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#### **AIMS AND SCOPE**

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

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

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ORIGINAL ARTICLE

#### **Retrospective Cohort Study**

## Analysis of vascular thrombus and clinicopathological factors in prognosis of gastric cancer: A retrospective cohort study

Guo-Yue Chen, Ping Ren, Zhen Gao, Hao-Ming Yang, Yan Jiao

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#### Abstract

#### BACKGROUND

Gastric cancer (GC) is one of the most common malignant tumors in the world, and its prognosis is closely related to many factors. In recent years, the incidence of vascular thrombosis in patients with GC has gradually attracted increasing attention, and studies have shown that it may have a significant impact on the survival rate and prognosis of patients. However, the specific mechanism underlying the association between vascular thrombosis and the prognosis of patients with GC remains unclear.

#### AIM

To analyze the relationships between vascular cancer support and other clinicopathological factors and their influence on the prognosis of patients with GC.

#### **METHODS**

This study retrospectively analyzed the clinicopathological data of 621 patients with GC and divided them into a positive group and a negative group according to the presence or absence of a vascular thrombus. The difference in the 5-year cumulative survival rate between the two groups was compared, and the relationships between vascular cancer thrombus and other clinicopathological factors and their influence on the prognosis of patients with GC were analyzed.

#### RESULTS

Among 621 patients with GC, the incidence of vascular thrombi was 31.7% (197 patients). Binary logistic regression analysis revealed that the degree of tumor differentiation, depth of invasion, and extent of lymph node metastasis were independent influencing factors for the occurrence of vascular thrombi in GC patients (P < 0.01). The trend of the  $\chi^2$  test showed that the degree of differen-



tiation, depth of invasion, and extent of lymph node metastasis were linearly correlated with the percentage of vascular thrombi in GC patients (P < 0.01), and the correlation between lymph node metastasis and vascular thrombi was more significant (r = 0.387). Univariate analysis revealed that the 5-year cumulative survival rate of the positive group was significantly lower than that of the negative group (46.7% *vs* 73.3%, P < 0.01). Multivariate analysis revealed that age, tumor diameter, TNM stage, and vascular thrombus were independent risk factors for the prognosis of GC patients (all P < 0.05). Further stratified analysis revealed that the 5-year cumulative survival rate of stage III GC patients in the thrombolase-positive group was significantly lower than that in the thrombolase-negative group (36.1% *vs* 51.4%; P < 0.05).

#### CONCLUSION

Vascular cancer status is an independent risk factor affecting the prognosis of patients with GC. The combination of vascular cancer suppositories and TNM staging can better judge the prognosis of patients with GC and guide more reasonable treatment.

Key Words: Vascular cancer thrombus; Gastric cancer; Survival prognosis; TNM staging; Retrospective study

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**Core Tip:** The relationships between vascular thrombosis and survival rate, recurrence rate and other prognostic indices were investigated by statistical analysis. The aim of this study was to summarize the potential mechanism by which vascular thrombosis influences the prognosis of patients with gastric cancer and to provide data and a theoretical basis for clinical treatment decision-making and individualized treatment strategies.

