990	0.150
CA50	0.912	0.872-0.952	0.020	< 0.001	28.985	0.990	0.780
CD3+	0.912	0.870-0.954	0.021	< 0.001	46.925	0.990	0.900
CD4+	0.978	0.962-0.995	0.008	< 0.001	26.725	0.990	0.480
CD8+	0.869	0.820-0.917	0.025	< 0.001	19.290	0.990	0.900
NK	0.980	0.965-0.995	0.008	< 0.001	32.430	0.990	0.370
CD4+/CD25	0.870	0.818-0.922	0.027	< 0.001	0.015	0.990	0.990

AUC: Area under curve; CEA: Carcinoembryonic antigen; NK: Natural killer.

proteins synthesized and secreted by tumor lesions during their occurrence and progression. They can exist in the nuclei, cytoplasm, and cytomembranes of tumor cells and can be detected after their entry into the blood, such as CEA, CA19-9, and CA242[14]. CEA is present on the surface of cancer cells differentiated from endodermal cells, 90% of which are involved in cell adhesion in colorectal cancer. CEA expression is higher in malignant tumors than in normal tissues, thus playing a crucial role in the occurrence, development, and prognosis of colorectal, pancreatic, and liver cancers[15]. CA19-9 is a mucin-type glycoprotein antigen that is mainly isolated from colorectal cancer tissues at an early stage and can accelerate the distant metastasis of cancer cells by mediating the adhesion of cachexia cells to vascular endothelial cells[16]. CA72-4 is a high-molecular-weight glycoprotein antigen, and its expression is extremely low in healthy conditions; usually, < 6 U/mL in the serum. When cancer lesions occur in the digestive system of the body, the expression of CA72-4 increases rapidly and continues thereafter[17]. CA50 is a sialic acid ester and a protein that cannot be detected in normal tissues. With cell deterioration, increased activity of glycosylation enzymes, and changes in glycosyl structure on the cell surface, CA50 has been confirmed to be closely related to the occurrence and progress of the colorectal and pancreatic cancers[18]. CA242 belongs to the sialylated mucin lipid antigen family and can identify the sialylated sugars shed by malignant tumor cells of many organs into the serum[19]. CC occurrence, progression, and prognosis are closely associated with the immune status of the body. T lymphocytes, the main effector cells of cellular

immunity, are pivotal in controlling the growth and reproduction of tumor cells[20]. CD3+ and CD4+ cells assist in humoral immunity by mediating immune responses and stimulating the anti-tumor effects of NK cells, cytotoxic T cells, and B lymphocytes. CD8+ cells are cytotoxic T cells with high killing activity that negatively regulate immune responses. NK cells are widely distributed in peripheral lymphocytes and blood and are congenital effector cells. They can help the body prevent the invasion of external viruses and bacteria and remove tumor cells to achieve innate immunity[21]. CD4+/CD25 cells exhibit an immunosuppressive effect mainly by secreting cytokines. These cells function as CD4+ and CD8+ T cells secreting their factors, which can inhibit the anti-tumor effect *in vivo* and assist the body in immune escape from malignant tumors. Notably, the expression and function of these cells help to maintain the normal immune ability of the body[22].

To explore the relationship between the above tumor factors, immune state-related indicators, and LM in patients with CC, the ROC curve was drawn in this study. The results indicated that the AUC of CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 for the prediction of LM in patients with CC were all > 0.80, with a high prediction value. This indicates that these indicators could be used clinically for the assessment of LM in patients with CC. However, the sample size of this study was limited, and a retrospective analysis was performed. Further, limitations in the inclusion of relevant indicators also exist. Therefore, the credibility of the study needs to be verified using a larger sample size.

CONCLUSION

The expression of tumor factors and immune state-related indicators in patients with CC is closely associated with LM. Clinical intervention for indicators with abnormal expression can be analyzed in a timely manner by detecting the expression of tumor factors and immune state-related indicators to reduce the risk of LM in patients with CC.

ARTICLE HIGHLIGHTS

Research background

Colon cancer (CC) has a high incidence. Liver metastasis (LM) easily occurs after radical resection of CC. The liver maintains a congenital adaptive immune system. Liver metastases after CC surgery significantly affect the patient's prognosis. Before LM, tumor cells secrete cytokines and exosomes to regulate the liver immune microenvironment and form an inhibitory immune microenvironment for the colonization of circulating tumor cells. Therefore, the immune function in patients after CC surgery is associated with LM.

Research motivation

LM after CC surgery seriously affects patient prognosis, and identifying the risk factors that affect LM after CC surgery is crucial for its early prevention and improving patient prognosis.

Research objectives

To observe the expression of immune function factors in patients with LM of CC and explore their correlation with LM.

Research methods

Analysis of variance and logistic regression analysis.

Research results

The expressions of serum carcinoembryonic antigen (CEA), CA19-9, CA242, CA72-4 and CA50 in patients in the occurrence group were significantly higher compared with the non-occurrence group, while the expression of CD3+, CD4+, CD8+, natural killer (NK) and CD4+/CD25 in patients in the occurrence group were significantly lower compared with the non-occurrence group ($P < 0.05$). Multivariate logistic regression indicated that the expressions of CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 were associated with LM in patients with CC. High expressions of serum CEA, CA19-9, CA242, CA72-4 and CA50, and low expressions of CD3+, CD4+, CD8+, NK, and CD4+/CD25 in patients with CC were risk factors for LM (OR > 1, $P < 0.05$). The ROC curve indicated that the AUC of CEA, CA19-9, CA242, CA72-4, CA50, CD3+, CD4+, CD8+, NK, and CD4+/CD25 in the prediction of LM in patients with CC were all > 0.80, with a high predictive value.

Research conclusions

The expression of tumor factors and immune state-related indices in patients with CC is closely associated with the occurrence of LM.

Research perspectives

Postoperative LM in patients with CC is related to many factors, including the immune system, which plays a crucial role in the body's resistance to tumors. When the immune system is destroyed or becomes dysfunctional, the immune state of the body is disordered, leading to the occurrence of diseases caused by immune disorders, including LM. Therefore, a

correlation between postoperative LM and immune function has been speculated in patients with CC.

FOOTNOTES

Author contributions: Xiong L and Liu FC contributed equally to this work; Xiong L and Liu FC designed the study; Xiong L contributed to the analysis of the manuscript; Xiong L and Liu FC involved in the data and writing of this article; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the [Xiangyang No. 1 People's Hospital, Hubei University of Medicine] Institutional Review Board (No. XYYYE20230123).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors have no conflicts of interest.

Data sharing statement: No additional data are available.

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S-Editor: Yan JP
L-Editor: A
P-Editor: Zhao S

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