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META-ANALYSIS

Meta-analysis of immunohistochemical expression of hypoxia inducible factor-1α as a prognostic role in gastric cancer

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Abstract

AIM: To conduct a meta-analysis to evaluate the prognostic role of hypoxia inducible factor-1α (HIF-1α) expression in gastric cancer.

METHODS: The PubMed, EMBASE, and Web of Science databases were searched systematically for all articles published in English before August, 2013. Pooled effect was calculated from the available data to evaluate the association between HIF-1α expression and 5-year overall survival and tumor clinicopathological features in gastric cancer patients. Pooled odds ratios (ORs) with 95%CIs were calculated using either a fixed-effects or a random-effects model.

RESULTS: Nine studies matched the selection criteria, which reported on 1103 subjects, 548 of whom had HIF-1α positive expression (50%). This meta-analysis indicated that HIF-1α positive expression in gastric cancer correlated with lower 5-year overall survival (OR = 0.36; 95%CI: 0.21-0.64), worse tumor differentiation (OR = 0.38; 95%CI: 0.23-0.64), deeper invasion (OR = 0.42; 95%CI: 0.32-0.57), higher rates of lymph node metastasis (OR = 2.23; 95%CI: 1.46-3.40), lymphatic invasion (OR = 2.50; 95%CI: 1.46-4.28), and vascular invasion (OR = 1.80; 95%CI: 1.29-2.51), and higher TNM stage (Ⅲ + Ⅳ) (OR = 0.31; 95%CI: 0.15-0.60).

CONCLUSION: HIF-1α positive expression indicates a poor prognosis for patients with gastric cancer. Further studies are required to confirm these results.

Key words: Hypoxia inducible factor-1α; Gastric cancer; 5-year overall survival; Clinicopathological features; Meta-analysis

Core tip: We conducted a meta-analysis to evaluate the correlation between hypoxia inducible factor-1α (HIF-1α) expression and clinical outcome in gastric cancer patients, and reported that HIF-1 positive expression indicates a poor prognosis for patients with gastric cancer. This is the first comprehensive and detailed meta-analysis to assess the association of HIF-1α positive expression with 5-year overall survival and tumor clinicopathological features for gastric cancer patients. We believed that the results will provide useful information for clinical decision-making regarding gastric cancer.

Lin S, Ma R, Zheng XY, Yu H, Liang X, Lin H, Cai XJ. Meta-analysis of immunohistochemical expression of hypoxia inducible factor-1α as a prognostic role in gastric cancer. *World J Gastroenterol* 2014; 20(4): 1107-1113 Available from: URL: http://

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide. Although the prognosis of gastric cancer has improved due to early diagnosis, radical operation, and the development of adjuvant therapy, patients with gastric cancer still have a poor prognosis[1,2]. The main prognostic factors for gastric cancer are clinicopathological features of the disease, including tumor differentiation, depth of invasion, lymph node metastasis and stage. However, the prognostic factors do not fully predict individual clinical outcome. As a result, there is great interest in finding better markers to identify patients with a poor prognosis at the time of diagnosis[3,4]. Hypoxia inducible factor-1 (HIF-1) is a basic helix-loop-helix transcription factor composed of HIF-1α and HIF-1β subunits; and HIF-1α determines HIF-1 activity[5]. Increased evidence has revealed that HIF-1α positive expression was associated with an unfavorable prognosis in many kinds of cancer[6,7].

One published meta-analysis has reported that HIF-1α in Asian patients was associated with poor overall survival (OS), but not with disease free survival (DFS)[8]. However, there have been no data about tumor clinicopathological features, which were known to provide useful information for tumor prognosis. Since that meta-analysis only included several studies of low quality, the data reported were not sufficient to derive conclusions with regards to the OS and DFS. Given that several high-quality studies have been published recently, we reviewed the currently available evidence in the medical literature to determine the association between HIF-1α positive expression and 5-year overall survival of gastric cancer as well as common clinicopathological features, and to assess the significance of HIF-1α positive expression in the prediction of clinical outcome of gastric cancer.

