What is The Impact of CSN5 on The Prognosis of Digestive System Cancers: A Systematic Review and Meta-Analysis

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Abstract

Background: Despite the understanding of COP9 signalosome subunit 5 (CSN5) in tumor genesis, there is no conclusive evidence on CSN5 value to predict digestive system tumor patients' survival and prognosis. The article was performed to evaluate the impact of CSN5 expression levels on survival consequence and clinicopathological parameters of digestive system neoplasm patients.

Methods: A comprehensive search was conducted through four databases. We utilized Hazard Ratio (HR) with a 95% confidence interval (CI) to evaluate the prognostic value of CSN5 in overall survival (OS) and recurrence free survival (RFS). We estimated the connection between CSN5 and clinicopathological parameters based on Odds Ratio (OR) with a corresponding 95% CI.

Results: The meta-analysis contained 22 studies, involving 2,193 patients diagnosed with digestive system tumor. High CSN5 expression level was indicated to predict poorer OS (HR = 2.28, 95% CI: 1.71–3.03; p < 0.00001). Additionally, high CSN5 was correlated with worse invasion depth (OR = 0.49, 95% CI: 0.25-0.96, p = 0.04), positive lymphatic metastasis (OR = 0.28, 95% CI: 0.16-0.47, p = 0.00001), positive distant metastasis (OR = 0.32, 95% CI: 0.13-0.76, p = 0.01) and poorer differentiation degree (OR = 0.34, 95% CI: 0.19-0.60, p = 0.0003). However, we could not find a correlation between CSN5 expression and age, gender, tumor stage, tumor size or vascular invasion. Furthermore, no significant publication bias was detected.

Conclusion: This meta-analysis demonstrated that the overexpression of CSN5 level could foresee poorer OS in digestive system cancer patients. Additionally, CSN5 level was related to tumor invasion depth, lymphatic metastasis, distant metastasis and differentiation degree.

Background

Digestive system neoplasm is regarded as a malignancy with high morbidity all over the world, with almost 6.1 million new cases diagnosed annually(1). Regardless of recent progress in clinical medicine, many patients with tumors are diagnosed at advanced stages. If early-stage patients were identified and treated before tumor deterioration, the mortality would diminish. Therefore, to achieve early detection and intervention of digestive system tumors, a call for reliable diagnostic and prognostic markers, with high sensitivity and specificity, is necessary.

C-Jun activation binding protein (Jab1) interacts with C-Jun at its activation domain and increases the stability of C-Jun or Jun D complexes acting on AP-1 transcription factor binding sites. It improves specifically the activation of downstream genes(2). Besides, Jab1 is known as COP9 signalosome subunit 5 (CSN5)(3) as well, participating in the regulation of signal transduction(4–6), cellular proliferation(7) and cell apoptosis(8), as well as deregulation of genomic stability and DNA repair(9). One of the most important functions of Jab1/CSN5 is to regulate protein degradation conducted by ubiquitin(10). Deregulation of Jab1/CSN5 can lead to oncogenesis by inactivating numerous vital proteins, such as p27(11). Besides, accumulating primary studies have indicated that Jab1/CSN5 was overexpressed in several human malignancies, like breast cancer(12), lung carcinoma(13), as well as digestive system cancers(14, 15) and had a potential relationship with their prognosis. However, there is no reliable study to conclude the clinical significance of CSN5 in the diagnosis and assessment of digestive system cancers.

This meta-analysis aims to discuss the potential significance of CSN5 as a novel marker in the diagnosis of human digestive system malignancy. An integrated method was utilized to search and analyze all published

primary articles regarding the prognosis prediction role of CSN5 in digestive system malignancies.

Methods

Eligibility Criteria

The following inclusion criteria were utilized to identify eligible studies: (1) human beings as study subjects and published articles with full-texts were prioritized; (2) patients diagnosed with digestive system cancer including colorectal cancer (CRC), gastric cancer (GC), hepatocellular carcinoma (HCC), pancreatic cancer (PC), gallbladder cancer (GBC) and esophageal squamous cell carcinoma (ESCC); (3) CSN5 expression levels were measured in clinical samples of digestive system cancer; (4) detection of the association between overall survival (OS) and recurrence free survival (RFS) and CSN5 was performed; (5) at least two parameters were used to assess the correlation of CSN5 with clinicopathological characteristics; (6) Hazard Ratio (HR), Odds Ratio (OR) and their 95% confidence interval (CI) could be calculated with sufficient materials contained in the articles included. The most comprehensive or most recent data was analyzed in the situation of repetitive studies.

