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ORIGINAL RESEARCH

Relationship Between MIC-1, VEGF, and TGF-β1 and Clinicopathologic Stage and Lymph Node Metastasis in Gastric Cancer

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Objective: This research investigated the relationship between serum macrophage inhibitory cytokine-1 (MIC-1), vascular endothelial growth factor (VEGF), and transforming growth factor-β1 (TGF-β1) levels and clinicopathologic features, lymph node metastasis (LNM), and prognosis of gastric cancer (GC) patients.

Methods: The GC group (GC patients, 198 cases)) and healthy group (healthy people, 100 cases) were established. The relationship between serum MIC-1, VEGF, TGF-β1, and clinical and pathological features in GC patients was analyzed. GC patients were divided into a metastasis group (77 patients) and a non-metastasis group (121 patients) based on whether they had LNM. The factors influencing LNM in GC patients were identified. The predictive value of serum MIC-1, VEGF, and TGF-β1 for LNM in GC patients and the relationship between serum MIC-1, VEGF, TGF-β1 levels and prognosis were analyzed.

Results: MIC-1, VEGF, and TGF-β1 were higher in GC. Serum MIC-1, VEGF, and TGF-β1 levels were higher in GC patients with tumor diameter ≥ 3 cm, T stage of T3 and T4, low/moderate differentiation, and LNM. Multivariate Logistic regression analysis showed that TNM stage, tumor differentiation, and serum MIC-1, VEGF, and TGF-β1 levels were risk factors for LNM in GC patients. The ROC results indicated that the combination of serum MIC-1, VEGF, and TGF-β1 had the highest AUC for predicting LNM in GV patients. The median survival time of patients with low serum MIC-1, VEGF, and TGF-β1 was higher than that of patients with high serum MIC-1, VEGF, and TGF-β1 (26.13 months vs 19.24 months, 27.06 months vs 20.18 months, and 24.20 months vs 20.08 months).

Conclusion: The changes of serum MIC-1, VEGF and TGF-β1 levels are related to the clinicopathological characteristics of GC patients, and the elevated levels of these indices are independent risk factors affecting LNM and prognosis of GC patients.

Keywords: gastric cancer, macrophage inhibitory cytokine-1, vascular endothelial growth factor, transforming growth factor-β1, lymph node metastasis, clinicopathological characteristics, prognosis

Introduction

Gastric cancer (GC) is a highly heterogeneous disease based on both its molecular profile and phenotypical features.[1] The most common cause of GC is Helicobacter pylori infection, while Epstein Barr Virus may be involved in 10% of cases.[2] Most GC patients are diagnosed late in their disease, which results in a low 5-year overall survival rate.[3] It is common for GC patients to have lymph node metastasis (LNM) when they are initially diagnosed or underwent surgery, which results in poor prognosis in most cases.[4] Early identification of LNM is crucial for the patient's outcome since LNM has been reported to be one of the most important prognostic factors in GC.[4] Despite intensive research into LNM in GC in recent years, the molecular mechanisms behind their formation are still unresolved.[5] It may therefore be possible to develop better methods of early detection of GC by exploring these mechanisms.

The multifaceted cytokine known as macrophage inhibitory cytokine-1 (MIC-1) shows increased levels in a range of cancers. MIC-1 is responsible for controlling several key cancer characteristics, such as proliferation and

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inflammation, preventing immune system damage, triggering cell invasion, metastasis, blood vessel formation, and resistance to cell death.[6] MIC-1 expression and serum levels are elevated after many stressful stimuli or during many disease processes, notably cancer.[7] There is evidence that MIC-1 can serve as a diagnostic marker in pancreatic cancer,[8] colorectal cancer,[9] and GC.[10] Xin Ge et al point out that in most patients with early GC, the level of serum MIC-1 is notably increased. MIC-1 has the potential to be a new diagnostic biomarker for early GC and can help assess the risk of developing GC.[10] It is noteworthy that Jaeseob Lee et al have confirmed that melanoma cells, in response to oxygen deprivation, produce MIC-1, which stimulates tumor vascularization during melanoma progression in vivo, ultimately accelerating tumor growth and metastasis.[11] It is evident that MIC-1 is closely related to cancer metastasis, thus selecting MIC-1 as the research subject aids in gaining a deeper understanding of the malignant biological behavior of GC. Moreover, vascular endothelial growth factor (VEGF) is a growth factor that has pro-angiogenic actions and also acts as an anti-apoptotic, mitogenic and permeabilizing factor on endothelial cells.[12] A fundamental function of VEGF signaling through its receptors is to suppress antitumor immune cell activity.[13] VEGF is highly expressed in GC and has a direct effect on its occurrence and development, and can be considered as crucial biomarkers for early diagnosis of GC and precancerous lesions.[14] VEGF seems to serve as a reliable indicator for disease onset and remission.[15] The presence of VEGF in GC patients has been shown to affect tumor incidence, metastasis, and prognosis.[16] Therefore, studying the expression level of VEGF in GC helps assess the malignancy of GC and predict the prognosis of patients. The widespread cytokine known as transforming growth factor-β1 (TGF-β1) ranks among the strong agents triggering metastasis.[17] TGF-β1 levels are associated with aggressive tumor features.[18,19] TGF-β1 holds the key to epithelial to mesenchymal transformation in cancer mechanisms of metastasis[20,21] and enhances the migration and invasion of metastatic GC cells into the liver.[22] Consequently, investigating the expression level of TGF-β1 in GC contributes to unveiling the metastatic mechanisms of GC.

