

Meta-analysis of the relationship between lymphovascular invasion and prognosis of patients with stage I gastric cancer

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Abstract

Lymphovascular invasion is considered to be a high-risk pathological feature after radical resection of gastric cancer, but the relationship between lymphovascular invasion and the prognosis of stage I gastric cancer is still controversial. Therefore, we used meta-analysis to systematically evaluate the relationship between lymphovascular invasion and the prognosis of stage I gastric cancer. Up to September 2, 2021, the databases of PubMed, EMBASE, Cochrane Library, CNKI, and Wanfang were searched. According to the inclusion and exclusion criteria, 2 researchers independently completed the screening of literature, extraction of data, and quality evaluation. Meta-analysis was performed using RevMan 5.4 software merged with HR and 95%CI. A total of 7508 patients with stage I gastric cancer were included in 9 studies, and the positive rate of lymphovascular invasion was 17%. Lymphovascular invasion was significantly associated with shorter overall survival (OS) (univariate: $HR = 4.05$, 95%CI: 1.91–8.58; multivariate: $HR = 2.10$, 95%CI: 1.37–3.22) and relapse-free survival (RFS) (univariate: $HR = 4.79$, 95%CI: 2.30–9.99; multiple: $HR = 2.17$, 95%CI: 1.56–3.00). This study indicates that lymphovascular invasion is an independent risk factor affecting the prognosis of patients with stage I gastric cancer, and can be used as a reference index for postoperative adjuvant therapy.

Abbreviations: CI = confidence interval, RFS = relapse-free survival, CSCO = Chinese Society of Clinical Oncology, HR = hazard ratio, NCCN = National Comprehensive Cancer Network, OS = overall survival.

Keywords: gastric cancer, lymphovascular invasion, meta-analysis, prognosis, Stage I

1. Introduction

Gastric cancer is the fifth most common cancer in the world with the fourth highest mortality rate.^[1] In recent years, with the popularization and application of endoscopic ultrasonography, fiberoptic gastroscopy, and other examination methods, the diagnosis rate of early gastric cancer has been increasing. The postoperative prognosis of patients with early gastric cancer is good, and the 5-year survival rate of stage I patients after standard radical resection can exceed 90%.^[2] However, follow-up found that there are still a small number of patients with poor prognosis, in which the mortality is due to distant metastasis. Lymphovascular invasion, including lymphatic invasion and vascular invasion, is an important way for tumor metastasis and spread.^[3] Some studies have shown that lymphovascular invasion is a strong risk factor for lymph node metastasis in early gastric cancer.^[4–6] At present, several studies in other solid tumors have confirmed that lymphovascular invasion is closely related to the prognosis of many kinds of malignant tumors such as lung cancer, breast cancer, and esophageal

cancer.^[7–9] However, the relationship between lymphovascular invasion and the prognosis of patients with stage I gastric cancer is still controversial. One view is that lymphovascular invasion is an independent prognostic factor in patients with stage I gastric cancer,^[10,11] while the other view is just the opposite.^[12,13] Therefore, in this study, meta-analysis was used to systematically evaluate the relationship between lymphovascular invasion and the prognosis of stage I gastric cancer, to provide the evidence-based basis for the comprehensive treatment of stage I gastric cancer.

2. Methods

2.1. Publication search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.^[14] The systematic literature search was performed through PubMed, EMBASE, Cochrane Library, CNKI,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethics statement: Ethical approval was not necessary because this article is a meta-analysis and it does not involve the participation of ethics committee.

Disclosure: The author reports no conflicts of interest in this work.

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and WanFang database, covering all articles published up to September 2, 2021. The following keywords were used to retrieve articles: “Stomach Neoplasms,” “early,” “Stage I,” “lymphovascular invasion,” “lymph vessel invasion,” “blood vessel invasion,” and “vascular cancer embolus.” References of the retrieved publications were also screened. The language was English or Chinese.

2.2. Literature inclusion and exclusion criteria

2.2.1. Inclusion criteria. (1) study on the relationship between postoperative lymphovascular invasion and prognosis of stage I

gastric cancer; (2) the literature is an original study, which can provide prognostic survival data; (3) the literature is published in Chinese or English; (4) the data are true and reliable.