Literature Search Strategy

The online databases of Web of Science, Pubmed, EMBASE and CNKI were searched for related researches published until April 11, 2021. The following keywords were used in the screen: “cancer or tumor or neoplasm or carcinoma” and “‘c-jun activation domain-binding protein 1’ or jab1 or ‘COP9 signalosome complex subunit 5 or Cop9 signalosome 5’ or CSN5 or COPS5”.

Data Extraction

All available data were extracted independently by two reviewers (Guo YH and Gao M). The evaluation of a third reviewer (Ma WJ) contributed to solving any disagreements over the information. To achieve survival analyses, first author’s name, year of publication, country, methods used to detect CSN5, cut-off value, follow-up time, clinicopathological features and information utilized to calculated HRs as well as the 95% CIs were acquired. For each survival outcome, two methods were used to measure HRs as well as the 95% CI: (1) the direct available data of HRs and 95% CIs in the articles was derived; (2) utilizing Engauge Digitizer version 4.1, HRs and 95% CIs were obtained indirectly from the Kaplan-Meier survival curves. The second method might trigger errors caused by variation. Additionally, we investigated the correlation between clinicopathologic parameters and CSN5 with ORs and 95% CIs.

Quality Assessment

Based on the Newcastle-Ottawa Scale (NOS), the quality of all eligible studies was investigated independently by two authors (Yao Y and Li JH). The disagreements in scoring were settled through consensus. Every study was judged given three aspects: (I) the selection of the groups of study (four points, one score for each); (II) the comparability (one point, up to two scores); and (III) the assessment of either exposure or outcome (three points, one score for each). A high-quality study was determined by a score > 7.

Statistical Analysis

The inter-study heterogeneity was estimated by the c^2-based Cochrane Q-test. The definition of statistically significant heterogeneity was a c^2 $p < 0.1$ or an I^2 index > 50%. Besides, if the inter-study heterogeneity was significant, a random-effect model was applied; otherwise, a fixed-effect model was performed. To evaluate the significance of CSN5 in the survival of digestive system cancer patients, HRs and their 95% CIs were utilized. The lower CSN5 expression patients carrying a better survival were identified as HR > 1. In contrast, the higher CSN5 expression in patients with a greater survival was recognized as HR < 1. We evaluated the connection between CSN5 expression and clinicopathologic parameters computing ORs and 95% CIs. The lower expressed CSN5 grouped with a poorer prognosis was referred to as OR > 1. Conversely, the higher CSN5 expression grouped with a worse prognosis corresponded to OR < 1.

The Stata 11.0 Software (Stata Corporation, College Station) accompanied by the Revman 5.3 Software (Revman, the Cochrane Collaboration) were utilized to make all pooled analyses in this meta-analysis. To inspect the stability of our assessment, a sensitivity analysis was performed successively omitting one study at a time. Begg's funnel plot, as well as Egger's test, were used to evaluate potential publication bias, and a p-value < 0.05 was considered statistically significant.

Results

Search Results

After the search in several international databases, we initially included 1,404 articles. We screened titles or abstracts, and 808 duplicates were excluded. Then, 536 articles - reviews, not for CSN5, not digestive system cancer, and not full-texts - were eliminated for meta-analysis. Besides, another 38 records were further excluded by screening the full texts, since they did not present sufficient data for analysis. Thus, the remaining 22 studies were utilized for further analysis. The selection process is described in **Figure 1**.

Study Characteristics

The principal features of the included researches are listed in **Table 1**. The studies analyzed were in the 2008-2020 publication range. The sum of patients in the included studies reached 2,193 with a range of 40–286. All studies included were performed in Asian countries, including 21 in China, and one in Japan. The Kaplan-Meier curves were adopted to calculate HRs and 95% CIs indirectly, due to an absence of HRs and 95% CIs in some articles.

Table 1 - Characteristics of studies included in the meta-analysis

Survival Analysis

After a pooled analysis of 22 studies with 2,193 patients, a combined HR of 2.28 (95% CI: 1.71–3.03; $p < 0.00001$; **Figure 2A**) was acquired to verify the significant association between poor OS of digestive system carcinomas and