Based on the significant roles of MIC-1, VEGF, and TGF-β1 in the initiation and progression of GC in cancer, as well as the established research background, this study was designed to explore the evaluation of MIC-1, VEGF, and TGF-β1 in clinical staging and LNM of GC patients, thereby offering an accurate detection methods to classify disease grade and thus improve prognosis.

Materials and Methods

Ethical Statement

This study conformed to the Declaration of Helsinki and has been approved by the Ethics Committee of Pingdingshan University, and the patients and their families gave informed consent.

Study Patients

GC patients (n = 198) admitted to Pingdingshan University from May 2018 to March 2021 were selected as the GC group, of which 102 cases were male and 96 cases were female, with an average age of (60.57 ± 4.86) years old. In the same period, 100 cases of healthy people with gastric physical examination at Pingdingshan University were selected as the healthy group, of which 54 cases were male and 46 cases were female, with an average age of (61.18 ± 5.33) years old. The difference between the two groups in terms of gender, age and other general information was not statistically significant ($P > 0.05$).

Inclusion Criteria

Patients in the GC group were newly diagnosed with GC by pathology and underwent gastrectomy with D2 lymph node dissection; Patients had complete preoperative laboratory test results; Patients had available lymph node tissue samples and complete clinical data and follow-up data.

Exclusion Criteria

Patients with comorbid severe cardiovascular and cerebrovascular diseases; Patients with a comorbid history of multiple tumors; Patients who received other treatments such as radiotherapy, chemotherapy and targeted drug therapy before surgery; Patients without follow-up data; Patients with comorbid psychiatric diseases and poor patient compliance.

Detection Methods

For the GC group, 5 mL of venous blood was drawn from the upper limb on an empty stomach 2 days before surgery upon admission, anticoagulated with 2% ethylenediaminetetraacetic acid, and centrifuged at 3000 r/min for 20 min. After centrifugation, the serum was separated carefully and stored at −80°C. Serum MIC-1, VEGF, and TGF-β1 were measured by enzyme-linked immunosorbent assay. All the test procedures were performed according to the MIC-1 kit (Boyao, Shanghai, China), VEGF kit (Shanghai Yuan Mu Biotechnology Co., Ltd., Shanghai, China), and TGF-β1 kit (Jingmei Biotech Co., Ltd., Shanghai, China).

Observation Indicators

Serum MIC-1, VEGF, and TGF-β1 between the GC group and the healthy group were compared. General data were collected, including gender, age, etc. Pathological data of GC patients were collected, including tumor size, TNM stage, degree of differentiation, and LNM. Serum MIC-1, VEGF and TGF-β1 levels in GC patients with different clinicopathologic features were measured to assess their relationship with clinicopathologic features of GC patients.

The clinical information of GC patients was collected, and the patients were divided into two subgroups: metastasis group and non-metastasis group, according to the presence of LNM. Relevant risk factors affecting LNM in GC patients were analyzed.

All GC patients were followed up for 36 months ending March 2024 by telephone and outpatient visits. Survival of GC patients was recorded. The median values of serum MIC-1, VEGF, and TGF-β1 levels of GC patients were used as the boundaries, and patients with lower than median values were considered as low level patients, and patients with higher than median values were considered as high level patients. The relationship between serum MIC-1, VEGF, and TGF-β1 levels and prognosis of GC patients was analyzed.

Statistical Analysis

SPSS 22.0 software (IBM, NY, USA) and GraphPad Prism 6.0 software (Graph Pad Inc., CA, USA) were applied to process the data, and the measurement data (in normal distribution and homogeneity of variance) were expressed as mean ± standard deviation, and enumeration data were expressed as n (%). The two-by-two comparison of the measurement data between groups was analyzed by *t*-test. Enumeration data were analyzed by χ^2 test. Univariate analysis and multivariate Logistic regression analysis were conducted to identify risk factors for LNM in GC patients. Receiver Operating Characteristic (ROC) curves were plotted to analyze the predictive value of serum MIC-1, VEGF, and TGF-β1 for LNM in GC patients. The optimal cut-off values were determined using the maximum Youden index method. Kaplan-Meier survival curves were used to analyze the relationship between serum MIC-1, VEGF, TGF-β1 and the prognosis of GC patients. The test level was $\alpha = 0.05$, and $P < 0.05$ was regarded as a statistically significant difference.