2.2.2. Exclusion criteria. (1) reviews, case reports, conference summaries, nonclinical reports, and repeated studies; (2) literature with incomplete data and no access to original data; (3) only reports of lymphatic invasion or vascular invasion.

2.3. Data extraction and literature quality evaluation

The articles were independently reviewed by 2 investigators to extract data and cross-checked them. In case of differences, they were decided by discussion or reference to the third researcher.

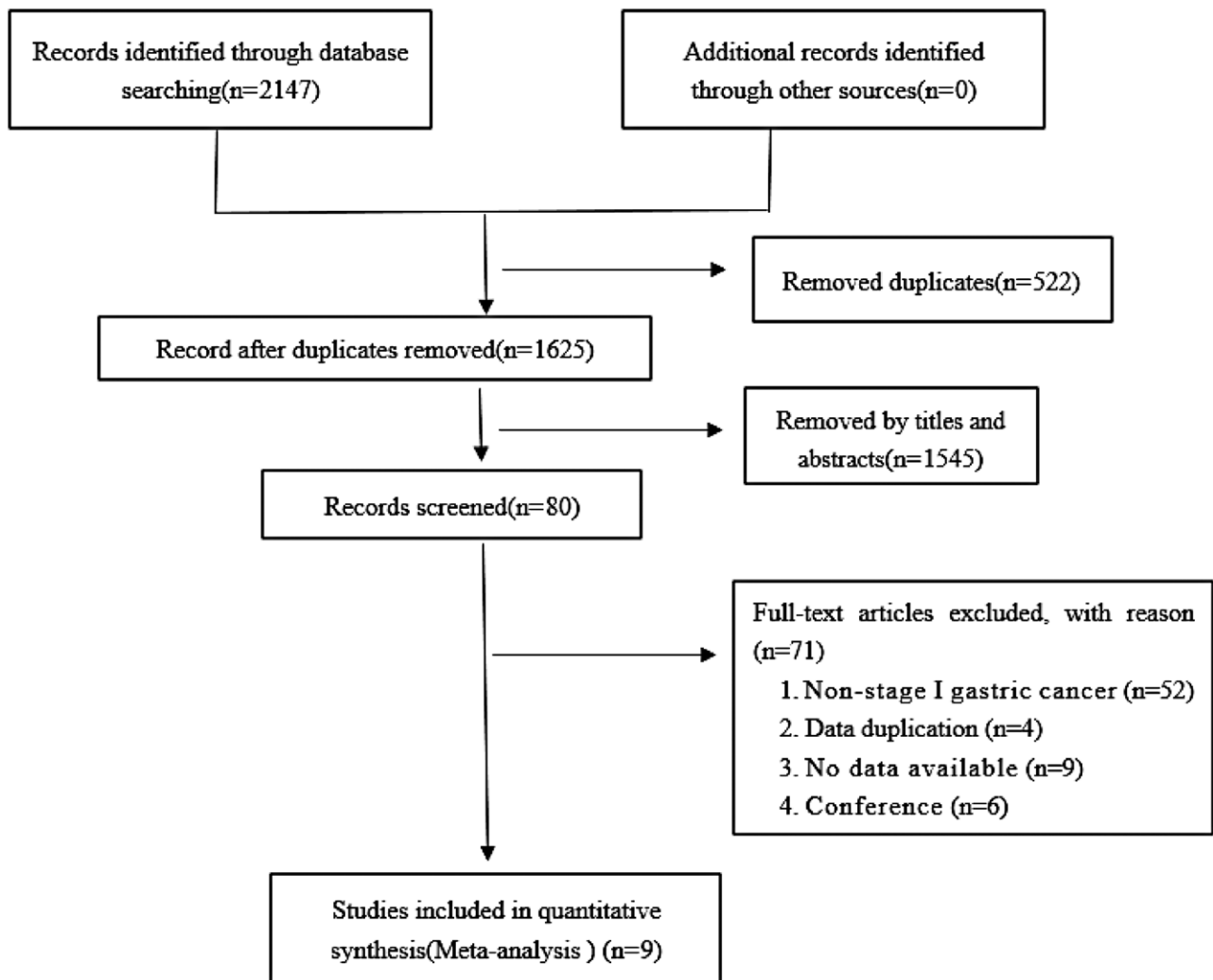


Figure 1. Literature screening flow chart.