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#### INTRODUCTION

Gastric cancer (GC), one of the main causes of cancer death in our country, is a cause of concern[1-3]. However, the lack of popularity of routine gastroscopy has become a prominent problem. According to statistics, 80% of patients have advanced GC, which means that the tumor has spread throughout the body and is quite serious[4-6]. Even after radical surgery and postoperative adjuvant therapy, the 5-year survival rate of patients with advanced GC is still only approximately 30%, which is undoubtedly a rather worrisome figure [7]. The unsatisfactory prognosis of patients with GC is closely related to the high recurrence and metastasis rates of GC. In this process, the vasculature plays a key role[8]. The vasculature is an important way for tumor cells to spread far away, and the vasculature suppository is the manifestation of tumor invasion of lymphatic vessels or blood vessels. However, there are still many different views on the effect of vascular cancer thrombus on the prognosis of GC patients. The presence of a vascular cancer thrombus is considered to be one of the indicators of the degree of malignancy of GC[9]. The spread of tumor cells through the vasculature often leads to rapid growth and spread of the tumor, which exacerbates worsening of the disease. Some studies have shown that patients with vascular cancer thrombus are more likely to experience postoperative recurrence and metastasis and have lower survival rates<sup>[10]</sup>. This view has been supported by some medical circles, which believe that vascular cancer embolus is not only a pathological feature but also a manifestation of the degree of malignancy of GC, thus affecting patient prognosis. However, some scholars have questioned this view. They believe that a vascular cancer thrombus does not necessarily indicate a poor prognosis. In some cases, even in the presence of a vascular cancer thrombus, after standard treatment, one can still obtain a good survival rate. This view highlights the importance of individual differences and treatment options in the prognosis of GC[11]. Compared with a single pathological indicator, it is more important to consider the overall condition of the patient, treatment plan, and postoperative recovery [12]. On the other hand, some studies have also shown that the formation of a vascular cancer thrombus may be closely related to the molecular biological characteristics of tumors. By altering gene expression and protein synthesis, tumor cells promote the formation of cancer plugs in blood vessels or lymphatic vessels in the vascular system<sup>[13]</sup>. This discovery provides a new idea for personalized therapy, and through an in-depth understanding of the molecular-level characteristics of patients' tumors, more precise treatment plans and improved treatment effectiveness are expected<sup>[14]</sup>. There is no consensus on the effect of vascular cancer suppositories on the prognosis of GC patients. Most of the current research focuses on pathology and molecular biology, but more clinical practice and large-scale studies are needed to verify these findings. In addition, for GC patients as a whole, it is critical to increase the prevalence of routine gastroscopy to detect and treat GC earlier and improve patient survival[15].

In this study, the clinicopathological data of 621 patients with GC were retrospectively analyzed to explore the relationships between vascular cancer thrombus and other clinicopathological factors and their influence on the prognosis of postoperative patients with GC.

#### MATERIALS AND METHODS

#### General clinical data analysis of patients

A total of 621 patients with GC who underwent radical gastrectomy at our hospital between January 2020 and January 2024, including 448 males and 173 females, were included in this study. The mean age was 68 years, and the age range was 34-81 years.

#### The inclusion and exclusion criteria

Primary GC treated with radical gastrectomy (R0 resection, D2 Lymph node dissection) and postoperative pathological examination confirming gastric adenocarcinoma. No neoadjuvant chemoradiotherapy was performed before surgery. The clinicopathological data were complete and reliable. All patients provided written informed consent for surgery. The exclusion criteria were as follows: Had distant metastasis, had a serious underlying disease, had other systemic malignancies, or died of complications during the perioperative period.

#### Pathological evaluation

HE staining was performed on pathological sections of GC tissue supplemented with D2-40 and CD34 immunohistochemical staining. The pathological examination was performed independently by two expert pathologists, and disagreements were resolved by discussion with a third expert. Photoscopically, cancer cells entering the tumor or outside the tumor's blood vessels or lymphatic vessel endothelium were diagnosed as vascular cancer embolus-positive (Figure 1). According to the 15<sup>th</sup> edition of the Japanese GC Treatment Protocol, tubular adenocarcinoma, papillary adenocarcinoma, and highly or moderately differentiated adenocarcinoma are considered to be well differentiated, while poorly differentiated adenocarcinoma, sigma-ring cell carcinoma, and mucinous adenocarcinoma are considered to be poorly differentiated.

#### Methods

The following data were collected: General data, including age and sex; clinicopathologic data, including tumor differentiation degree, tumor diameter, Borrmann classification, depth of invasion, lymph node metastasis, TNM stage, number of lymph nodes detected, and vascular cancer embolus. Follow-up was conducted by telephone, email, and outpatient review until January 2024, and the 5-year cumulative survival rate was calculated.