Results

Serum MIC-1, VEGF, and TGF-β1 Levels Between the GC Group and the Healthy Group

MIC-1, VEGF, and TGF-β1 in the GC group were significantly higher than those in the healthy group ($P < 0.05$). It is suggested that MIC-1, VEGF, and TGF-β1 may be involved in GC (Table 1).

Serum MIC-1, VEGF, and TGF-β1 Levels in GC Patients with Different Clinicopathologic Features

Serum MIC-1, VEGF, and TGF-β1 levels were higher in GC patients with tumor diameters ≥ 3 cm, T stages T3 and T4, low/moderate differentiation, and LNM than those with tumor diameters < 3 cm, T stages T1 and T2, high differentiation, and no LNM ($P < 0.05$). Changes in serum MIC-1, VEGF, and TGF-β1 levels were not related to gender and age, while changes in serum levels of MIC-1, VEGF, and TGF-β1 were associated with the clinicopathological characteristics of GC patients (Table 2).

Table 1 Comparison of Serum MIC-1, VEGF, and TGF-β1 Levels Between the Two Groups

Groups	MIC-1 (μg/L)	VEGF (pg/mL)	TGF-β1 (pg/mL)
GC group (n=198)	23.12 ± 4.84	410.23 ± 61.18	519.93 ± 93.36
Healthy group (n=100)	3.29 ± 0.91	92.86 ± 12.84	59.04 ± 9.57
P-value	< 0.001	< 0.001	< 0.001

Abbreviations: GC, gastric cancer; MIC-1, Macrophage inhibitory cytokine-1; VEGF, Vascular endothelial growth factor; TGF-β1, Transforming growth factor-β1.

Table 2 Comparison of Serum MIC-1, VEGF, and TGF-β1 Levels in GC Patients with Different Clinicopathologic Features

Categorization	n	MIC-1 (μg/L)	VEGF (pg/mL)	TGF-β1 (pg/mL)
Gender				
Male	102	22.79 ± 4.87	406.53 ± 60.92	513.57 ± 92.41
Female	96	23.47 ± 4.80	414.17 ± 61.52	524.61 ± 94.51
Age				
≥ 60 years	111	23.19 ± 5.26	412.28 ± 64.57	521.82 ± 98.91
< 60 years	87	23.04 ± 4.27	407.62 ± 56.81	515.23 ± 6.19
Tumor diameter				
< 3 cm	92	20.24 ± 3.89	375.79 ± 48.65	466.38 ± 74.91
≥ 3 cm	106	25.62 ± 4.15*	440.13 ± 55.03*	564.53 ± 83.49*
T stage				
T1 and T2	107	21.25 ± 4.73	387.22 ± 59.67	483.79 ± 91.39
T3 and T4	91	25.33 ± 3.98*	437.30 ± 51.26*	560.24 ± 77.77*
Degree of differentiation				
Low/moderate differentiation	114	25.21 ± 3.77	437.18 ± 45.97	560.07 ± 69.74
High differentiation	84	20.29 ± 4.71*	373.66 ± 60.45*	463.09 ± 92.66*
Lymph node metastasis				
Yes	77	25.72 ± 3.79	443.37 ± 46.29	569.45 ± 70.22
No	121	21.47 ± 4.72*	389.15 ± 60.29*	486.77 ± 92.22*

Note: Comparison with the group with different corresponding clinicopathologic features, *$P < 0.05$.
Abbreviations: GC, gastric cancer; MIC-1, Macrophage inhibitory cytokine-1; VEGF, Vascular endothelial growth factor; TGF-β1, Transforming growth factor-β1; TNM, tumor node metastasis.

Baseline Characteristics and Serum MIC-1, VEGF, and TGF-β1 Levels Between GC Patients with and without LNM

GC patients were divided into a metastasis group (77 cases) and a non-metastasis group (121 cases) based on the presence of LNM. Comparison of relevant indicators between the two groups showed no statistically significant difference in gender and age between the two groups ($P > 0.05$). However, the proportion of patients with a tumor diameter ≥3 cm, T stage T3 and T4, and low to moderate differentiation was higher in the metastasis group than in the non-metastasis group ($P < 0.05$). Additionally, the serum levels of MIC-1, VEGF, and TGF-β1 were higher in the metastasis group than in the non-metastasis group ($P < 0.05$) (Table 3). These results indicated that tumor diameter, TNM stage, degree of differentiation, and serum levels of MIC-1, VEGF, and TGF-β1 were associated with LNM in GC patients.

