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Original Article

Meta-analysis of the expression of notch signaling pathway in gastric cancer cells and tissues and its clinical parameters

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Abstract: Objective: To perform a meta-analysis on the expression of the Notch signaling pathway in gastric cancer (GC) cells and tissues and its association with clinical parameters. Methods: Relevant literature on "the expression of the Notch signaling pathway in gastric cancer cells and tissues and its clinical parameters" was retrieved from both Chinese and English databases, including China National Knowledge Infrastructure (CNKI), Wanfang Data, PubMed, and Web of Science. Results: A total of 17 studies published between 2009 and 2025 were included. Using meta-analysis of continuous variables with a random-effects model, Notch1 expression was significantly higher in the study group than in the control group (MD = 0.19, 95% CI: 0.04-0.34, Z = 2.53, P = 0.01), whereas no statistically significant difference was observed in Notch2 expression between the two groups (MD = 0.21, 95% CI: -0.01-0.44, Z = 1.84, P = 0.07). The apoptosis rate was significantly higher in the study group than in the control group (MD = 9.46, 95% CI: 8.16-10.76, Z = 14.24, P < 0.01). Using meta-analysis of continuous variables with a fixed-effect model, Hes1 expression was significantly higher in the study group than in the control group (MD = 0.19, 95% CI: 0.20-0.39, Z = 6.05, P < 0.01), as was COX-2 expression (MD = 1.88, 95% CI: 1.67-2.09, Z = 17.53, P < 0.01). Using meta-analysis of dichotomous variables with a fixed-effect model, the rate of lymph node metastasis was significantly higher in the study group than in the control group (OR = 2.15, 95% CI: 1.55-2.74, Z = 7.03, P < 0.01). Funnel plot analysis, Egger's test, and Begg's test indicated no significant publication bias in this meta-analysis. Conclusion: In gastric cancer cells and tissues, Notch signaling pathway-related molecules, including Notch1, Notch2, Hes1, and COX-2 are highly expressed and are associated with apoptosis and lymph node metastasis.

Keywords: Notch signaling pathway, gastric cancer (GC), Hes1, COX-2, lymph node metastasis

Introduction

With the continuous advancement of clinical medicine, the early screening rate and 5-year survival rate for gastric cancer (GC) have significantly improved. However, the incidence and mortality of GC, as well as the rate of postoperative recurrence, remain high [1]. The underlying reasons are associated with the incomplete disruption of the tumor microenvironment, increased drug resistance, and the complex mechanisms and pathways involved in tumor-related metastasis [2]. A study by Jiang Y et al. [3] demonstrated that immune defense and the "metabolic antagonism" mechanism within the tumor microenvironment play a crucial role in regulating the heterogeneity of gastric cancer and enhancing the cytotoxicity of CD8+ effector T cells. For example, nicotinamide N-methyltransferase (NNMT), expressed by fibroblasts, is activated via the Notch signaling pathway by the transcription factor RBP-J [4]. The activated NNMT interacts with nicotinamide phosphoribosyltransferase (NAMPT), thereby maintaining a dynamic balance between nicotinamide and 1-methylnicotinamide, and subsequently upregulates or downregulates CD8+ T cell function [5]. Meanwhile, the Notch signaling pathway can also interact with other metabolic pathways such as PI3K/AKT and HGF/c-Met, thereby promoting the progression of gastric cancer or reducing the expression of NAMPT in macrophages [6].

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In normal gastric mucosa, the Notch signaling pathway and its associated metabolic factors primarily promote the differentiation of gastric epithelial cells into glands [7]. Among them, Notch1, a transmembrane protein, plays multiple roles in regulating cell differentiation, proliferation rate, and apoptosis. It not only maintains normal tissue function and intracellular and extracellular homeostasis, but also serves as a key cytokine in the development of drug resistance in gastric cancer patients [8, 9]. During the progression of GC, Notch1 can activate cyclooxygenase-2 (COX-2), which catalyzes the conversion of arachidonic acid into prostaglandins, thereby accelerating tumor microenvironment remodeling and angiogenesis, and promoting lymph node metastasis and inflammatory infiltration [10]. Overexpression of Notch2 may promote nuclear translocation of oncogenes, leading to uncontrolled cell proliferation or inhibition of apoptosis, which ultimately contributes to tumorigenesis [11]. In addition, the Notch signaling pathway can upregulate PHLDB2 expression and activate the AKT pathway to promote gastric mucosal carcinogenesis. Therefore, some researchers suggest that Notch1 and Notch2 could serve as therapeutic targets for GC [12]. However, the clinical application of the Notch signaling pathway in GC remains limited, and the underlying molecular mechanisms have not yet been fully understood. Therefore, this study conducted a meta-analysis on the expression of the Notch signaling pathway in GC cells and tissues, along with relevant clinical parameters, to clarify its clinical significance.

Materials and methods

Source of data

Relevant literature on the expression of the Notch signaling pathway in gastric cancer cells and tissues, along with associated clinical parameters, was retrieved from both Chinese and English databases. The final search was conducted on April 22, 2025, covering publications from 2000 to that date. In Chinese databases, including CNKI (China National Knowledge Infrastructure), Wanfang Data, and platforms under the Chinese Medical Association, the search terms used included: *gastric cancer*, *gastric cancer tissue*, *Notch signaling pathway*, *Notch inhibitors*, and *gastric cancer stem cells*. In English databases such as Google Scholar, Wiley Online Library, PubMed, Web of Science, Cochrane Library, and Springer Link, the following search terms were used: *gastric cancer*, *gastric cancer tissue*, *Notch signaling pathway*, *Notch inhibitors*, *Notch1*, *Notch2*, *Notch3*, and *gastric cancer stem cells*. Boolean operators AND and OR, Medical Subject Headings (MeSH), and precise searches of titles and abstracts were also used. AND indicated that two or more terms connected by AND had to be present simultaneously, thereby narrowing the search scope, whereas OR indicated that either term A or term B could be present, thereby broadening the search scope. An example of the search strategy was: ("Stomach Neoplasms"[MeSH Terms]) AND ("Notch1"[Title/Abstract]).

Literature selection

Inclusion criteria: The inclusion criteria for the selected studies were as follows: (1) Published from 2000 to the date of the final search; (2) Included patients diagnosed with primary gastric cancer; (3) Whose research methods and objectives were closely related to "Notch" and "gastric cancer"; (4) Involved participants without a history of gastrointestinal surgery or diseases that could affect the results, such as severe cardiovascular or cerebrovascular diseases, congenital immune disorders, or genetic mutations.

Exclusion criteria: The exclusion criteria were as follows: (1) Unpublished studies, studies retracted by journals, or studies involving academic or copyright disputes; (2) Studies with incomplete information; (3) Duplicate reports; (4) Studies with obvious errors or deficiencies in study design, research data, or statistical methods; and (5) Systematic reviews, bibliometric analyses, network pharmacology analyses, survey reports, descriptive studies, case reports, theoretical reviews, personal experience summaries, animal experiments, scientific conference proceedings, other meta-analyses, and similar types of literature.