Table 1

The included cohort studies were scored according to the NOS scale.

Category	Entries	Study								
		①	②	③	④	⑤	⑥	⑦	⑧	⑨
Section	Representation of the exposure cohort	☆	☆	☆	☆	☆	☆	☆	☆	☆
	Representation of the nonexposed cohort	☆	☆	☆	☆	☆	☆	☆	☆	☆
	Determination of exposure	☆	☆	☆	☆	☆	☆	☆	☆	☆
Comparability	No outcome event occurred before the study began	☆	☆	☆☆	☆	☆☆	☆	☆☆	☆☆	☆☆
	Comparability of cases and controls on the basis of the design and analysis	☆	☆	☆☆	☆	☆☆	☆	☆☆	☆☆	☆☆
Outcome	Results determination method	☆	☆	☆☆	☆	☆☆	☆	☆☆	☆☆	☆☆
	Adequate follow-up time	☆	☆	☆☆	☆	☆☆	☆	☆☆	☆☆	☆☆
Total scores	Complete follow-up	☆	☆	☆☆	☆	☆☆	☆	☆☆	☆☆	☆☆
		7	7	8	7	8	7	8	7	7

Notes: ①L Shang; ②Park; ③DU; ④Araki; ⑤Kunisaki; ⑥Liu; ⑦Yu; ⑧Mei; ⑨CAO

The extracted data include first author, country, year of publication, study design, number of included cases, number of lymphovascular invasion cases and positive rate, hazard ratio (HR), and 95% confidence interval (CI). If the HR and 95% CI, are not directly provided in the original text, according to the method provided by Tierney et al,^[15] Getdata Dragh Digitizer Software is used to extract the data from the Kaplan-Meier survival curve, and the HR and 95% CI values are analyzed and calculated. If the report is unknown or lacks information, try to contact the author by email to obtain further unpublished data. Newcastle-Ottawa Scale (NOS)^[16] was used to evaluate the quality of included studies.

2.4. Statistical analysis

RevMan5.4 software is used for data processing. The HR and 95% CI were used for the evaluation of survival data, and the forest map of meta-analysis was drawn. Q test and I² statistics were used to assess heterogeneity. If homogeneity was good (P ≥ 0.1, I² ≤ 50%), the fixed-effects model was used, and if heterogeneity was high (P < 0.1, I² > 50%), the random-effects model

was used. All P values were 2-sided, and P < 0.05 was considered statistically significant.

3. Results

3.1. Literature Search and Study characteristics

A total of 2147 articles were retrieved, and 522 repeated articles were excluded by title, year, and author information. Then after reading abstracts and full-text screening, 1616 articles that did not meet the criteria were excluded and finally included 9 studies^[10-13,17-21] (Fig. 1). All were retrospective cohort studies. In the study of Kunisaki,^[13] the lymphovascular invasion was divided into mild and moderate to severe subgroups, and the HR and 95% CI of OS were obtained, respectively. Therefore, it can be thought of as 2 separate queues.

The 9 included articles included 10 cohorts, including 7508 postoperative patients with stage I gastric cancer. The NOS scores of the 9 articles were all 7 points (Table 1). Key baseline characteristics of patients were fully described in all included studies, as shown in Table 2.

Table 2
Basic characteristics of the included literature

Study	Year	Country	Number of patients	TNM staging	Positive rate of lymphovascular invasion (%)	Staining Method	Main outcome indicators
L Shang ^[12]	2018	China	469	I	11	HE and IHC	OS
Park ^[17]	2016	Korea	2783	I	8	—	RFS
DU ^[10]	2012	China	384	I	10	—	OS
Araki ^[11]	2017	Japan	124	IB	38	IHC	OS, RFS
Kunisaki ^[13]	2010	Japan	1880	I	17	HE	OS
Kunisaki* ^[13]	2010	Japan	1880	I	11	HE	OS
Liu ^[18]	2010	China	185	I	7	HE	OS
Yu ^[19]	2020	Korea	253	IB	27	HE	RFS
Mej ^[20]	2020	China	372	I	5	HE	RFS
CAO ^[21]	2016	China, America	1058	I	29	—	RFS

Notes: In the study of Kunisaki^[13] lymphovascular invasion was divided into mild and moderate to severe subgroups, and HR and 95% CI of OS were obtained by follow-up, respectively. Therefore, it can be regarded as 2 separate queues. HE = hematoxylin-eosin, IHC = immunohistochemistry.