#### Statistical analysis

IBM SPSS 25.0 statistical software was used for statistical analysis. The  $\chi^2$  test or Fisher's exact probability test was used for single-factor analysis of the statistical data. Binary logistic regression analysis was used for multivariate analysis. Correlations between variables were analyzed using the trend- $\chi^2$  test. The Kaplan-Meier method was used to construct survival curves, and the log-rank method was used for single-factor analysis. The observation indicators with statistical significance (P < 0.1) in the single factor analysis were included in the Cox proportional risk regression model for multifactor analysis. P < 0.05 indicated that the difference was statistically significant.

#### RESULTS

#### Relationship between vascular thrombus and other clinicopathological factors in GC

A total of 621 patients with GC were included in this study, including 197 patients (31.7%) in the thrombus-positive group and 424 patients (68.3%) in the thrombus-negative group. Univariate analysis revealed that the degree of tumor differentiation, tumor diameter, Borrmann classification, depth of invasion, lymph node metastasis, and TNM stage were the influencing factors for the occurrence of vascular embolus in patients with GC (P < 0.01) (Table 1).

#### Binary logistic regression analysis

The degree of tumor differentiation, depth of invasion, and degree of lymph node metastasis were found to be independent factors influencing the occurrence of vascular thrombus in GC patients (Table 2). The trend of the  $\chi^2$  test showed that the degree of tumor differentiation, depth of invasion, and extent of lymph node metastasis were linearly correlated with the percentage of vascular thrombolus positivity in patients with GC (all P < 0.01), and the correlation between lymph node metastasis and vascular thrombolus invasion was more significant (r = 0.387) (Table 3).

#### Analysis of prognostic factors in patients with GC

For GC patients, the prognostic factors were the degree of tumor differentiation, tumor diameter, Borrmann classification, depth of invasion, lymph node metastasis, TNM stage of the tumor, and presence of a vascular cancer embolus (all *P* < 0.05). The 5-year cumulative survival rate of patients with Thrompos-positive GC was significantly lower than that of



#### Table 1 Relationship between vascular cancer thrombi and other clinical and pathological factors, n (%) Vascular cancer thrombus **Clinical pathological factors** Cases X2 P value Negative Positive Gender Male 448307 (68.5) 141 (31.5) 46 0.83 Female 173 117 (67.6) 56 (32.4) Age (years) 0.092 95 (31.1) 0.76 ≤ 60 305 210 (68.9) > 60 316 102 (32.3) 214 (67.7) Degree of differentiation Well differentiated 131 110 (84.0) 21 (16.0) 18.876 90.0 Poorly differentiated 490 314 (64.1) 176 (35.9) Tumor diameter (cm) $\leq 4$ 334 247 (74.0) 87 (26.0) 10.746 < 0.01 >4 287 177 (61.7) 110 (38.3) Borrmann typing 56.480 90.0 Early gastric cancer 143 132 (92.3) 11 (7.7) 25 Type I 18 (72.0) 7 (28.0) Type II 10 9 (90.0) 1 (10.0) Type III 397 241 (60.7) 156 (39.3) Type IV 46 24 (52.2) 22 (47.8) Invasion depth T1 143 132 (92.3) 11 (7.7) 78.397 < 0.01 T2 103 81 (78.6) 22 (21.4) T3 19 17 (89.5) 2 (10.5 Т4 356 194 (54.5) 162 (45.5) Number of lymph node metastases 99.640 NO 254 212 (83.5) 42 (16.5) 90.0 N1 23 (19.2) 120 97 (80.8) N2 119 67 (56.3) 52 (43.7 N3 48 (37.5 80 (62.5) 128 TNM staging Ι 195 173 (88.7) 22 (11.3) 83.903 < 0.01 Π 134 103 (76.9) 31 (23.1) III 292 148 (50.7) 144 (49.3) Number of detected lymph nodes 335 220 (65.7) 115 (34.3) 2.280 0.13 $\geq 16$ < 16 286 204 (71.3) 82 (28.7)

patients with Thrompos-negative GC (46.7% vs 73.3%, P < 0.01) (Figure 2).