MATERIALS AND METHODS

Study selection

The PubMed, EMBASE, and Web of Science databases were searched systematically for all articles published in English before August, 2013. The terms used for the search were: "HIF-1α" or "hypoxia-inducible factor-1α" and "Gastric Cancer" or "Gastric Neoplasm" or "Stomach Neoplasm".

Reference lists of all retrieved articles were also manually searched for additional studies. Two reviewers independently extracted the data from each study. All relevant text, tables, and figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by discussion and consensus.

Inclusion and exclusion criteria

Only studies in the English language were considered for inclusion. In addition, each study had to fulfill the following criteria: (1) patients with gastric cancer diagnosed by pathology; (2) studies that examined the relationship between HIF-1α and survival of gastric cancer; (3) studies that utilized immunohistochemistry to determine the expression of HIF-1α in paraffin-embedded surgical specimens; and (4) the most informative article when multiple articles were published by the same authors or groups.

Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies lacking a control group were excluded. The studies or data were also excluded for: (1) overlapping articles or duplicate data; (2) articles about cell lines or animals; (3) being impossible to extract the appropriate data from the published results; (4) conference records; (5) studies lacking information on survival; or (6) patients who had previous chemotherapy or radiotherapy.

Outcomes of interest and data extraction

We mainly aimed at evaluating the prognostic value of HIF-1α positive expression in gastric cancer patients regarding 5-year overall survival. Our second aim was to assess the association of HIF-1α positive expression with tumor clinicopathological features, such as tumor differentiation, depth of tumor invasion, lymph node metastasis, lymphatic invasion, vascular invasion, and tumor node metastasis (TNM) stage. Overall survival was measured from the date of medical resection to either the day of death or the day of the last follow-up visit.

Two reviewers independently extracted the following parameters from each study: (1) first author and year of publication; (2) study population characteristics; (3) number of subjects who were included in studies; and (4) 5-year overall survival and clinicopathological features.

Qualitative assessment

Quality assessment was performed with the Newcastle-Ottawa quality assessment scale (NOS).

Statistical analysis

The meta-analysis was performed using the Review Manager (RevMan) software, (version 5.2; Cochrane collaboration, http://ims.cochrane.org/revman/download). We analyzed dichotomous variables using estimation of odds ratio (OR) with 95%CI. The pooled effect was calculated using either a fixed-effects or a random-effects model. Heterogeneity between studies was evaluated using the χ^2 and I^2 tests, and we considered heterogeneity present if the I^2 statistic was $\geqslant$ 50%. $P < 0.05$ was considered significant. Assessment of publication bias for each of the pooled study groups was performed using a funnel plot.

RESULTS

Selection of trials

The initial search strategy retrieved 221 publications. After screening all titles, abstracts, and full texts, nine studies[9-17] met our entry criteria and were retrieved for more detailed evaluation (Figure 1). All nine studies were ret-

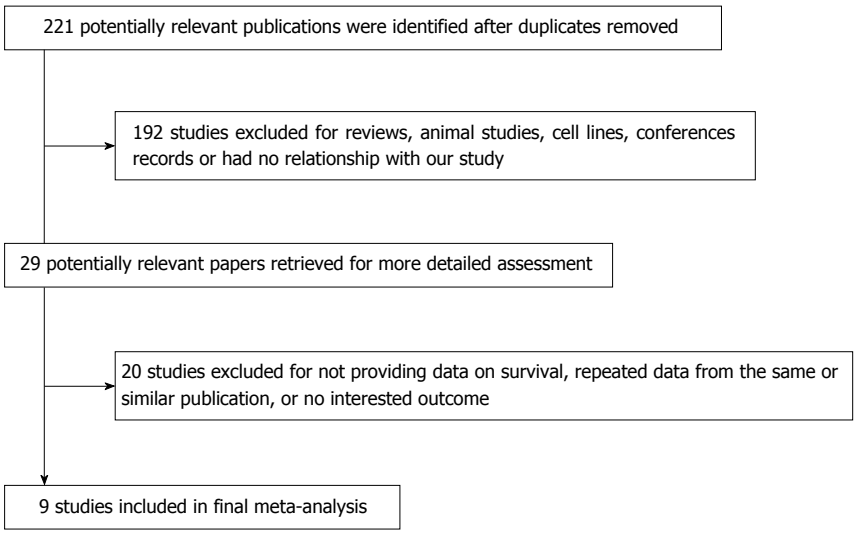


Figure 1 Flow diagram indicating the process of selecting articles for meta-analysis.