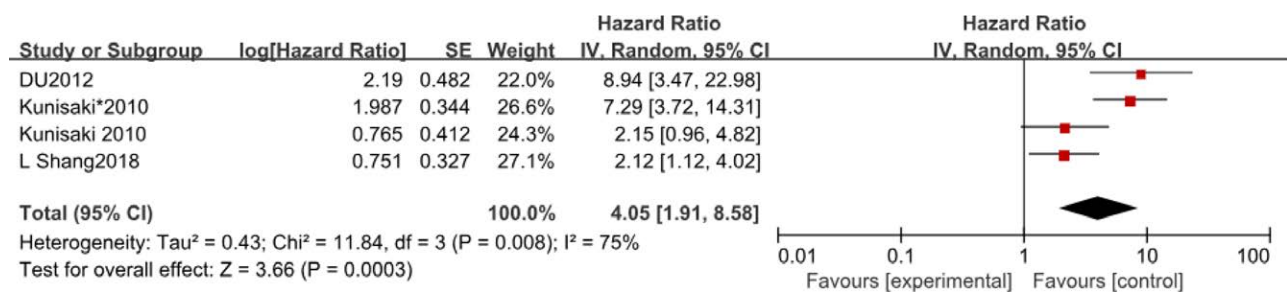


Figure 2. Univariate analysis of the relationship between lymphovascular invasion and OS in patients with stage I gastric cancer.

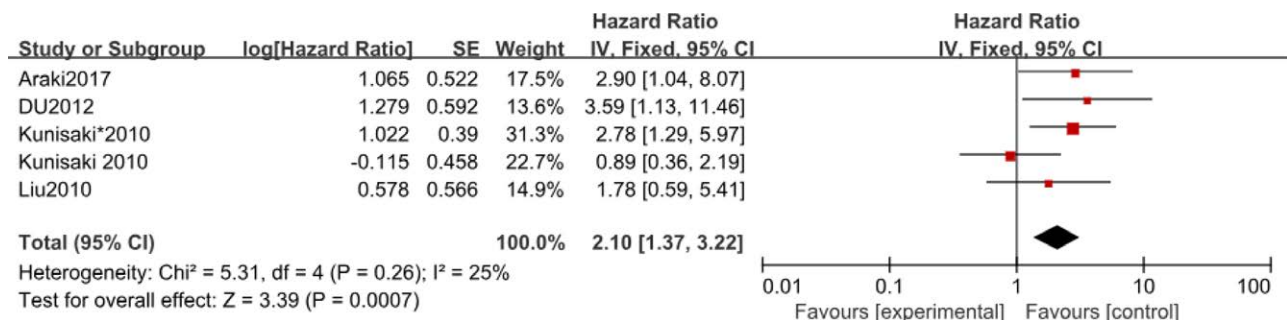


Figure 3. Multivariate analysis of the relationship between lymphovascular invasion and OS in patients with stage I gastric cancer.

3.2. Meta-analysis results

3.2.1. OS. Five studies^[10–13,18] provided OS data from a total of 6 cohorts, of which 4 cohorts provided HR and 95% CI for univariate analysis. Five cohorts provided a multivariate analysis of HR and 95%CI. The heterogeneity test showed high heterogeneity among studies in the univariate group ($P = 0.008, I^2 = 75\%$). The heterogeneity among studies was small in the multifactorial group ($P = 0.26, I^2 = 25\%$). Random-effect model analysis was used in the univariate group and fixed-effect model analysis was used in the multivariate group. The results showed that lymphovascular invasion significantly shortened the OS of stage I gastric cancer patients in both the univariate and multivariate groups (univariate: $HR = 4.05, 95\%CI: 1.91–8.58$; multivariate: $HR = 2.10, 95\%CI: 1.37–3.22$) (see Figs. 2 and 3).