Primary indicators: The primary indicators were as follows: (1) Expression of Notch1; (2) Expression of Notch2; (3) Expression of Hes1; (4) Survival time; (5) Expression of miR-124; (6) Expression of the Notch1 ligand Jagged-1 (JAG-1); (7) Expression of Hes5; (8) Immunohistochemistry (IHC) score; (9) Lymph node metasta-

sis; (10) Expression of γ-tocotrienol (γ-T3); (11) Expression of protein O-fucosyltransferase 1 (Pofut1); (12) Gender; (13) apoptosis rate; (14) Expression of Caspase-9 protein; (15) Expression of COX-2; (16) Expression of the drug resistance protein P-glycoprotein (P-gP); (17) Expression of programmed death-ligand 1 (PD-L1); and (18) Delta-like ligand 4 (DLL4).

Literature screening and information extraction

The titles of the retrieved articles were imported into the "NoteExpress 3.2 Literature Retrieval and Management" system for duplicate checking. After duplicate removal, the titles and abstracts were carefully reviewed to exclude low-quality or poorly relevant studies. Two researchers then independently screened the literature based on the inclusion and exclusion criteria and extracted the relevant information for summary. In case of disagreement, a third reviewer with greater clinical experience and a higher professional title was consulted to make the final decision. Extracted information included: (1) Basic information such as first author, publication year, and country; (2) Baseline characteristics of the study participants; (3) Study type, methods, research content, primary outcomes, and study findings; (4) Key factors affecting risk of bias assessment.

Literature quality evaluation

The quality of the final included studies was assessed using the Risk of Bias Assessment Tool in Cochrane's Review Manager 5.4. The assessment covered the following aspects: (1) The grouping method used, such as random sequence allocation, grouping by disease type, admission time, or treatment methods, which may lead to selection bias; (2) Whether allocation concealment was implemented, which could cause selection bias; (3) The use of double blinding, including blinding of patients and researchers, which could lead to performance bias; (4) Whether the outcome assessors were blinded, which could cause detection bias; (5) The completeness of outcome data, which could cause attrition bias; (6) Selective reporting of outcomes, which could cause reporting bias; (7) Other sources of bias, such as unreliable data, studies targeting specific populations, or potential research misconduct or concerns regarding data authenticity. The risk of bias for each of the seven domains was classified as: "low risk", "high risk", or "unclear risk". After the evaluation, the results were summarized, and a risk of bias graph was generated using the "figure" function in Review Manager 5.4 software.

Statistical analysis

Data processing was performed using the meta-analysis module in Stata 18.0. For dichotomous variables, the effect measure was the odds ratio (OR) with a 95% confidence interval (CI). For continuous variables, the effect measure was the mean difference (MD) with a 95% CI. If the units of continuous variables were different across studies, the standardized mean difference (SMD) with a 95% CI was used to represent the pooled effect measure. The Q-test was used to assess the heterogeneity among the included studies, and the I^2 statistic was applied to quantify the extent of heterogeneity. If there was no statistically significant heterogeneity among the study results ($P > 0.1$, $I^2 \leq 50\%$), a fixed-effect model was used to calculate the pooled OR and 95% CI. When statistically significant heterogeneity was present ($P \leq 0.1$, $I^2 > 50\%$), a random-effects model was used to calculate the pooled OR and 95% CI, and a forest plot was generated. Sensitivity analysis of the pooled effects was performed using the leave-one-out method. If removal of an individual study did not substantially alter the direction or statistical significance of the pooled effect, the meta-analysis results were considered robust; otherwise, the study was considered to have a substantial influence on the pooled result. For the pooled outcome with the largest number of included studies, funnel plot analysis and tests for small-study effects were performed to assess potential bias, using either the nonparametric rank-correlation Begg test or the regression-based Egger test. A P value < 0.05 was considered indicative of statistical significance.

Results

Literature screening results

After searching the databases using both Chinese and English keywords, a total of 1,572 articles related to the expression of the Notch

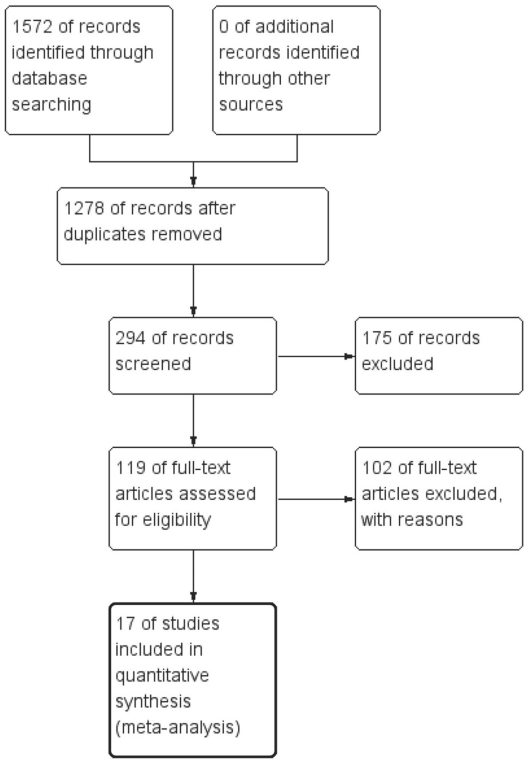


Figure 1. Literature search process.

signaling pathway in gastric cancer cells and tissues, as well as associated clinical parameters, were initially identified. The titles of the articles were imported into the "NoteExpress 3.2 Literature Retrieval and Management" system for duplicate checking, resulting in the removal of 1,278 articles, leaving 294 articles. After reviewing the titles and abstracts, 175 articles with low relevance or poor quality were excluded, leaving 119 articles. Following the inclusion and exclusion criteria, 102 additional articles were excluded, and finally, 17 articles were included in this meta-analysis. The literature search process is shown in **Figure 1**.

Basic characteristics of included studies

The final 17 included studies [13-29], published between 2009 and 2025, involved a total of 34 groups and 1,629 patients. Among them, nine studies [14-16, 18, 20, 23, 25, 27, 29] were randomized controlled trials, while eight studies [13, 17, 19, 21, 22, 24, 26, 28] were non-randomized controlled trials. Seven studies [13-19] were in English, and ten studies [20-29] were in Chinese. Details are provided in **Table 1**.

Literature quality evaluation

In the 17 included studies, 11 studies [13, 14, 19, 22-29] used random number tables or computer-generated random numbers for grouping, all of which were rated as "low risk"; 6 studies [15-18, 20, 21] were grouped by disease type or pathological type, all of which were rated as "unclear risk". Eleven studies [13-17, 22-24, 26-28] implemented allocation concealment and blinding, all rated as "low risk"; 6 studies [18-21, 25, 29] did not describe allocation concealment, double blinding, or blinding of outcome assessment, all rated as "unclear risk". All 17 studies had complete research data. Fifteen studies [14-26, 28, 29] showed no selective reporting or reporting bias, and no other biases, all rated as "low risk"; 2 studies [13, 27] had selective reporting, rated as "high risk", as shown in **Figure 2**.

Meta-analysis of primary indicators

Meta-analysis of Notch1: All 17 studies [13-29] reported the expression of Notch1, involving a total of 34 groups and 1,629 patients. A meta-analysis of continuous variables revealed significant heterogeneity among the studies ($P < 0.01$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the Notch1 expression in the study group was significantly higher than in the control group (MD = 0.19, 95% CI: 0.04-0.34, $Z = 2.53$, $P = 0.01$). In the subgroups, Notch1 expression was significantly higher in both the "GC + Drug resistance" and "GC + Lymph node metastasis" groups than in the control group (both $P < 0.05$), as shown in **Figure 3**. Sensitivity analysis using the leave-one-out method showed that the pooled MD fluctuated slightly between 0.17 and 0.28 (all $P < 0.05$), with the direction of the effect remaining consistent with that of the primary analysis, indicating that the pooled results were robust, as shown in **Figure 4**.