Table 1 Characteristics of the included studies

Ref.	Country of origin	Sample size (M/F, *n*)	Mean/median age (yr)	Study quality (points)	5-yr OS rate analysis	Expression rate
Zhan *et al*[9]	China	60 (38/22)	56.5	6/9	Reported	58.3%
Lu *et al*[10]	China	68 (43/25)	49.86	5/9	NR	52.9%
Isobe *et al*[11]	Japan	128 (91/37)	67.3	6/9	Reported	65.6%
Qiu *et al*[12]	China	188 (127/61)	57	6/9	Reported	54.6%
Oh *et al*[13]	South Korea	114 (67/47)	59	5/9	NR	15.8%
Kolev *et al*[14]	Japan	152 (110/42)	59.5	6/9	Reported	62.5%
Cabuk *et al*[15]	Turkey	51 (30/21)	63	4/9	NR	71%
Sumiyoshi *et al*[16]	Japan	216 (148/68)	65.2	5/9	NR	39.4%/85
Mizokami *et al*[17]	Japan	126 (83/41)	65.3	6/9	Reported	38.9%

Study quality was listed using the results of the Newcastle -Ottawa questionnaire. M: Male; F: Female; NR: Not reported; OS: Overall survival.

rospectively analyzed, and their characteristics are summarized in Table 1. Sample sizes ranged from 51 to 216, and the total number was 1103, 548 of whom had HIF-1α positive expression (50%). Of nine included studies, five provided data on 5-year overall survival. The studies were conducted in four countries (China, Japan, South Korea and Turkey).

Correlation between HIF-1α positive expression and 5-year overall survival

The 5-year overall survival was extracted from five studies. Meta-analysis indicated that patients with HIF-1α positive expression suffered with a lower 5-year overall survival (OR = 0.36; 95%CI: 0.21-0.64). The random effects model was used because of the heterogeneity (I^2 = 50.0%) (Figure 2A).

Correlation between HIF-1α positive expression and tumor clinicopathological features

Analysis of the pooled data showed that HIF-1α positive expression in gastric cancer was associated with biologically aggressive phenotypes such as tumor differentiation (OR = 0.38; 95%CI: 0.23-0.64; random effects model) (Figure 2B), depth of invasion (OR = 0.42; 95%CI: 0.32-0.57; fixed effects model) (Figure 2C), lymph node metastasis (OR = 2.23; 95%CI: 1.46-3.40; random effects model) (Figure 2D), lymphatic invasion (OR = 2.50; 95%CI: 1.46-4.28; random effects model) (Figure 2E), vascular invasion (OR = 1.80; 95%CI: 1.29-2.51; fixed effects model) (Figure 2F) and TNM stages Ⅲ + Ⅳ (OR = 0.31; 95%CI: 0.15-0.60; random effects model) (Figure 2G). In other words, the incidence of HIF-1α positive expression was significantly higher in the poorly differentiated and undifferentiated gastric cancer than in well and moderately differentiated types, and significantly lower in carcinomas in stages Ⅰ + Ⅱ than in stages Ⅲ + Ⅳ. HIF-1α positive expression was correlated with higher proportions of depth of invasion, lymphatic invasion, vascular invasion and lymph node metastasis.

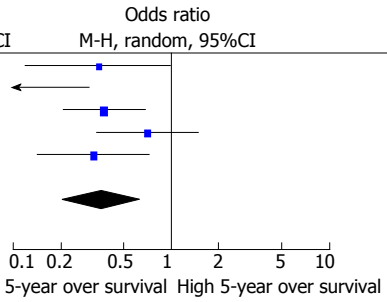
Publication bias

We used the inverted funnel plot to assess publication bias for all comparisons, and inspected its asymmetry visually. The shapes of the funnel plots showed a low potential for publication bias (Figure 3). Moreover, we used an influence analysis to evaluate the influence of a single study on the summary effect. The meta-analysis was not dominated by any individual study, and removing any study at a time made no difference.