3.2.2. RFS. Five studies^[11,17,19–21] provided RFS data, and 2 of them provided HR and 95%CI for univariate analysis. Four studies provided a multivariate analysis of HR and 95%CI. Heterogeneity test results showed small heterogeneity among studies (univariate: $P = 0.66, I^2 = 0\%$; univariate: $P = 0.53, I^2 = 0\%$). The results of fixed-effect model analysis showed that lymphovascular invasion significantly shortened the RFS of patients with stage I gastric cancer (univariate: $HR = 4.79, 95\%CI: 2.30–9.99$; multivariate: $HR=2.17, 95\%CI: 1.56–3.00$) (see Figs. 4 and 5).

3.2.3. Sensitivity analysis and publication bias. Sensitivity analysis was performed for each meta-analysis, and 1 study was deleted at a time to assess the stability of the results. These analyses show that the corresponding HR and 95%CI do not change obviously, indicating that our results are stable. Finally, the funnel plot was used to judge the bias degree of literature publication, and the funnel plot does not show any obvious evidence of asymmetry, suggesting that the possibility of publication bias is low (see Fig. 6).

4. Discussion

According to the 2021 gastric Cancer CSCO guidelines, patients with stage I gastric cancer (T1N0M0, T1N1M0, and T2N0M0) do not need routine adjuvant chemotherapy after

radical resection.^[22] In clinical practice, some doctors will carry out adjuvant treatment on the high-risk factors that may affect the prognosis of patients with stage I gastric cancer. Lymphovascular invasion, as an important pathological parameter in patients with gastric cancer, is considered to be an important step in tumor recurrence and metastasis,^[23] and has been proved to be an independent predictor of poor prognosis of many solid tumors.^[20] In endometrial carcinoma, cervical cancer, and malignant tumors of the head and neck, postoperative pathology suggests that lymphovascular invasion is an indication for further adjuvant therapy.^[24–26] Although many studies have shown that lymphovascular invasion is an independent predictor of poor OS and RFS in gastric cancer, most studies include stage II–IV patients. However, in postoperative patients with stage I gastric cancer, the impact of lymphovascular invasion on the prognosis of patients is still controversial; so we use meta-analysis to further clarify the relationship between the 2, to help identify high-risk patients who may benefit from postoperative adjuvant therapy.

After literature screening according to inclusion and exclusion criteria, a total of 9 studies were included in this study, including 10 cohorts, including 7508 postoperative patients with stage I gastric cancer, of which the positive rate of vascular invasion was 17%. The results of our meta-analysis showed that lymphovascular invasion was significantly associated with poor OS and RFS in stage I gastric cancer patients, regardless of univariate analysis or multivariate analysis, suggesting that lymphovascular invasion is an independent risk factor affecting the prognosis of stage I gastric cancer patients. In the meta-analysis of this paper, the positive rate of lymphovascular invasion reported by each study varied greatly, ranging from 5% to 38%. The reasons may be as follows: (1) most of the studies used optical microscope and hematoxylin-eosin (HE) staining to detect lymphovascular invasion. It is difficult to accurately judge lymphovascular invasion by HE staining on some pathological films, resulting in a low detection rate. Immunostaining technique can be used to judge vascular and lymphatic invasion by specific markers, with higher sensitivity and specificity. (2) In different regions, patients receive different surgical methods, which will affect the detection rate. In addition, the difference in the ability of pathologists also leads to the difference in detection rate. (3) The definition of lymphovascular invasion degree is different in different laboratories. Therefore, criteria for