Multivariate Logistic Regression Analysis of Risk Factors for LNM in GC Patients

Multivariate Logistic regression analysis was performed with LNM as the dependent variable and tumor diameter, T stage, degree of differentiation, and serum levels of MIC-1, VEGF, and TGF-β1 (which showed significant differences in univariate analysis) as independent variables. The results showed that T stage, degree of differentiation, and serum levels of MIC-1,

Table 3 Comparison of Baseline Characteristics and Serum MIC-1, VEGF, TGF-β1 Levels Between GC Patients with and without LNM

Categorization	Metastasis Group (n = 77)	Non-Metastasis Group (n = 121)	OR (95% CI)	*P* value
Gender			1.120 (0.632–1.985)	0.697
Male	41 (53.25%)	61 (50.41%)		
Female	36 (46.75%)	60 (49.59%)		
Age			1.278 (0.717–2.281)	0.406
≥ 60 years	46 (59.74%)	65 (53.72%)		
<60 years	31 (40.26%)	56 (46.28%)		
Tumor diameter			3.431 (1.861–6.328)	< 0.001
< 3 cm	22 (28.57%)	70 (57.85%)		
≥ 3 cm	55 (71.43%)	51 (42.15%)		
T stage			3.613 (1.982–6.588)	< 0.001
T1 and T2	27 (35.06%)	80 (66.12%)		
T3 and T4	50 (64.94%)	41 (33.88%)		
Degree of differentiation			0.345 (0.187–0.639)	0.001
Low/Moderate differentiation	56 (72.73%)	58 (47.93%)		
High differentiation	21 (27.27%)	63 (52.07%)		
MIC-1 (μg/L)	25.72 ± 3.79	21.47 ± 4.72	1.248 (1.153–1.350)	< 0.001
VEGF (pg/mL)	443.37 ± 46.29	389.15 ± 60.29	1.018 (1.012–1.025)	< 0.001
TGF-β1 (pg/mL)	569.45 ± 70.22	486.77 ± 92.22	1.012 (1.008–1.016)	< 0.001

Abbreviations: GC, gastric cancer; MIC-1, Macrophage inhibitory cytokine-1; VEGF, Vascular endothelial growth factor; TGF-β1, Transforming growth factor-β1; TNM, tumor node metastasis; LNM, lymph node metastasis.

VEGF, and TGF-β1 were independent risk factors for LNM in GC patients ($P < 0.05$), which implied that the elevated levels of serum MIC-1, VEGF, and TGF-β1 were independent risk factors for LNM in GC patients (Table 4).

Predictive Performance of Serum MIC-1, VEGF, and TGF-β1 Levels for LNM in GC Patients

ROC curves were plotted with LNM as the dependent variable and serum levels of MIC-1, VEGF, and TGF-β1 as test variables. The areas under the curve for serum MIC-1, VEGF, TGF-β1, and their combination in predicting LNM in GC patients were (95% CI), (95% CI), (95% CI), and (95% CI), respectively. The combination of serum MIC-1, VEGF, and TGF-β1 had the highest AUC for predicting LNM in GC patients, with a sensitivity of 93.50% and a specificity of 54.50% (Figure 1 and Table 5).

Table 4 Multifactorial Analysis of Factors Affecting the Occurrence of LNM in GC Patients

Items	*β*	*SE*	*Wald*	P-value	*Exp(B)*	95% CI	
						Lower Limit	Upper Limit
Tumor diameter	0.324	0.395	0.675	0.411	0.723	0.333	1.567
TNM staging	1.199	0.376	10.144	0.01	11.274	1.539	15.357
Degree of differentiation	−1.007	0.372	7.331	0.007	7.364	1.32	8.671
MIC-1	2.147	0.933	8.545	0.004	7.203	1.029	8.562
VEGF	2.053	0.193	6.085	0.025	8.225	2.527	12.029
TGF-β1	3.248	0.677	2.3	0.032	7.227	1.916	8.725

Abbreviations: GC, gastric cancer; MIC-1, Macrophage inhibitory cytokine-1; VEGF, Vascular endothelial growth factor; TGF-β1, Transforming growth factor-β1; TNM, tumor node metastasis; LNM, lymph node metastasis.