Meta-analysis of Notch2: Seven studies [13, 14, 17, 20-22, 24] reported the expression of Notch2, involving a total of 14 groups and 582 patients. A meta-analysis of continuous variables revealed significant heterogeneity among the studies ($P < 0.01$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results showed no statistically significant difference in Notch2 expression between the study

Table 1. Basic characteristics of included studies

Author	Year	n	Study group	Control group	Randomized controlled	Disease	Outcome index
Sun Y et al. [13]	2011	126	74	52	NO	GC	① ② ③
Bauer L et al. [14]	2015	226	142	84	Yes	GC	① ② ④
Jiang L et al. [15]	2016	160	80	80	Yes	GC	① ③ ⑤ ⑥ ⑦
Huang B et al. [16]	2019	128	64	64	Yes	GC + Lymph node metastasis	① ⑧ ⑨
Xie L et al. [17]	2023	30	18	12	NO	GC	① ② ⑩
Dong S et al. [18]	2023	40	20	20	Yes	GC	① ⑪
Ma H et al. [19]	2022	128	64	64	NO	GC + Lymph node metastasis	① ⑧ ⑨ ⑫
Wang MF et al. [20]	2011	16	8	8	Yes	GC + Apoptosis	① ② ⑬ ⑭
Liu M et al. [21]	2018	65	34	31	NO	GC	① ② ⑨ ⑮
Bo H et al. [22]	2018	24	12	12	NO	GC	① ② ⑥ ⑮
David L et al. [23]	2009	70	35	35	Yes	GC + Drug resistance	① ⑬ ⑯
Mu LS et al. [24]	2025	95	60	35	NO	GC	① ② ③ ⑨ ⑮ ⑰
Zhang JW et al. [25]	2011	40	20	20	Yes	GC	① ③ ⑦ ⑬
Gou CY et al. [26]	2010	130	108	22	NO	GC	① ⑬ ⑮
Zhou MK et al. [27]	2012	120	60	60	Yes	GC	① ③ ⑥ ⑨ ⑬ ⑮
Zhang FH [28]	2014	105	55	50	NO	GC	① ③ ⑬ ⑱
Yang XD et al. [29]	2009	126	63	63	Yes	GC	① ⑥ ⑮ ⑱

Note: ① Expression of Notch1; ② Expression of Notch2; ③ Expression of Hes1; ④ Survival time; ⑤ Expression of miR-124; ⑥ Expression of JAG-1; ⑦ Expression of Hes5; ⑧ IHC score; ⑨ Lymph node metastasis; ⑩ Expression of γ-T3; ⑪ Expression of Pofut1; ⑫ Gender; ⑬ Apoptosis rate; ⑭ Expression of Caspase-9 protein; ⑮ Expression of COX-2; ⑯ Expression of drug resistance protein P-gP; ⑰ Expression of PD-L1; ⑱ Expression of DLL4.

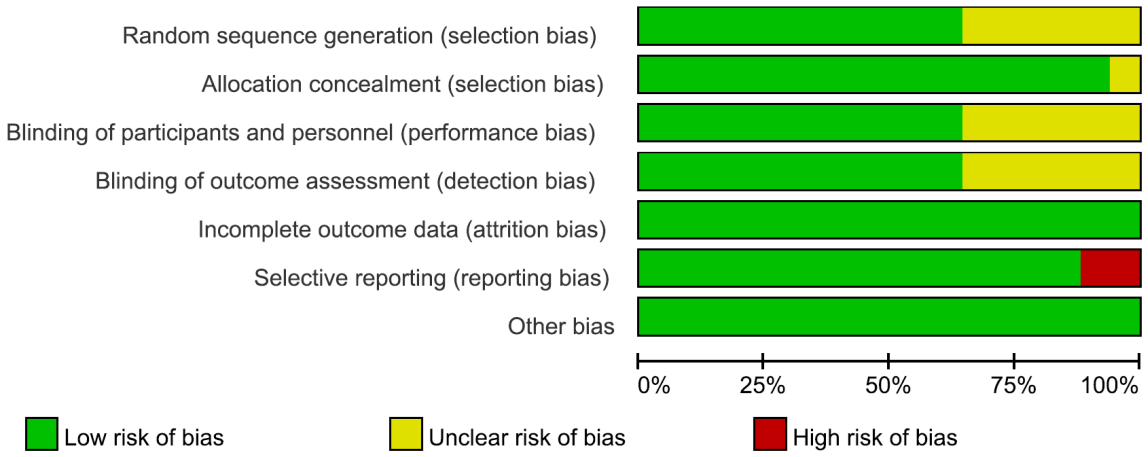


Figure 2. Quality assessment of the literature.

and control groups (MD = 0.21, 95% CI: -0.01-0.44, $Z = 1.84$, $P = 0.07$). No statistically significant differences were observed between any of the subgroups and the control group (all $P > 0.05$), as shown in **Figure 5**. Sensitivity analysis showed that after Study 22 was excluded, the pooled MD was 0.27 ($P < 0.001$), with a change in the direction of the effect, indicating that this study had a substantial influence on the pooled result, as shown in **Figure 6**.

Meta-analysis of Hes1: Six studies [13, 15, 24, 25, 27, 28] reported the expression of Hes1, involving a total of 12 groups and 646 patients. A meta-analysis of continuous variables revealed no statistically significant heterogeneity among the studies ($P > 0.01$, $I^2 < 50\%$), so a fixed-effect model was used for analysis. The results confirmed that the Hes1 expression in the study group was significantly higher than in the control group (MD = 0.19, 95% CI:

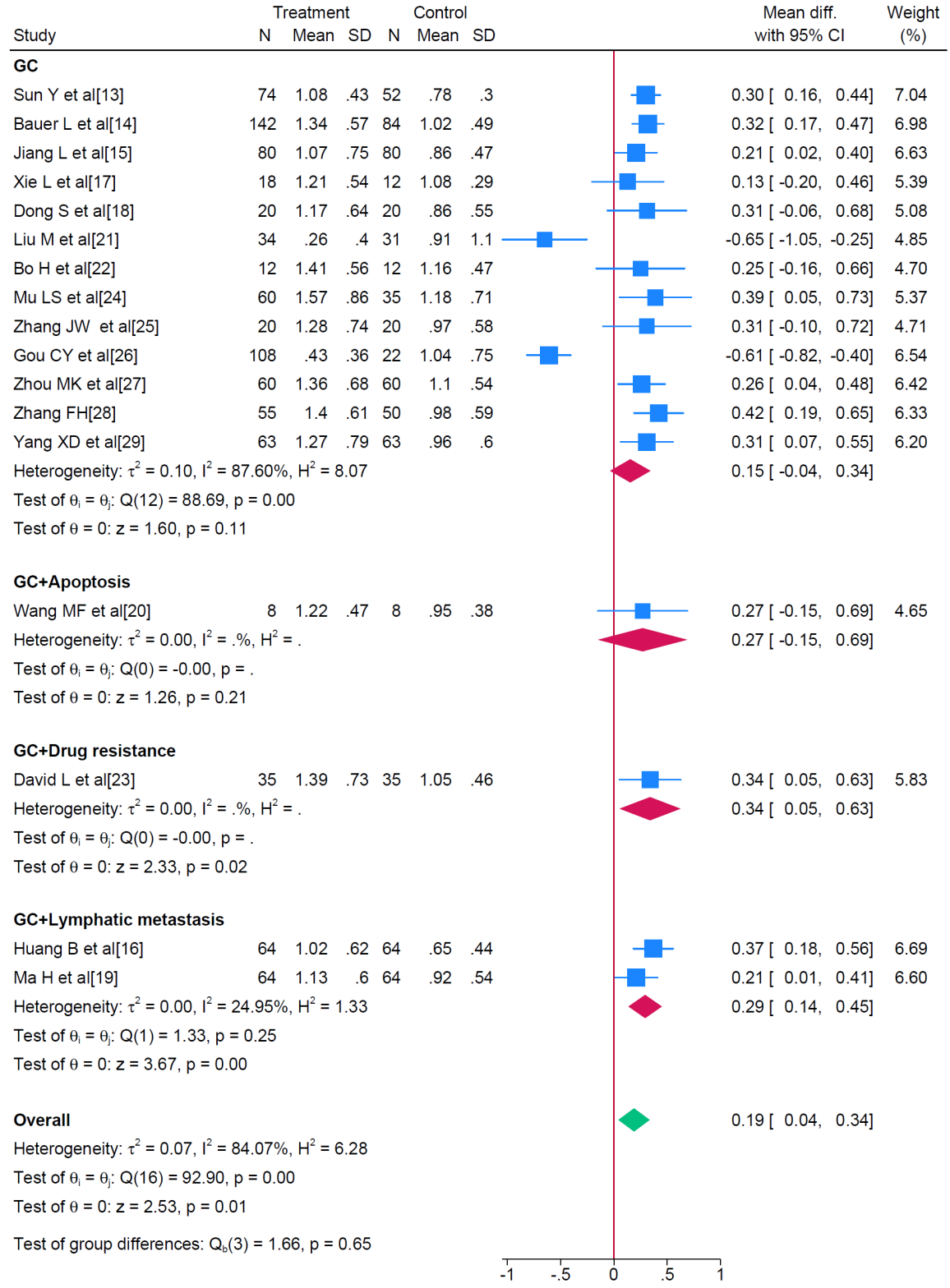


Figure 3. Meta-analysis of Notch1.

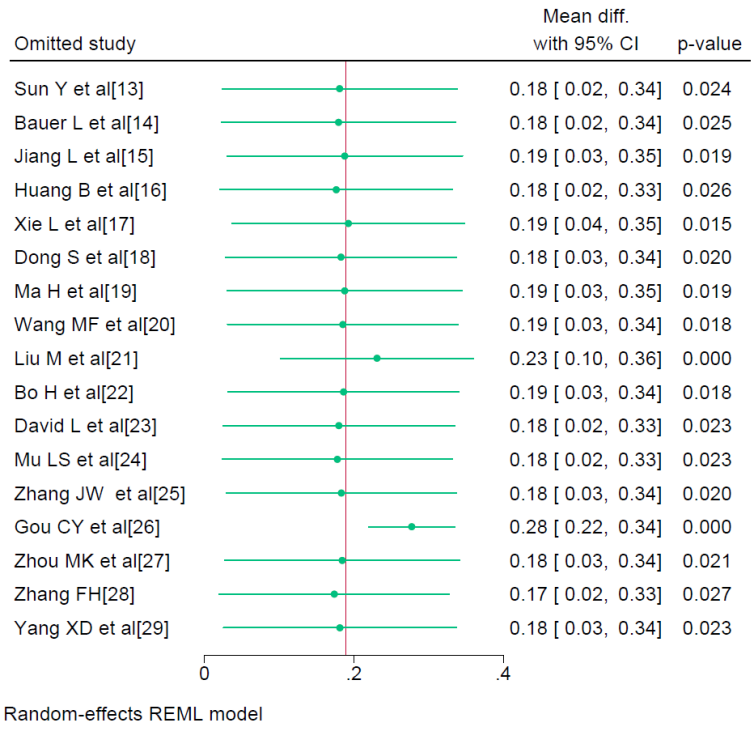


Figure 4. Sensitivity analysis of Notch1.

0.20-0.39, Z = 6.05, P < 0.01), as shown in **Figure 7**. Sensitivity analysis showed that the pooled MD fluctuated slightly between 0.26 and 0.38 (all P < 0.001), with the direction of the effect remaining consistent with that of the primary analysis, indicating that the pooled results were robust, as shown in **Figure 8**.

Meta-analysis of lymph node metastasis: Five studies [16, 19, 21, 24, 27] reported lymph node metastasis, involving a total of 10 groups and 536 patients. A meta-analysis of dichotomous variables revealed no statistically significant heterogeneity among the studies (P > 0.01, I^2 < 50%), so a fixed-effect model was used for analysis. The results confirmed that the rate of lymph node metastasis in the study group was significantly higher than in the control group (OR = 2.15, 95% CI: 1.55-2.74, Z = 7.03, P < 0.01). In the subgroups, the rates of lymph node metastasis in both the "GC" and "GC + Lymph node metastasis" groups were significantly higher than those in the control group (both P < 0.01), as shown in **Figure 9**. Sensitivity analysis showed that the pooled MD fluctuated slightly between 2.04 and 2.23 (all P < 0.001), with the direction of the effect remaining consistent with that of the primary analysis, indicating that the pooled results were robust, as shown in **Figure 10**.

Meta-analysis of cell apoptosis rate: Six studies [20, 23, 25-28] reported the apoptosis rate, involving a total of 12 groups and 481 patients. A meta-analysis of continuous variables revealed significant heterogeneity among the studies (P < 0.1, I^2 > 50%), so a random-effects model was used for analysis. The results confirmed that the apoptosis rate in the study group was significantly higher than in the control group (MD = 9.46, 95% CI: 8.16-10.76, Z = 14.24, P < 0.01). The apoptosis rates in all subgroups were significantly higher than in the control group (all P < 0.01), as shown in **Figure 11**. Sensitivity analysis showed that the pooled MD varied slightly, ranging from 9.12 to 9.96 (all P < 0.001), with the direction of the effect remaining consistent with that of the primary analysis, indicating that the pooled results were robust, as shown in **Figure 12**.

Meta-analysis of COX-2: Six studies [21, 22, 24, 26, 27, 29] reported the expression of COX-2, involving a total of 12 groups and 560 patients. A meta-analysis of continuous variables revealed low heterogeneity among the studies (P > 0.1, I^2 < 50%), so a fixed-effect model was used for analysis. The results confirmed that the COX-2 expression in the study group was significantly higher than in the control group (MD = 1.88, 95% CI: 1.67-2.09, Z = 17.53, P < 0.01), as shown in **Figure 13**. Sensitivity analysis showed that the pooled MD fluctuated slightly between 1.80 and 1.97 after excluding any one study (all P < 0.001), indicating that the pooled results were robust, as shown in **Figure 14**.