A

Study or subgroup	HIF-1α positive Events	Total	HIF-1α negative Events	Total	Weight	Odds ratio M-H, random, 95%CI
1 Zhan H *et al*. 2013	12	35	15	25	17.1%	0.35 [0.12, 1.01]
3 Isobe T *et al*. 2013	53	84	43	44	6.6%	0.04 [0.01, 0.30]
4 Qiu MZ *et al*. 2011	36	110	44	78	28.9%	0.38 [0.21, 0.68]
6 Kolev Y *et al*. 2008	65	95	43	57	24.7%	0.71 [0.34, 1.48]
9 Mizokami, K *et al* 2006	29	49	63	77	22.8%	0.32 [0.14, 0.73]
Total (95%CI)		373		281	100.0%	0.36 [0.21, 0.64]
Total events	195		208			

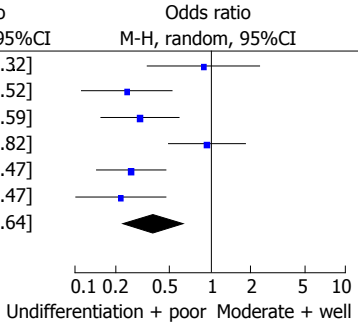
Heterogeneity: Tau^2 = 0.19; χ^2 = 7.94, df = 4 (P = 0.09); I^2 = 50%
Test for overall effect: Z = 3.53 (P = 0.0004)



B

Study or subgroup	HIF-1α positive Events	Total	HIF-1α negative Events	Total	Weight	Odds ratio M-H, random, 95%CI
2 Lu XX *et al*. 2013	17	36	16	32	13.6%	0.89 [0.34, 2.32]
3 Isobe T *et al*. 2013	25	84	28	44	16.1%	0.24 [0.11, 0.52]
4 Qiu MZ *et al*. 2011	20	110	33	78	17.7%	0.30 [0.16, 0.59]
6 Kolev Y *et al*. 2008	47	95	29	57	17.8%	0.95 [0.49, 1.82]
8 Sumiyoshi. Y *et al* 2006	23	85	77	131	18.8%	0.26 [0.14, 0.47]
9 Mizokami, K *et al* 2006	18	49	56	77	16.1%	0.22 [0.10, 0.47]
Total (95%CI)		459		419	100.0%	0.38 [0.23, 0.64]
Total events	150		239			

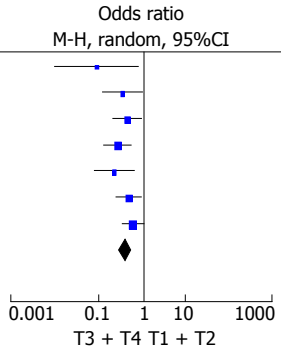
Heterogeneity: Tau^2 = 0.29; χ^2 = 15.84, df = 5 (P = 0.007); I^2 = 68%
Test for overall effect: Z = 3.61 (P = 0.0003)



C

Study or subgroup	HIF-1α positive Events	Total	HIF-1α negative Events	Total	Weight	Odds ratio M-H, random, 95%CI
1 Zhan H *et al*. 2013	1	35	6	25	5.0%	0.09 [0.01, 0.83]
2 Lu XX *et al*. 20139	8	36	14	32	8.5%	0.37 [0.13, 1.05]
3 Isobe T *et al*. 2013	32	84	25	44	15.0%	0.47 [0.22, 0.98]
4 Qiu MZ *et al*. 2011	15	110	28	78	20.9%	0.28 [0.14, 0.58]
5 Oh SY *et al*. 2008	7	18	70	96	10.0%	0.24 [0.08, 0.67]
6 Kolev Y *et al*. 2008	41	95	34	57	17.8%	0.51 [0.26, 1.00]
8 Sumiyoshi. Y *et al* 2006	45	85	84	131	22.9%	0.63 [0.36, 1.10]
Total (95%CI)		463		463	100.0%	0.42 [0.32, 0.57]
Total events	149		261			