First author, year	nation	Cancer type	Case number(High/Low)	Cut-off value	Detection method	Outcome	Follow-up time
Liu C,2020(14)	China	CRC	189(92/97)	Positive cells: +	IHC	OS	>140months
Wang L,2020(16)	China	GC	90(55/35)	Score=8	IHC	OS	>70months
Zhou R,2018(17)	China	CRC	116(69/47)	Positive cells: +	IHC	OS	>125months
Shen Q,2020(18)	China	ESCC	124(65/59)	NA	IHC	OS	>60months
Pan YB,2017(19)	China	CRC	286(143/143)	NA	cDNA	RFS	192months
Mao LX,2019(20)	China	PC	106(70/36)	NA	IHC	NA	NA
Kugimiya N,2017(21)	Japan	CRC	50(17/33)	ROC	RT-PCR	RFS	>38months
Liu HL,2018(22)	China	HCC	102(73/29)	NA	IHC	OS	>80months
Wang Y,2014(23)	China	HCC	67(41/26)	Score=3	IHC	OS	60months
Hsu MC,2008(24)	China	HCC	99(37/62)	Staining color: T=N	IHC	NA	NA
Chen L,2010(15)	China	HCC	76(43/33)	Positive cells=69%	IHC	OS	60months
Wang F,2009(25)	China	ESCC	90(75/15)	Positive cells=10%	IHC	OS	60months
Zheng L,2016(26)	China	ESCC	187(122/65)	Positive cells=50%	IHC	OS	>45months
Guo ZQ,2014(27)	China	CRC	80(66/14)	Positive cells=30%	IHC	NA	NA
Yang F,2013(28)	China	GC	80(57/23)	Score=1	IHC	NA	NA
Zhang SW,2014(29)	China	CRC	94(81/13)	Score=1	IHC	NA	NA
Cao Y,2013(30)	China	HCC	40(28/12)	Positive cells=25%	IHC	NA	NA
Yang SH,2013(31)	China	CRC	74(60/74)	Score=1	IHC	OS	60months
Shi H,2010(32)	China	ESCC	60(47/13)	Positive cells=25%	IHC	NA	NA
Gu GJ,2017(33)	China	GBC	65(39/26)	Score=3	IHC	NA	NA

Zhang LY,2011(34)	China	ESCC	58(37/21)	Positive cells=25%	IHC	NA	NA
Li S,2012(35)	China	GC	60(43/17)	Score=1	IHC	OS	>60months

high expression of CSN5. We detected non-significant heterogeneity (c^2 = 0.36; freedom degrees = 11; p = 0.95; I^2 = 0%). A fixed-effect model was applied when the study presented low heterogeneity. The subgroup analysis of the relation between CSN5 expression and OS in tumor types indicated that high expression of CSN5 was correlated with poor OS in CRC (HR = 1.83, 95% CI: 1.05–3.19; p = 0.03; **Figure 2B**). Additionally, CSN5 overexpression was shown to be obviously related to poor OS in HCC (HR = 2.80, 95% CI: 1.76–4.45; p < 0.00001; **Figure 2C**). Moreover, a worse OS was discovered in ESCC patients with CSN5 high-expression as well (HR = 2.52, 95% CI: 1.23–5.15; p = 0.01; **Figure 2D**). However, we did not detect a significant correlation between CSN5 expression and RFS (**Figure S1**).

Association of CSN5 Expression with Clinical Parameters

Correlation analysis outcome between clinicopathologic features and CSN5 level is presented in **Table 2.** A high CSN5 expression was found to be significantly associated with poorer invasion depth (OR = 0.49, 95% CI: 0.25-0.96, p = 0.04; **Figure 3A**), positive lymphatic metastasis (OR = 0.28, 95% CI: 0.16-0.47, p = 0.00001; **Figure 3B**), positive distant metastasis (OR = 0.32, 95% CI: 0.13-0.76, p = 0.01; **Figure 3C**) and poorer differentiation degree (OR = 0.34, 95% CI: 0.19-0.60, p = 0.0003; **Figure 3D**). However, the CSN5 level did not significantly correlate with age, gender, tumor stage, tumor size or vascular invasion (**Table 2**). In tumor-types subgroup analysis, patients with positive lymphatic metastasis in the groups of CRC (OR = 0.21, 95% CI: 0.07-0.66, p = 0.008), GC (OR = 0.28, 95% CI: 0.16-0.51, p < 0.0001) and ESCC (OR = 0.24, 95% CI: 0.12-0.48, p < 0.0001) presented a correlation with high CSN5 expression. A correlation was detected between the level of CSN5 and differentiation degree in GC (OR = 0.21, 95% CI: 0.08-0.53, p = 0.001) and CRC (OR = 0.39, 95% CI: 0.17-0.89, p = 0.03). However, the expression of CSN5 had no significant connection with invasion depth in CRC and ESCC, as well as differentiation degree in ESCC. Some tumor types were not available for analysis.