Publication bias analysis

In the funnel plot of Notch1, the pooled effect sizes showed an asymmetric distribution, with some studies falling outside the 95% confi-

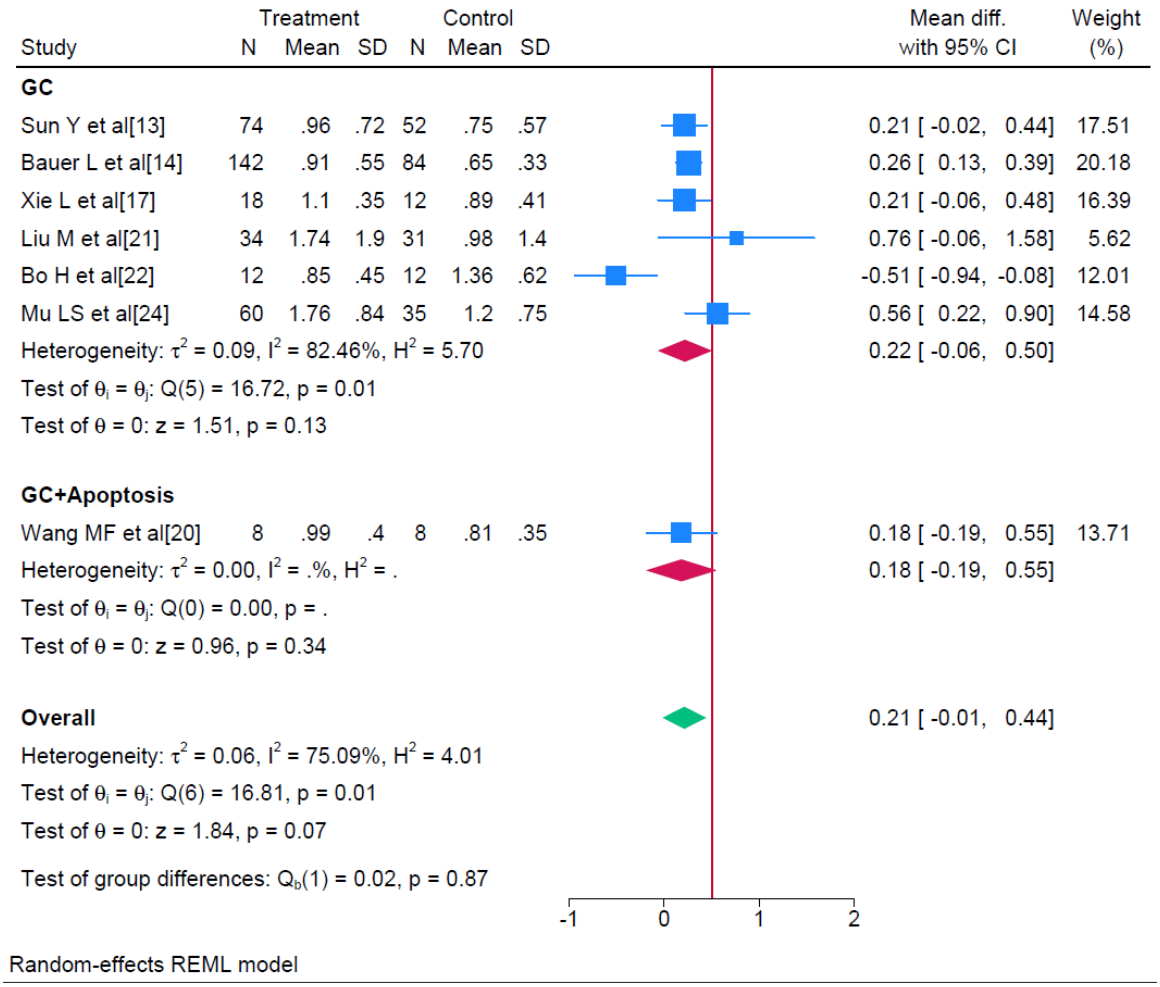


Figure 5. Meta-analysis of Notch2.

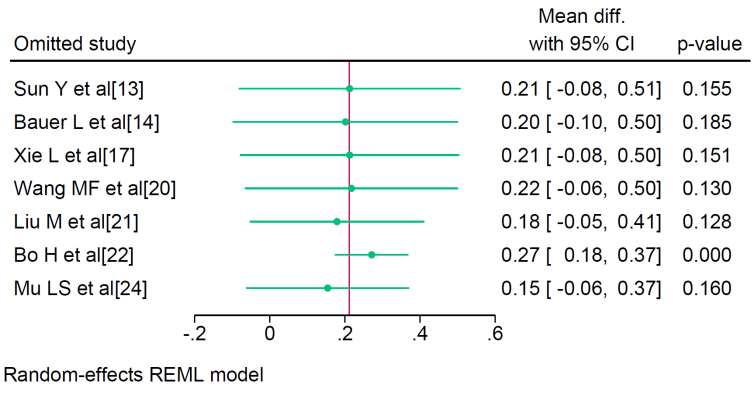


Figure 6. Sensitivity analysis of Notch2.

dence interval (CI), indicating the possibility of publication bias, as shown in **Figure 15**. Further assessment using Begg's and Egger's tests showed no significant publication bias (Begg's test: Z = -1.19, P = 0.266; Egger's test: Z = -0.43, P = 0.668).

Other indicators

For indicators ④-⑧, ⑩-⑫, ⑭, and ⑯-⑱, there were fewer reported studies, and thus, no pooled analysis or meta-analysis was conducted.

Discussion

GC is a malignant tumor of the digestive tract arising from the abnormal proliferation of gastric mucosal epithelial cells, with adenocarcinoma being the most common type. It is closely associated with risk factors such as *Helicobacter pylori* (Hp) infection, high-salt diet, and smoking [30]. These risk factors can stimulate the Notch signaling cascade, in which different receptors and cytokines are involved in cell migration, inflammation, immunity, micro-

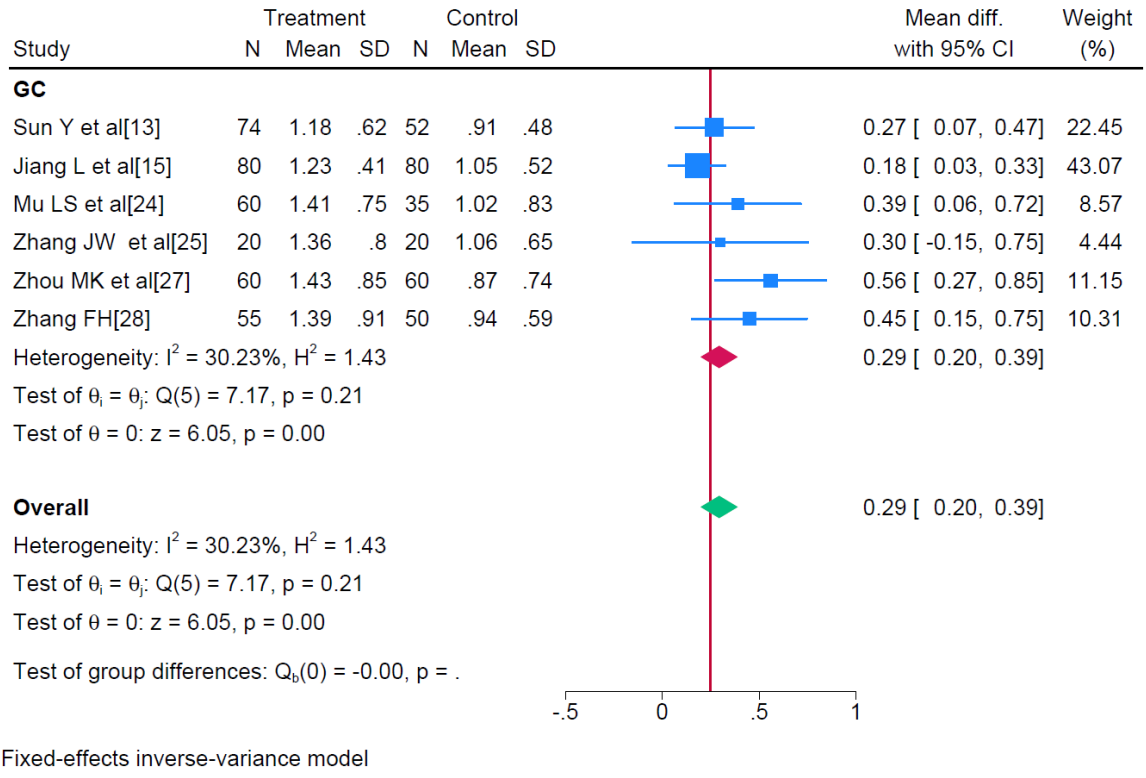


Figure 7. Meta-analysis of Hes1.