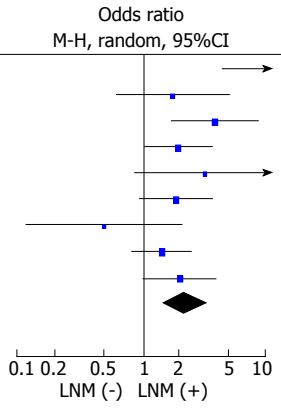
Heterogeneity: χ^2 = 6.68, df = 6 (P = 0.35); I^2 = 10%
Test for overall effect: Z = 5.72 (P < 0.00001)



D

Study or subgroup	HIF-1α positive Events	Total	HIF-1α negative Events	Total	Weight	Odds ratio M-H, random, 95%CI
1 Zhan H *et al*. 2013	32	35	9	25	6.2%	18.96 [4.50, 79.87]
2 Lu XX *et al*. 2013	27	36	20	32	9.5%	1.80 [0.64, 5.09]
3 Isobe T *et al*. 2013	50	84	12	44	12.5%	3.92 [1.77, 8.67]
4 Qiu MZ *et al*. 2011	82	110	44	74	14.9%	2.00 [1.06, 3.76]
5 Oh SY *et al*. 2008	15	18	58	96	7.1%	3.28 [0.89, 12.08]
6 Kolev Y *et al*. 2008	50	95	21	57	14.2%	1.90 [0.97, 3.73]
7 Cabuk, D. *et al*. 2007	24	36	12	15	6.2%	0.50 [0.12, 2.12]
8 Sumiyoshi. Y *et al* 2006	49	85	63	131	16.2%	1.47 [0.85, 2.55]
9 Mizokami, K *et al* 2006	25	49	26	77	13.3%	2.04 [0.98, 4.25]
Total (95%CI)		548		551	100.0%	2.23 [1.46, 3.40]
Total events	354		265			

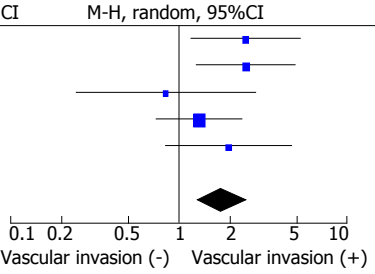
Heterogeneity: Tau^2 = 0.21; χ^2 = 17.46, df = 8 (P = 0.03); I^2 = 54%
Test for overall effect: Z = 3.72 (P = 0.0002)



E

Study or subgroup	HIF-1α positive Events	Total	HIF-1α negative Events	Total	Weight	Odds ratio M-H, random, 95%CI
3 Isobe T *et al*. 2013	55	84	19	44	16.8%	2.50 [1.18, 5.27]
6 Kolev Y *et al*. 2008	58	95	22	57	20.8%	2.49 [1.27, 4.89]
7 Cabuk, D. *et al*. 2007	20	36	9	15	11.0%	0.83 [0.24, 2.84]
8 Sumiyoshi. Y *et al* 2006	29	85	37	131	37.3%	1.32 [0.73, 2.73]
9 Mizokami, K *et al* 2006	14	49	13	77	14.1%	1.97 [0.83, 4.65]
Total (95%CI)		349		324	100.0%	1.80 [1.29, 2.51]
Total events	176		100			

Heterogeneity: χ^2 = 4.29, df = 4 (P = 0.37); I^2 = 7%
Test for overall effect: Z = 3.46 (P = 0.0005)

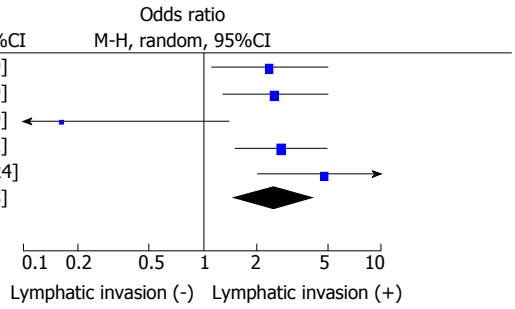


F

Study or subgroup	HIF-1α positive Events	Total	HIF-1α negative Events	Total	Weight	Odds ratio M-H, random, 95%CI
3 Isobe T *et al*. 2013	54	84	19	44	22.7%	2.37 [0.12, 4.99]
6 Kolev Y *et al*. 2008	66	95	27	57	24.5%	2.53 [1.28, 4.99]
7 Cabuk, D. *et al*. 2007	25	36	14	15	5.4%	0.16 [0.02, 1.39]
8 Sumiyoshi. Y *et al* 2006	61	85	63	131	27.3%	2.74 [1.53, 4.92]
9 Mizokami, K *et al* 2006	40	49	37	77	20.1%	4.80 [2.05, 11.24]
Total (95%CI)		349		324	100.0%	2.50 [1.46, 4.28]
Total events	246		160			