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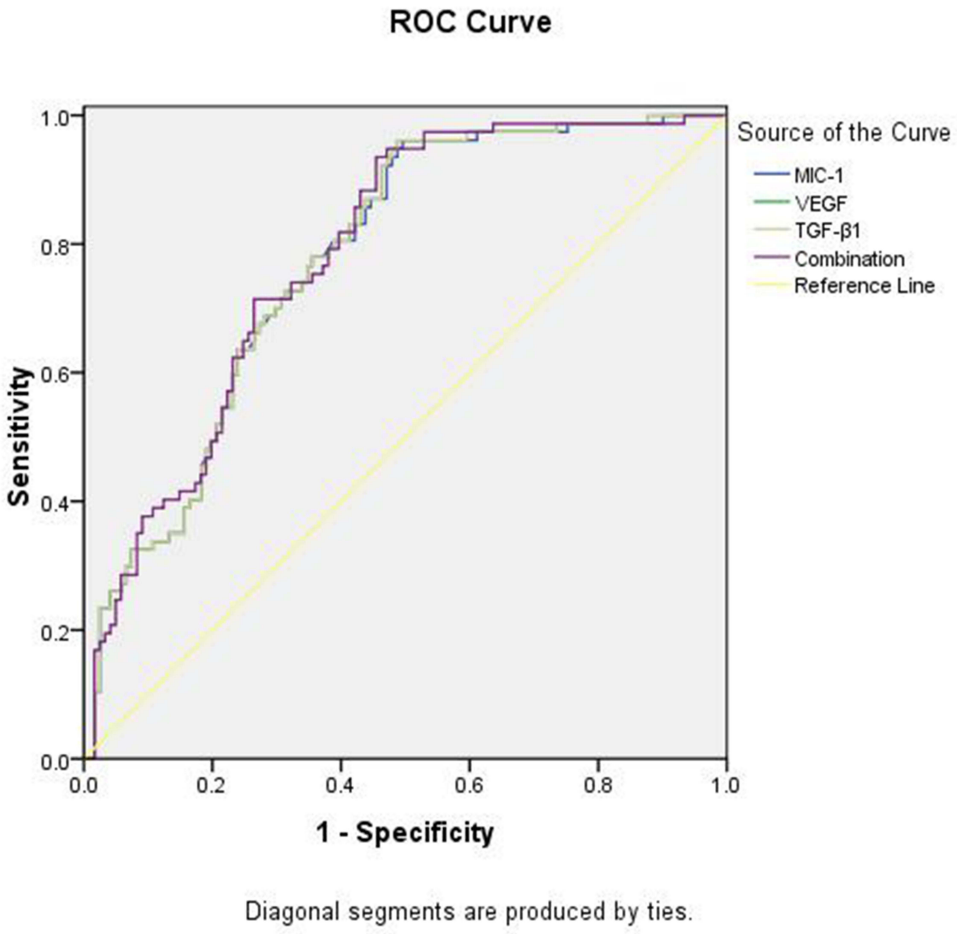

Figure 1 ROC curves for predicting LNM in GC patients using serum MIC-1, VEGF, and TGF-β1 levels.

Relationship Between Survival Prognosis and Serum MIC-1, VEGF, and TGF-β1 Levels in Patients with GC

There were 42 deaths and 156 survivors of GC patients during the follow-up period. The median values of serum MIC-1, VEGF, and TGF-β1 levels in GC patients were used as the boundaries, and patients with lower than median values were considered as low-level patients, while those with higher than median values were considered as high-level patients. The median survival of patients with low serum MIC-1, VEGF, and TGF-β1 was significantly longer than that of patients with high levels (26.13 months vs 19.24 months, 27.06 months vs 20.18 months, and 24.20 months vs 20.08 months) ($P < 0.05$) (Figures 2–4).

Table 5 Predictive Performance of Serum MIC-1, VEGF, and TGF-β1 Levels for LNM in GC Patients

Variable	AUC	Cut-Off Value	Sensitivity/%	Specificity/%	Youden Index	95% CI	*P*-value
MIC-1	0.774	20.43 μg/L	96.1	49.6	0.465	0.710–0.838	< 0.001
VEGF	0.776	378.83 pg/mL	96.1	51.2	0.473	0.712–0.840	< 0.001
TGF-β1	0.776	471.55 pg/mL	96.1	51.2	0.473	0.712–0.840	< 0.001
Combination	0.783	/	93.5	54.5	0.480	0.720–0.845	< 0.001