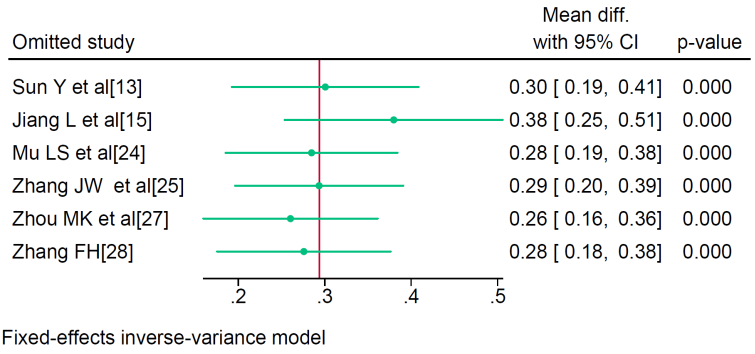


Figure 8. Sensitivity analysis of Hes1.

vascular formation, and other processes, thereby promoting cancer progression and enhancing drug resistance [31]. This suggests that blocking the expression of Notch signaling pathway-related receptors or cytokines may represent a potential new therapeutic approach for advanced GC. The results of this study showed that Notch1 expression was significantly higher in the study group than in the control group, including in the "GC + Drug resistance" and "GC + Lymph node metastasis" subgroups. These findings suggest that the expression of Notch signaling pathway-related receptors is significantly associated with tumor infiltration depth, TNM stage, and drug resistance mechanisms. A meta-analysis [32] also showed that the expression levels of Notch1, Notch2, and Hes1 in GC tissues were significantly higher than those in the control group (healthy individuals), and the expression of Notch1 was significantly associated with lymph node metastasis, distant metastasis, the spread pattern, and the degree of differentiation of GC. However, in studies 21 and 26, the expression of Notch1 in adjacent tissues (control group) was significantly higher than in cancer tissues (study group). This is because, in the early stages of tumor development, abnormal cell proliferation stimulates negative feedback mechanisms that compensatorily suppress the overexpression of Notch1 receptors and their ligands, while normal or adjacent tissues still require Notch1/2 to regulate cell metabolism

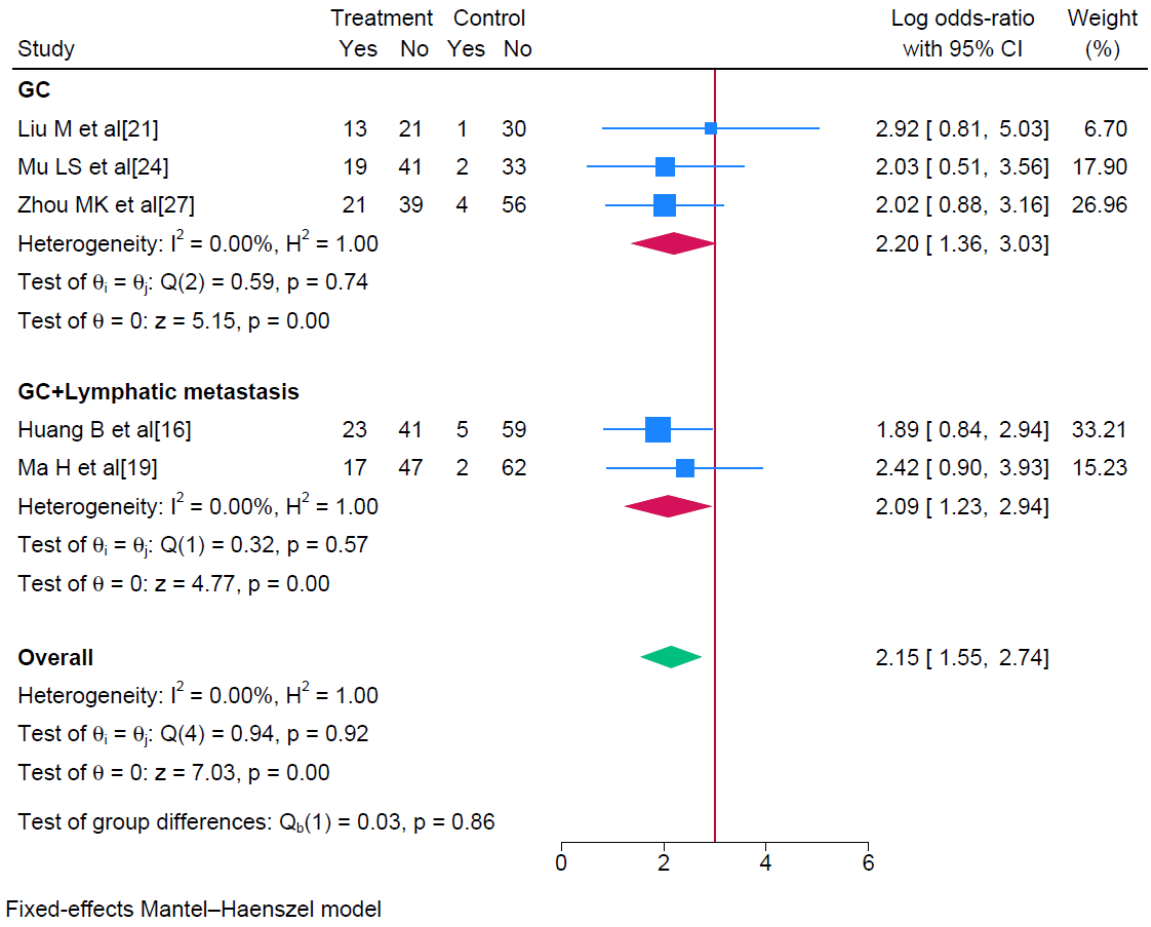


Figure 9. Meta-analysis of lymph node metastasis.

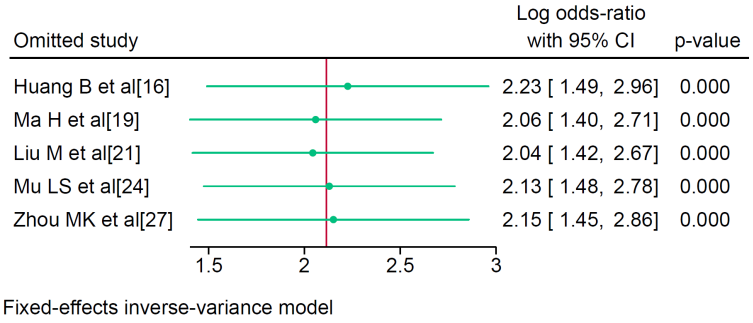


Figure 10. Sensitivity analysis of lymph node metastasis.

and renewal in tissues such as the skin, intestine, and nervous system, to maintain the normal function and structure of organs and tissues [33, 34].