Heterogeneity: Tau^2 = 0.19; χ^2 = 8.59, df = 4 (P = 0.07); I^2 = 53%

Test for overall effect: Z = 3.33 (P = 0.0009)



G

Study or subgroup	HIF-1α positive Events	Total	HIF-1α negative Events	Total	Weight	Odds ratio M-H, random, 95%CI
1 Zhan H *et al*. 2013	3	35	16	25	11.5%	0.05 [0.01, 0.22]
2 Lu XX *et al*. 2013	10	36	16	22	13.8%	0.14 [0.04, 0.47]
4 Qiu MZ *et al*. 2011	41	110	56	78	19.9%	0.23 [0.12, 0.44]
5 Oh SY *et al*. 2008	7	18	60	96	15.4%	0.38 [0.14, 1.07]
6 Kolev Y *et al*. 2008	62	95	42	57	18.8%	0.67 [0.32, 1.39]
8 Sumiyoshi. Y *et al* 2006	45	85	80	131	20.7%	0.72 [0.41, 1.25]
Total (95%CI)		379		409	100.0%	0.31 [0.15, 0.60]
Total events	168		270			

Heterogeneity: Tau^2 = 0.50; χ^2 = 19.56, df = 5 (P = 0.002); I^2 = 74%

Test for overall effect: Z = 3.43 (P = 0.0006)

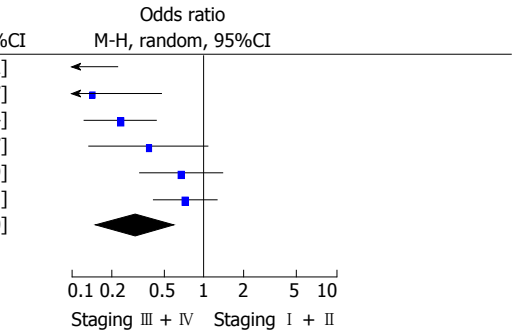


Figure 2 Forest plots. A: The results of the meta-analysis for 5-year overall survival; B: The results of the meta-analysis for tumor differentiation; C: The results of the meta-analysis for depth of invasion; D: The results of the meta-analysis for lymph node metastasis (LNM); E: The results of the meta-analysis for vascular invasion; F: The results of the meta-analysis for lymphatic invasion; G: The results of the meta-analysis for tumor node metastasis stage.

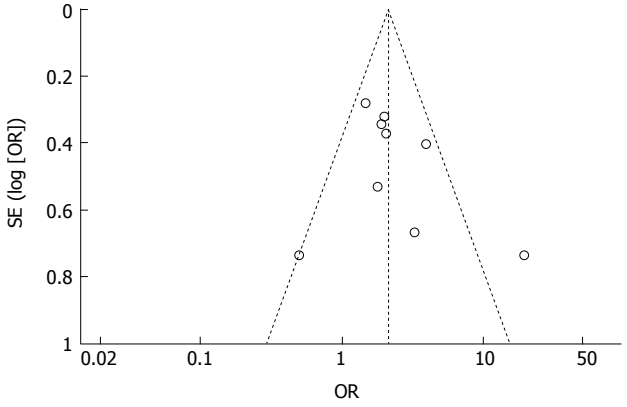


Figure 3 Funnel plot of studies of hypoxia inducible factor-1α positive expression in gastric cancer.

DISCUSSION

Meta-analysis has been traditionally applied and was mostly confined to randomized controlled trials (RCTs), and meta-analytical techniques using non-randomized controlled trials (NRCTs) might be a good method for use in some clinical settings in which either the number or the sample size of the RCTs is insufficient[18,19]. To our best knowledge, our study is the first comprehensive and detailed meta-analysis to assess the association of HIF-1α positive expression with 5-year overall survival and tumor clinicopathological features in gastric cancer patients. We believe that our results will provide useful information for clinical decision-making regarding gastric cancer.