Publication bias and Sensitivity Analyses

To evaluate potential publication bias, Begg's funnel plot and Egger's test were conducted. We successively omitted one study at a time in the sensitivity analysis. The results of publication bias and sensitivity analysis within the included studies are demonstrated in **Figures 4**, **S2,** and **S3**. No significant publication bias was detected in OS analysis (Egger's test: p = 0.112). Sensitivity analysis results indicated the robustness and reliability of our estimates since the pooled results for OS could not be significantly altered by only one trial. Publication bias results and sensitivity analysis in RFS are in **Figure S2**. Moreover, the analysis of the clinicopathological parameters (**Table 2)** demonstrated that no remarkable publication bias existed. Regarding sensitivity analysis, none of the pooled ORs for invasion depth, lymphatic metastasis and differentiation degree was remarkably affected by eliminating any single study (**Figure 5**). However, the sensitivity analysis of ORs for distant metastasis indicated a lack of stability. The results of the other clinicopathological characteristics in the analysis of publication bias and sensitivity are in **Figure S3**.

Table 2 - Correlation of high CSN5 expression with clinicopathological parameters

Parameters	Studies	Case number	Pooled OR(95%CI)	P	Heterogeneity		Model	Publication bias
					I2	P		
Age	5	406	1.37 [0.89, 2.13]	0.16	0%	0.72	Fixed	0.462
Gender	17	1487	1.00 [0.78, 1.27]	0.97	34%	0.08	Fixed	0.343
TNM stage	9	721	0.81 [0.34, 1.91]	0.63	80%	<0.00001	Random	0.536
Tumor size	8	749	0.83 [0.60, 1.16]	0.27	37%	0.14	Fixed	0.536
Invasion depth	6	591	0.49 [0.25, 0.96]	0.04	56%	0.04	Random	0.26
Lymphatic metastasis	15	1294	0.28 [0.16, 0.47]	<0.00001	68%	<0.00001	Random	0.701
Distant metastasis	3	246	0.32 [0.13, 0.76]	0.01	0%	0.42	Fixed	1
Differentiation degree	11	984	0.34 [0.19, 0.60]	0.0003	55%	0.01	Random	1
Venous invasion	4	322	1.11 [0.22, 5.53]	0.9	82%	0.0009	Random	1

Discussion

Numerous essential signal transduction pathways in oncology, related to Jab1/CSN5, were in several studies. Several tumoral features, such as cell cycle, cell apoptosis, and DNA damage repair, were considered to be correlated with Jab1/CSN5. Recently, different researches have been performed to investigate the diagnostic value of CSN5 to predict survival in digestive system cancers. However, the results remain inconclusive. To illustrate this question and discuss the potential significance of CSN5 as an indicator for diagnosis and assessment, we implemented a meta-analysis of original articles to assess the value of CSN5 on prognosis consequences in digestive system cancer patients.

We conducted a meta-analysis of 22 eligible articles, containing 2,193 patients, to discuss the correlation between CSN5 overexpression and survival outcomes as well as clinical parameters. The predictive role of overexpressed CSN5 was proved by this meta-analysis for greater invasion depth, positive lymphatic metastasis, positive distant metastasis, poorer differentiation degree and poor survival. In the subgroup survival analysis of gastric cancer, although it did not display a positive result, a positive tendency was found. Probably, this occurred due to inadequate studies included. We detected that there was no significant association between CSN5 expression and RFS in patients with digestive system cancer. This result might be assigned to the deviation when we acquired HRs from the Kaplan–Meier curves, extracted in the included studies. Another cause might be the loss of sufficient research for pooled analysis with only 2 studies involving relevant information. Moreover, it is also possible that CSN5 did not influence the recurrence of digestive system cancers. In the sensitivity analysis, the ORs of distant metastasis did not show sufficient robustness, which might be due to the different number of positive distant

metastasis cases in all three studies. Certain clinicopathological characteristics did not show an obvious difference regarding the expression of CSN5, which might account for the variation of the cut-off value and the lack of studies with a large sample.

Interestingly, it was reported that CSN5 acted as a novel potential therapeutic target against tumors. Recently, it was reported that an inhibitor of Jab1/CSN5 (CSN5i-3) functions as a selective and orally available medicine, inhibiting the deneddylating activity of the CSN(36, 37). The expression of CSN5 in tumor tissue can have a promising future for the indication of CSN5 medication. Our study discussed, without precedent, that high CSN5 expression in tumor tissue of digestive system cancer patients is connected to poorer overall survival (OS), a result in favor of the clinical significance of CSN5 for the prediction of digestive system neoplasm patients' survival.