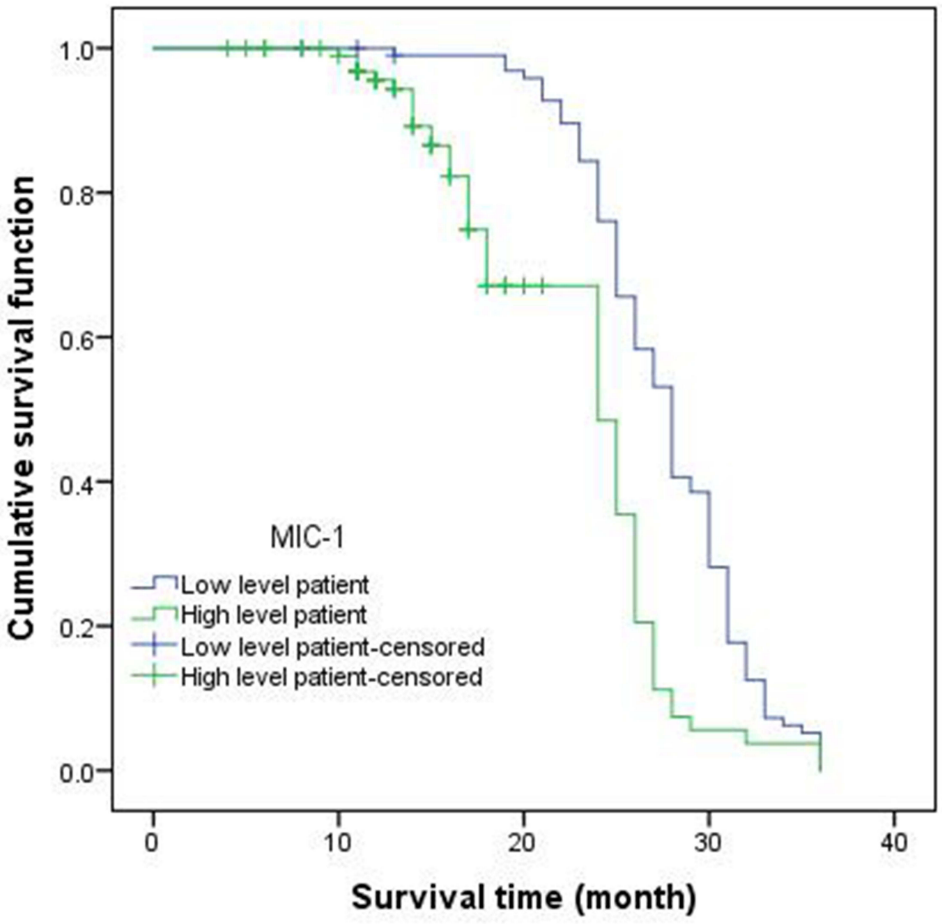

Figure 2 Effect of MIC-1 expression level on survival of GC patients.

Discussion

GC is the fourth most common cause of cancer-related deaths worldwide.[23] There are likely to be new developments in the field of staging GC, such as incorporating biological or genomic markers and/or creating more accurate staging systems.[24] In the early detection and prognosis determination of GC, serum biomarker panels may serve as novel biomarkers.[25] Therefore, this study focused on serum markers (MIC-1, VEGF, and TGF-β1) in GC patients and finally verified that the changes of serum MIC-1, VEGF and TGF-β1 levels were related to the clinicopathological characteristics, LNM, and prognosis of GC patients.

This study demonstrated that the expression levels of MIC-1, VEGF, and TGF-β1 in GC patients were higher than those in the healthy group, suggesting that these three growth factors may perform crucial roles in the initiation and progression of GC. As mentioned earlier, in the majority of patients with early GC, serum MIC-1 levels are notably increased.[10] Additionally, Kohei Shitara et al report that elevated VEGF expression is a hallmark of gastric carcinomas, making VEGF a promising target for GC treatment strategies.[26] TGF-β1 has the effects of regulating epithelial cell growth, tumor progression, and cell cycle. Generally, malignant tumors have abnormal TGF-β signaling pathways.[27]

We further found that patients with GC who had a tumor diameter ≥3cm, T stages of T3 and T4, low/moderate differentiation, and LNM had higher levels of MIC-1, VEGF, and TGF-β1 in their serum. This indicates that the levels of MIC-1, VEGF, and TGF-β1 are closely related to clinicopathological features such as the malignancy, invasion depth, and LNM of GC. Additionally, the levels of serum MIC-1, VEGF, and TGF-β1 in the metastatic group were higher than those in the non-metastatic group, further confirming the relationship between MIC-1, VEGF, TGF-β1, and LNM. As reported, MIC-1 can promote tumor development by directly stimulating cancer cells in an autocrine manner and by