However, with the increased tumor cell infiltration and the occurrence of immune evasion, cell signaling in the tumor microenvironment continuously stimulates the expression of Notch1/2 and other Notch family receptors, leading to dysregulation of cell differentiation and tissue homeostasis [35]. Therefore, the study group exhibited significantly higher rates of lymph node metastasis and cell apoptosis than the control group. To disrupt the tumor microenvironment and improve cell infiltration, Ku SY et al. [36] pointed out that silencing or knockout of Notch1/2 can inhibit the activity of the Notch signaling cascade, downregulate the expression of Notch1 and Hes1, and block the binding of Notch receptors to ligands (such as DLL4 and JAG-1). A study by Yao Y et al. [37] showed that the inhibition of Notch signaling activity can block multiple signaling axes, such as Notch1-COX-2, Notch2-COX-2, and Dll4-Notch1, thereby reducing abnormal cell proliferation

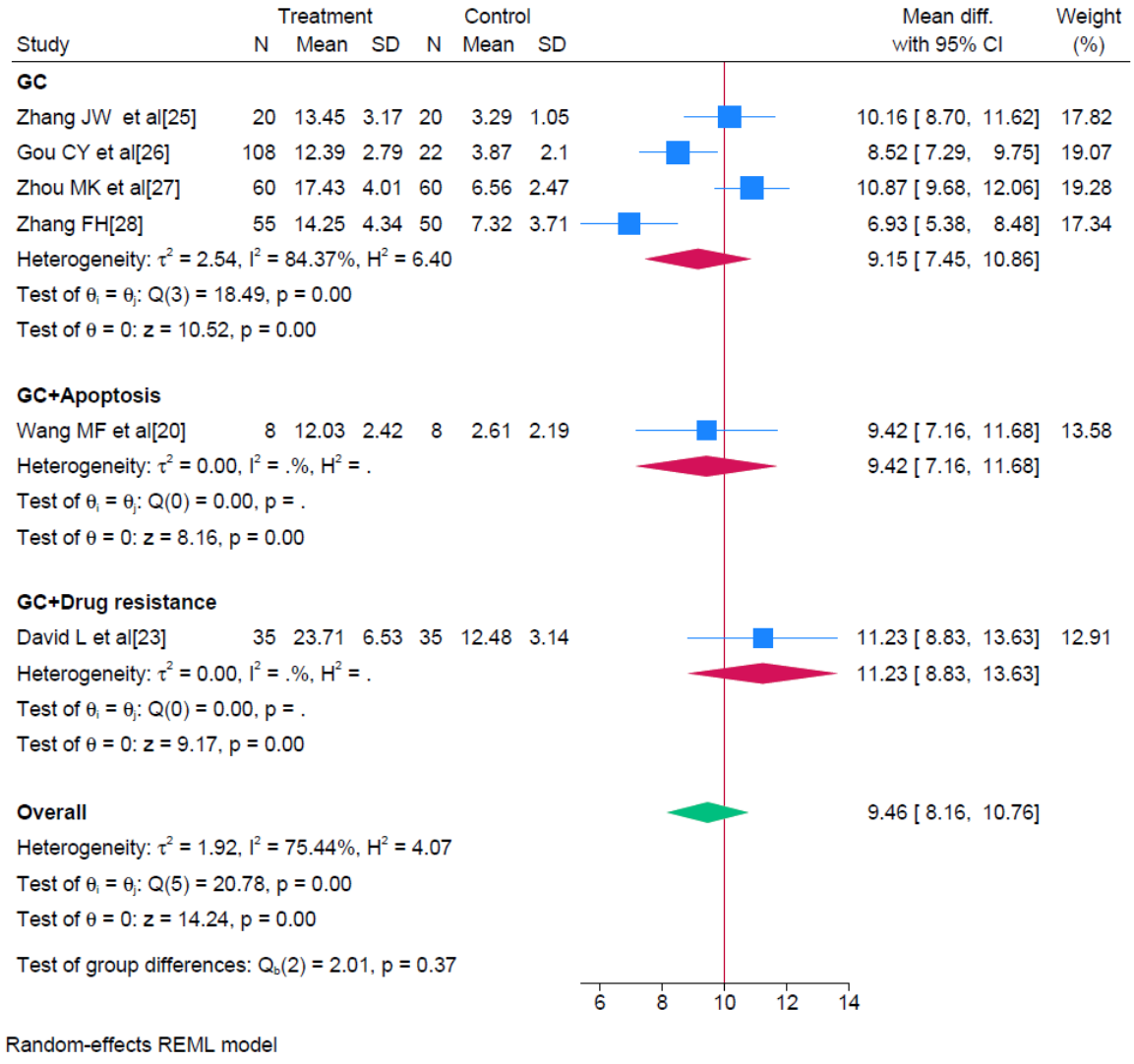


Figure 11. Meta-analysis of apoptosis rate.

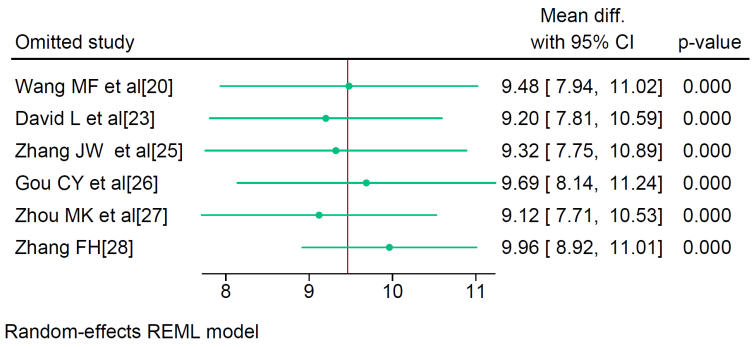


Figure 12. Sensitivity analysis of apoptosis rate.

and migration. Notably, comparison of different studies in the present study revealed that although Notch2 can promote GC progression by binding to the COX-2 promoter, the expression profiles of Notch1/2 differ substantially among different GC cell lines, such as the intestinal-type GC cell line MKN28 and the diffuse-type GC cell line MKN45 [38, 39]. For example, in Study 22, Notch2 expression in GC tissues was significantly lower than that in normal tissues, while the level of its ligand JAG1 did not change significantly. Therefore, after Study 22 was excluded, the pooled effect size (MD) and statistical significance of Notch2 changed substantially.