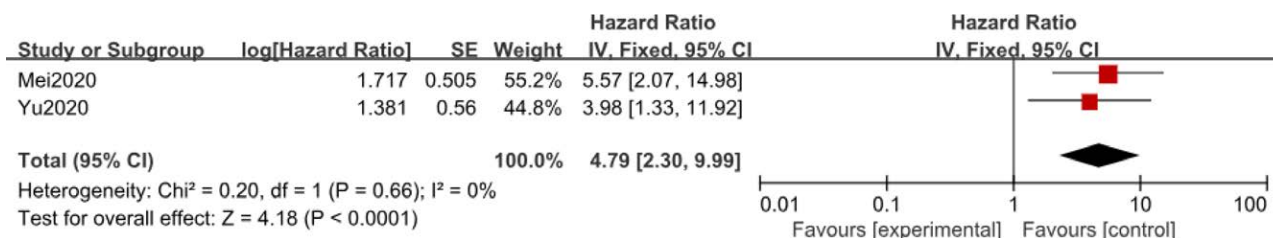


Figure 4. Univariate analysis of the relationship between lymphovascular invasion and RFS in patients with stage I gastric cancer.

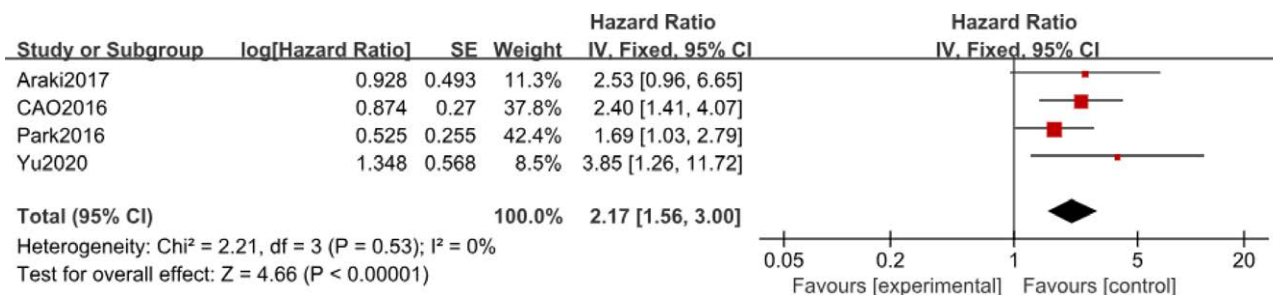


Figure 5. Multivariate analysis of the relationship between lymphovascular invasion and RFS in patients with stage I gastric cancer.

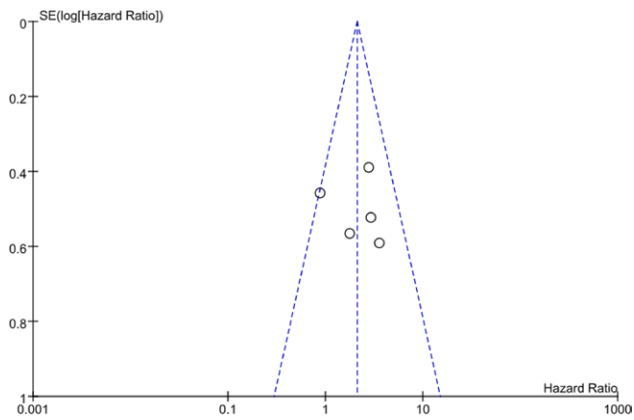


Figure 6. Funnel plot of multivariate analysis of the relationship between lymphovascular invasion and OS in patients with stage I gastric cancer.

the assessment and reporting of lymphovascular invasion should be established in the future.

In addition, there are some limitations to our study. First of all, only 9 studies were included, all of which were retrospective cohort studies with a low level of evidence. Secondly, due to inconsistencies or data loss in the relevant original data provided by the included studies, subgroup analysis could not be conducted by race, region, T stage, N stage, the severity of lymphovascular invasion, and other factors that may affect the prognosis. At present, NCCN and other guidelines do not regard the lymphovascular invasion as the basis for the postoperative treatment of patients with stage I gastric cancer. Based on the results of systematic analysis, we believe that lymphovascular invasion is closely related to the prognosis of patients with stage I gastric cancer, and it is necessary to conduct a large-scale multicenter prospective study to further verify the reliability of lymphovascular invasion as a prognostic factor for stage I gastric cancer patients and as a basis for determining postoperative adjuvant therapy.

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