#### Clinical multifactor analysis

The results showed that age, tumor diameter, TNM stage, and vascular cancer thrombus were independent risk factors affecting the prognosis of GC patients (Table 4). Further stratified analysis revealed that the 5-year cumulative survival rate of patients with TNM stage III GC in the thrombolase-positive group was significantly lower than that in the

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#### Chen GY et al. Correlation analysis of vascular thrombus in GC

| Table 2 Binary logistic regression analysis of the influencing factors of vascular cancer thrombus |       |        |       |             |         |  |  |
|--|-------|--------|-------|-------------|---------|--|--|
| Clinical pathological factors  | β     | Wald   | OR    | 95%CI       | P value |  |  |
| Degree of differentiation  | 0.770 | 8.111  | 2.161 | 1.272-3.671 | < 0.01  |  |  |
| Invasion depth   | 1.254 | 29.495 | 3.504 | 2.229-5.510 | < 0.01  |  |  |
| Lymph node metastasis  | 0.731 | 11.004 | 2.078 | 1.349-3.201 | < 0.01  |  |  |

| Table 3 Trend of influencing factors of vascular thrombus in patients with gastric cancer by $\chi^2$ test |                |       |                |  |  |
|--|----------------|-------|----------------|--|--|
| Clinical pathological factors  | X <sup>2</sup> | R     | <i>P</i> value |  |  |
| Degree of differentiation  | 18.845         | 0.174 | < 0.01         |  |  |
| Invasion depth   | 73.914         | 0.345 | < 0.01         |  |  |
| Lymph node metastasis  | 92.693         | 0.387 | < 0.01         |  |  |

#### Table 4 Multivariate analysis of prognostic factors in 621 postoperative gastric cancer patients

| Clinical pathological factors     | β     | Wald   | OR    | 95%CI        | P value |
|-----------------------------------|-------|--------|-------|--------------|---------|
| Age > 60 years old                | 0.268 | 3.834  | 1.307 | 1.000-1.709  | < 0.05  |
| Tumor diameter > 4 cm             | 0.515 | 12.005 | 1.673 | 1.251-2.239  | < 0.01  |
| Vascular cancer thrombus positive | 0.413 | 8.561  | 1.512 | 1.146-1.994  | < 0.01  |
| TNM II stage                      | 1.087 | 13.431 | 2.966 | 1.658-5.305  | < 0.01  |
| TNM III stage                     | 1.853 | 47.009 | 6.380 | 3.756-10.836 | < 0.01  |



Figure 1 A cancer embolus can be seen in the labeled vessel (arrow). A: Cancer suppositories can be seen in the vessels labeled by HE staining (× 200) (arrow); B: CD34-positive and D2-40-negative vessels are marked as blood vessels (arrow) with cancer thrombus (× 400); C: CD34 and D2-40 were both marked as lymphatic vessels (arrow) with cancer embolus (× 400).

thrombolase-negative group (36.1% vs 51.4%, P < 0.05).

#### DISCUSSION

Vascular cancer suppositories are the invasion of blood vessels and lymphatic vessels by tumor cells, which is a common pathological manifestation and occurs in postoperative specimens of various malignant tumors[16-18]. As a potential prognostic factor, vascular cancer suppositories are receiving increasing attention from clinicians. In hepatocellular carcinoma, vascular cancer suppositories have become reliable indicators of hepatocellular carcinoma stage and prognosis prediction because they can accurately predict patient prognosis<sup>[19]</sup>. Some studies<sup>[20-22]</sup> have shown that vascular cancer suppositories are associated with poor prognosis in patients with GC, but vascular cancer suppositories have not been included in the TNM staging of GC. This retrospective study attempted to investigate the effect of a vascular cancer thrombus on the prognosis of patients with GC.