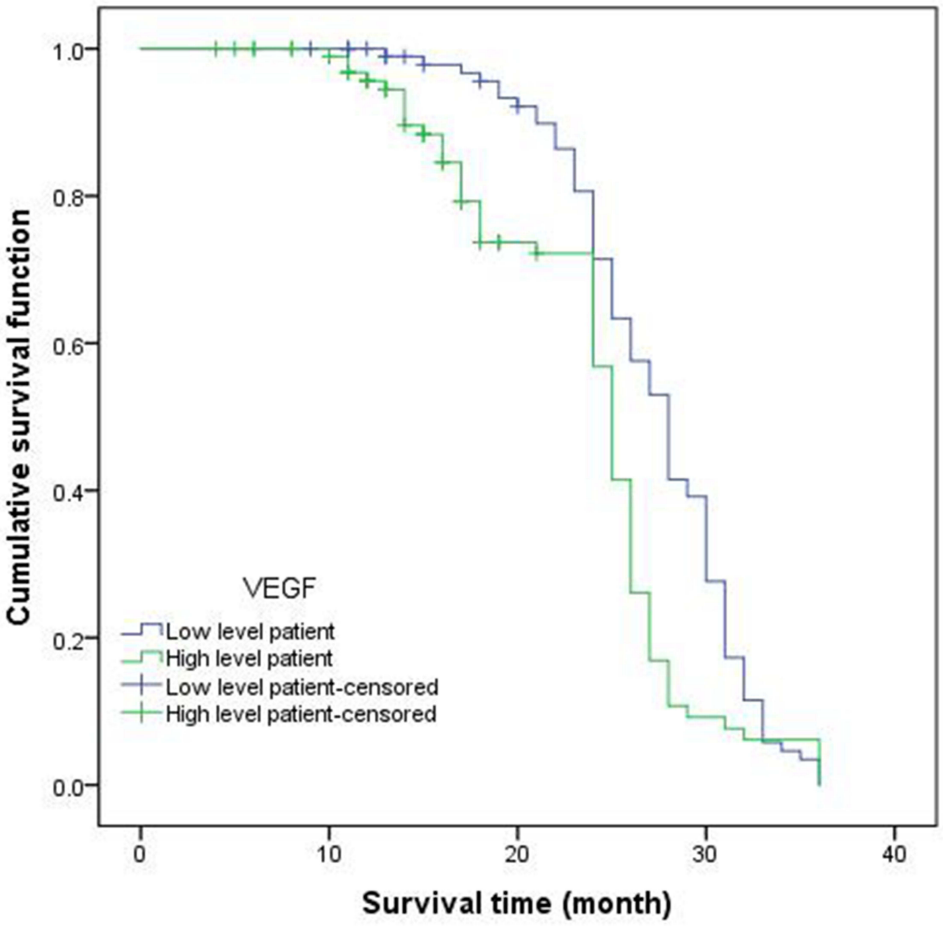

Figure 3 Effect of VEGF expression level on survival of GC patients.

activating cancer-promoting interactions between cancer cells and stromal cells in the tumor microenvironment.[28] Researchers have found that serum MIC-1 levels correlate positively with tumor size and can promote the growth and metastasis of melanoma in animals.[11] Moreover, VEGF is a highly specific vascular growth factor, which is mainly involved in the formation and regulation of new blood vessels. It has a certain correlation with GC, and is also involved in tumor metastasis and invasion.[29] Regulating VEGF inhibits hepatocellular and colon cancer metastasis.[30,31] There is a positive correlation between VEGF protein expression and TNM staging and LNM in GC patients.[32] The data presented by Sile Chen et al indicate that the activation of VEGF signaling enhances CRMP4 expression, which in turn promotes gastric tumor growth and metastasis.[29] As reported, levels of TGF-β1 are notably elevated in gastrointestinal cancer, showing a correlation with TNM staging.[33] The research conducted by Yangbing Jin and others indicates that the interaction between early growth response 1, TGF-β1, CD44s, and STAT3 signaling pathways in mesothelial and GC cells triggers epithelial-mesenchymal transformation and stemness characteristics, suggesting a possible therapeutic approach for peritoneal metastasis of GC.[34] Meanwhile, this study confirmed that T stage, degree of differentiation, and serum levels of MIC-1, VEGF, and TGF-β1 were independent risk factors for LNM in GC patients. This suggests that these factors have important reference value in predicting the risk of LNM in GC patients. Combining the research on the three factors MIC-1, VEGF, and TGF-β1, we can find that their expression levels in GC are significantly associated with LNM. High expression of MIC-1, VEGF, and TGF-β1 often indicates a higher risk of LNM. Therefore, these serum markers may not only serve as early warning signals for GC LNM but also provide new clues for the etiological study of GC LNM.