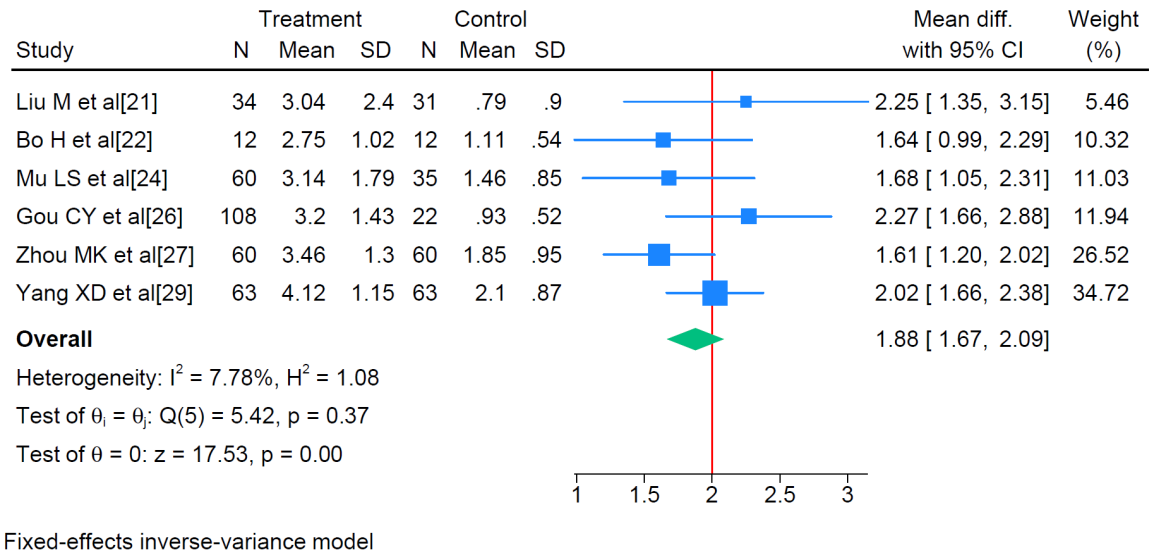


Figure 13. Meta-analysis of COX-2.

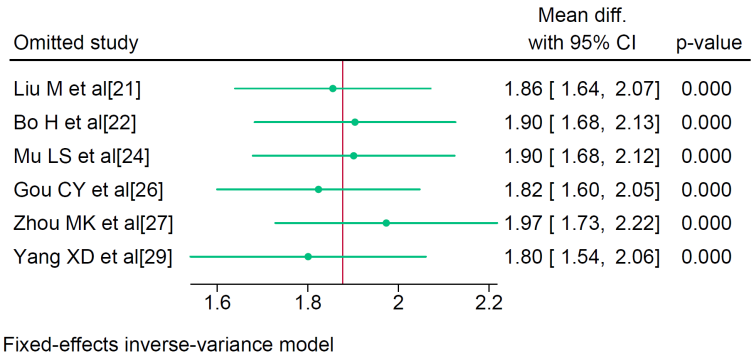


Figure 14. Sensitivity analysis of COX-2.

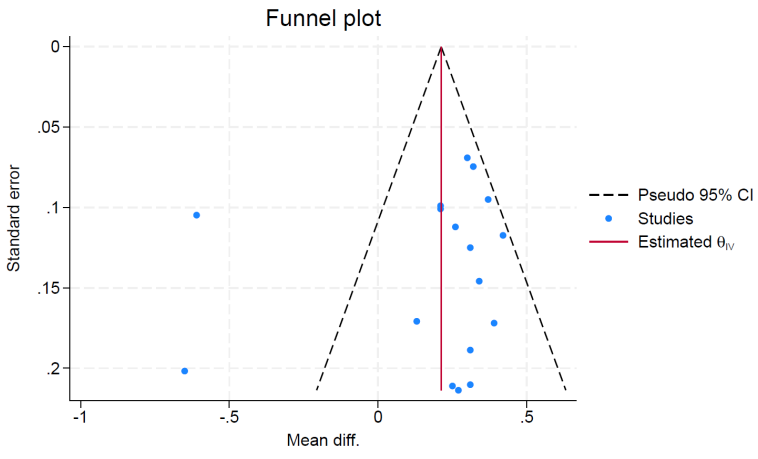


Figure 15. Funnel plot analysis of Notch1.

Shi Q et al. [40] also pointed out that the Notch signaling pathway can enhance the chemoresistance of tumor cells and strengthen drug resistance through multiple mechanisms. (1) Aberrant activation of the Notch signaling pathway enhances the stemness characteristics of cancer stem cells (CSCs), thereby increasing the resistance of GC cells to oxaliplatin [41]. (2) Upregulation of Notch1/2 promotes the expression of the drug resistance protein P-glycoprotein (P-gP), thereby increasing resistance to 5-fluorouracil and aggravating the toxic side effects of chemotherapy in patients with GC [42]. (3) With increased Notch signaling activity, the cell-mediated functions of other signaling pathways, such as Wnt, Ras, MAPK, and NF-kB, are also enhanced, thereby amplifying inflammatory responses, impairing the cytotoxic activity of NK cells, and contributing to the development of multidrug resistance [43, 44]; (4) Aberrant activation of the Notch signaling pathway or Notch1 mutations can lead to dysregulated expression of the downstream target gene Hes1, affecting the nervous system and vascu-

lar functions, thereby reducing drug efficacy [45]. Although Notch inhibitors (such as γ-secretase inhibitors) can be used clinically to block the cascade effects of the Notch signaling pathway, there is still a lack of efficient lead compounds [46]. Moreover, different pathological types of GC or drug-resistant cellular phenotypes may require different targeted drugs against Notch receptors and ligands, and relatively few clinical trials have been conducted in this area to date [47]. Takahashi H et al. [48] also found that when using osimertinib to treat epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer, although this Notch inhibitor demonstrated significant anti-tumor activity, its effects were short-lived, and most patients developed resistance to chemotherapy after treatment.

Recent studies suggest that these phenomena may be related to crosstalk among multiple biological cascades involving mitochondria. The WSGC peptide can inhibit the Notch pathway and downregulate mitophagy, thereby restoring mitochondrial homeostasis and increasing the sensitivity of gastric cancer cells to chemotherapy [49]. In addition, the Notch signaling pathway is not the only pathway for gastric cancer cell proliferation and tissue infiltration. The inhibition of a single signaling pathway is also difficult to achieve effective tumor control or remission. The genetic map of gastric adenocarcinoma shows that both human gastric adenocarcinoma tissues and chemically induced mouse gastric tumors exhibit enhanced Notch and mTORC1 signaling pathway activity, with these pathways targeting HES1 and phosphorylated S6 ribosomal protein, respectively [50]. Chang Z et al. [51] found that the extracellular matrix protein THBS2 can also upregulate the levels of Notch3, HES1, and other cytokines via the Notch signaling pathway. Inhibition of THBS2 can reduce tumor cell activity and delay GC progression and liver metastasis. Therefore, in the treatment of gastric cancer, in addition to targeted chemotherapy, combined targeted therapies should be adopted to achieve dual or multiple signaling pathway inhibition.

Conclusion

In gastric cancer cells and tissues, Notch1, Hes1, and COX-2, which are associated with the Notch signaling pathway, are highly expressed, with cell apoptosis and lymph node metastasis also observed, whereas the expression of Notch2 is relatively complex. If Notch inhibitors are to be considered potential therapeutic agents for GC in clinical practice, more rigorous *in vivo* and *in vitro* studies are still required. Moreover, the Notch signaling pathway comprises multiple transmembrane receptors and ligands, whose functions vary significantly across different anotomical sites and pathological subtypes of gastric cancer. This paper only conducted a meta-analysis of the literature on Notch1/2, and the depth of the analysis remains limited. In future clinical research, a comprehensive knowledge base of the Notch signaling pathway should be established to further explore its potential value in different types of GC.

Disclosure of conflict of interest

None.

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