Previous studies[23-25] have shown that the incidence of vascular thrombus in GC patients ranges from 12.9% to 44.3%, while the incidence of vascular thrombus in this study was 37.1%. The incidence of vascular cancer thrombus varies among different study centers, which may be affected by the sample size and detection methods included in the

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Figure 2 Survival curves of patients with positive and negative vascular thrombi.

study. The main detection methods for vascular cancer suppositories include HE staining and immunohistochemistry (IHC)[26]. At present, the most recognized method for the detection of vascular cancer suppositories in the literature is IHC[27]. Artifacts generated by peritumoral tissue edema or tumor tissue shrinkage may affect the detection of vascular cancer suppositories in HE staining, which is more objective and accurate than HE staining[28]. In this study, HE staining supplemented with CD34 and D2-40 dual IHC was used to improve the accuracy of the diagnosis of vascular cancer thrombus.

In this study, the degree of tumor differentiation, depth of invasion, and extent of lymph node metastasis were independent influencing factors for the occurrence of vascular thrombus in patients with GC. The trend  $\chi^2$  test showed that the deeper the tumor invasion depth and the greater the number of lymph node metastases, the greater the incidence of vascular cancer thrombus. The results of relevant studies[29-31] were similar to those of the present study. Another study [32] revealed increased levels of vascular endothelial growth factor (VEGF) in the tumor tissues of patients with positive vascular cancer embolus, which provided a reasonable explanation for the correlation between vascular cancer embolus and the depth of tumor invasion and lymph node metastasis. With increasing tumor growth and depth of tumor invasion, more blood vessels are needed, and tumor tissues promote neovascularization through the production of VEGF [33-35]. However, due to the incomplete basement membrane, new blood vessels increase the chances of tumor cells invading the vascular system, and the number of vascular cancer thrombi and lymph node metastases also increases[36].

There is no consensus on the effect of vascular cancer suppositories on the prognosis of patients with GC[37]. The results of relevant studies[38-40] show that the prognosis of patients with positive vascular thrombi is worse than that of patients with negative vascular thrombi, but vascular thrombi are not an independent prognostic factor for GC. Another study[41] of 1007 patients with GC showed that vascular cancer suppositories can reduce the 5-year cumulative survival rate of patients with GC and are an independent prognostic factor for GC. The results of a study[42] on 1398 patients with GC showed that vascular cancer suppositories derived for GC, and stratified analysis showed that vascular cancer suppositories only affected the prognosis of patients with TNM stage III GC, which was consistent with the results of this study. We believe that we should pay more attention to the role of thrombi in the prognosis of patients is still worse than that of thrombus-negative patients[44]. It is suggested that more active follow-up should be carried out for stage III GC patients with positive vascular thrombi to detect tumor recurrence and distant metastasis in a timely manner and formulate more reasonable treatment strategies[45].

In conclusion, vascular cancer support is an independent prognostic factor for patients with GC. The combination of vascular cancer suppositories and the 8<sup>th</sup> edition of the TNM for GC can help patients with GC better judge their prognosis and guide more reasonable treatment. In particular, for patients with stage III GC with a positive vascular embolus, in addition to postoperative adjuvant treatment, more active follow-up observation is recommended.

#### CONCLUSION

The correlation between vascular thrombosis and the clinicopathological features and prognosis of patients with GC was discussed retrospectively. Multivariate analysis further confirmed that vascular thrombosis and several clinicopathological factors, such as tumor stage and patient age, were found to be independent risk factors affecting the prognosis of GC patients. These findings suggest that in the clinical management of GC, attention should be given to early screening and intervention for vascular thrombosis to optimize treatment strategies and improve patient prognosis and survival.

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#### FOOTNOTES

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