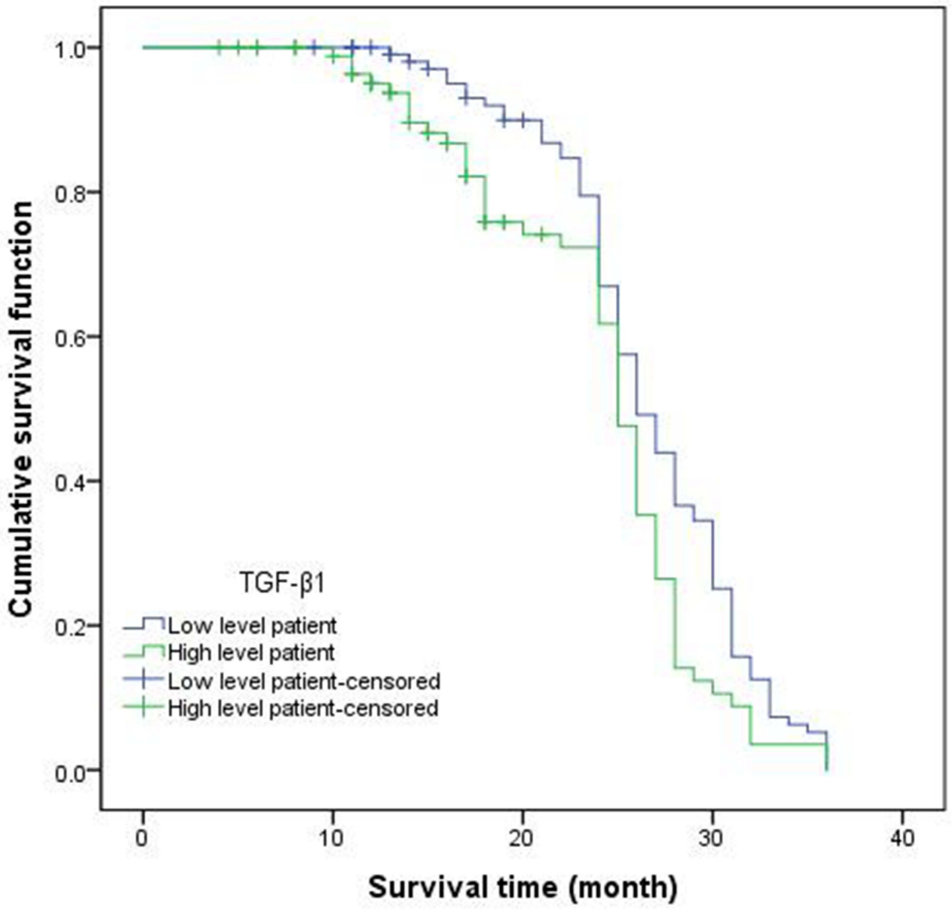

Figure 4 Effect of TGF-β1 expression level on survival of GC patients.

Furthermore, this study also revealed that the combination of serum MIC-1, VEGF, and TGF-β1 has the highest AUC for predicting LNM in GC patients, with a sensitivity of 93.50% and a specificity of 54.50%. This indicates that the combined detection of these three growth factors can improve the accuracy of predicting LNM in GC patients. Additionally, patients with low levels of serum MIC-1, VEGF, and TGF-β1 had a significantly longer median survival time than those with high levels. This suggests that high levels of MIC-1, VEGF, and TGF-β1 may be associated with poor prognosis in GC patients. As previous studies have revealed, MIC-1 expression has been associated with decreased survival in cancer patients, and it is supported as a metastasis-promoting protein.[35] For instance, MIC-1 is a complementary screening biomarker that correlates with liver metastases and a poor prognosis in colorectal cancer patients.[9] MIC-1 can be used as an important indicator for predicting disease prognosis.[36] Additionally, a higher TMN stage and shorter overall survival are associated with VEGF overexpression in esophageal cancer patients.[37] In pancreatic adenocarcinomas, tumor size, TNM staging, and VEGF expression are reported to be associated with poor prognoses.[38] Concerning TGF-β1, its presence shows a notable association with LNM, serving as a standalone prognostic element in intrahepatic cholangiocarcinoma.[39]

In summary, this study confirms that changes in serum levels of MIC-1, VEGF, and TGF-β1 are related to the clinicopathological features of GC patients, and elevated levels of these indicators are independent risk factors for LNM in GC patients. High levels of serum MIC-1, VEGF, and TGF-β1 are associated with poor prognosis. This study provides new insights for the prognosis assessment and targeted therapy of GC. However, this study has some limitations, such as a limited sample size and insufficient research on the specific mechanisms of action of MIC-1, VEGF, and TGF-β1 in GC. In the future, it is necessary to expand the sample size and conduct more in-depth research on the specific

mechanisms of action of MIC-1, VEGF, and TGF-β1 in GC, including how they regulate the biological behaviors of GC cells such as proliferation, invasion, and metastasis. This will help provide new targets for the precision therapy of GC.

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