Nowadays, many studies about the role of HIF-1α in tumors have already been conducted and the relationship between HIF-1α and tumors has been confirmed. HIF-1α plays a role in the tumor formation, progression and metastasis by activating genes which are related to regulation of angiogenesis, cell survival and metabolism[20-22]. Not all gastric cancers express HIF-1α and 548 (50%) of 1103 gastric cancer patients had HIF-1α positive expression in this meta-analysis. However, once gastric cancer cells acquire HIF-1α expression, they transform to have more aggressive and metastatic behavior. The meta-analysis about prognostic significance of HIF-1α has been studied in several cancers such as non-small cell lung cancer and hepatocellular carcinoma[5,23], and HIF-1α positive expression indicates a poor prognosis. In this study, we found that the 5-year overall survival in the HIF-1α positive group was significantly lower than that in the HIF-1α negative group. Thus, HIF-1α was a poor prognosis factor for gastric cancer patients.

Our result also demonstrated that HIF-1α positive expression was correlated with increased vascular invasion and lymphatic invasion. The presence of vascular invasion and lymphatic invasion may indicate increased biological aggressiveness and a greater possibility of systemic diffusion. As shown in previous studies, vascular invasion and lymphatic invasion were the main risk factors for tumor occurrence and had the close relation with tumor invasiveness[24,25]. Moreover, we analyzed the relationship between the expression of HIF-1α and clinicopathologic features of gastric cancer, and found that the expression of HIF-1α was related to higher proportions of poor tumor differentiation, deep invasion, lymph node metastasis and TNM stages Ⅲ + Ⅳ. This indicates that HIF-1α positive expression is closely

related to the poor biological behavior of gastric cancer.

There are several limitations to this meta-analysis, and consequently, the results should be interpreted with caution. First, the data came from NRCTs, and the overall level of clinical evidence was low. Abraham *et al*[26] had found that meta-analyses carried out on well designed NRCTs of surgical procedures were probably as accurate as those carried out on RCTs. Second, there was heterogeneity across studies. We applied a random-effects model to take variation between studies into consideration, and we believe that the heterogeneity would have had very limited influence. Third, reports in languages other than English were excluded. The risk of language bias had to be considered, but it may not result in any notable bias in the assessment of interventional effectiveness. Finally, publication bias was present in our analysis. The reason was that investigative groups might be more likely to report positive results, and that studies with significant outcomes are more likely to be published.

In conclusion, the results of this meta-analysis of 1103 patients showed that HIF-1α positive expression was associated with poor 5-year overall survival and clinicopathological features in patients with gastric cancer. Moreover, HIF-1α positive expression could be a useful prognostic marker for gastric cancer. Further studies are required to confirm these results.

ACKNOWLEDGMENTS

The authors would like to thank all of the patients and clinical investigators who were involved in the studies selected for this meta-analysis.

COMMENTS

Background

Although the prognosis of gastric cancer has improved, patients with gastric cancer still have a poor prognosis. The present prognostic factors do not fully predict individual clinical outcome. As a result, there is great interest in finding better markers to identify patients with a poor prognosis at the time of diagnosis.

Research frontiers

Meta-analysis was used to evaluate the prognostic role of hypoxia inducible factor-1α (HIF-1α) expression in gastric cancer in this study.

Innovations and breakthroughs

To the best knowledge, this is the first comprehensive and detailed meta-analysis to assess the association of HIF-1α expression with 5-year overall survival and tumor clinicopathological features in gastric cancer.

Applications

This study reported that the HIF-1α positive expression was associated with poor 5-year overall survival and clinicopathological features in patients with gastric cancer. In addition, HIF-1α positive expression could be a useful prognostic marker for gastric cancer.

Peer review

This manuscript describes an interesting meta-analysis of the HIF-1α positive expression associated with poor 5-year overall survival and clinicopathological features in patients with gastric cancer. In addition, HIF-1α positive expression could be a useful prognostic marker for gastric cancer. The manuscript was very well prepared and written and can be accepted for publication.

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