Our result should be explained by the limitations and considerations below. Firstly, the included studies were all published in Asia, with 21 in China and one in Japan. Therefore, our results may not apply to other ethnicities. Secondly, given that HRs in all studies included could not be acquired, HRs and relevant data were acquired from the Kaplan-Meier survival curves, which may lead to errors due to variation. Thirdly, certain heterogeneity founded in clinicopathological features analysis may be explained by the absence of standardization of quantification and cut-off thresholds. Moreover, the variation of detection method, with one study with clinical cDNA microarrays, another one with RT-PCR, and the remaining with IHC, can result in errors, since the RNA level of CSN5 in tumor cells might differ from protein level. However, even when we eliminated the two studies (cDNA microarrays and RT-PCR), the results remained the same. These findings suggested that further detailed clinic studies with a uniform assessment assay should be performed to elucidate the prognostic value of CSN5 in digestive system neoplasm.

Conclusion

The current meta-analysis demonstrated that high CSN5 expression levels predict poorer OS in patients with digestive system neoplasm. Furthermore, the high CSN5 expression is related to greater invasion depth, positive lymphatic metastasis and distant metastasis, as well as poorer differentiation degree. Our results indicated that CSN5 had the potential to be an effective prognostic biomarker and a therapeutic target for digestive system tumors.

Abbreviations

CSN5 COP9 signalosome subunit 5

HR Hazard Ratio

CI Confidence interval

OS overall survival

RFS recurrence free survival

OR Odds Ratio

CRC Colorectal cancer

GC Gastric cancer

HCC Hepatocellular carcinoma

PC Pancreatic cancer

GBC Gallbladder cancer

ESCC Esophageal squamous cell carcinoma

Declarations

Ethics approval and consent to participate Because this is a meta-analysis. There is no need for Ethics approval and consent to participate in this study. Consent for publication The manuscript is approved by all authors for publication. Availability of data and material All the data and materials have not been published. They are all in availability. Competing interests There is no competing interest in this study. Funding This work was supported by the Program of Excellent Doctoral (postdoctoral) of Zhongnan Hospital of Wuhan University (Grant No. ZNYB2020004), the Fundamental Research Funds for the Central Universities (2042021kf0147) and Zhongnan Hospital of Wuhan University Science,Techonology and Innovation Seed Fund(CXPY2020015). Author Contribution WJ M conceived and designed the protocol and the study. YH G and M G identified studies to be screened. YH G, M G, WJ M, and Y Y identified studies regarding eligibility, extracted data, and assessed the methodological quality of included studies. JH L and X C performed the analysis with assistance from XX W and Z C. YF Y revised the manuscript. All authors read and approved the final manuscript. Acknowledgments This work was supported by the Program of Excellent Doctoral (postdoctoral) of Zhongnan Hospital of Wuhan University (Grant No. ZNYB2020004), the Fundamental Research Funds for the Central Universities (2042021kf0147) and Zhongnan Hospital of Wuhan University Science,Techonology and Innovation Seed Fund(CXPY2020015).

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Figures

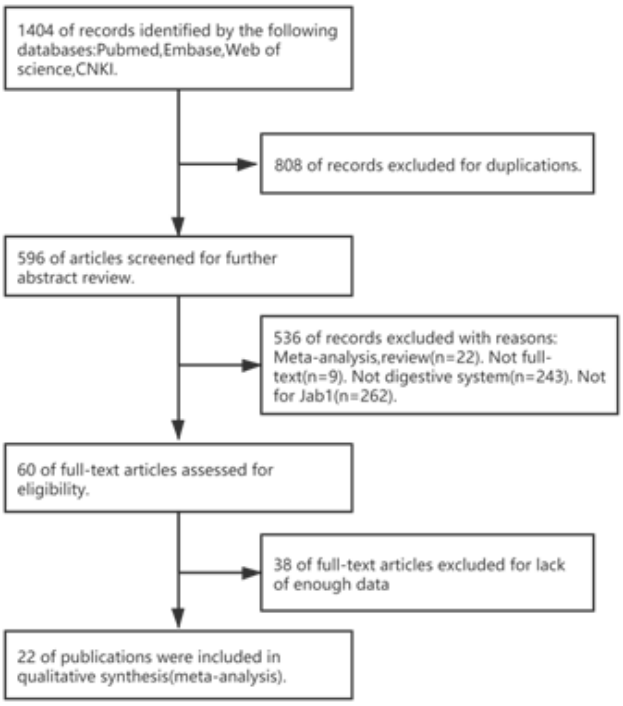

Figure 1

Flowchart of study search and literature selection

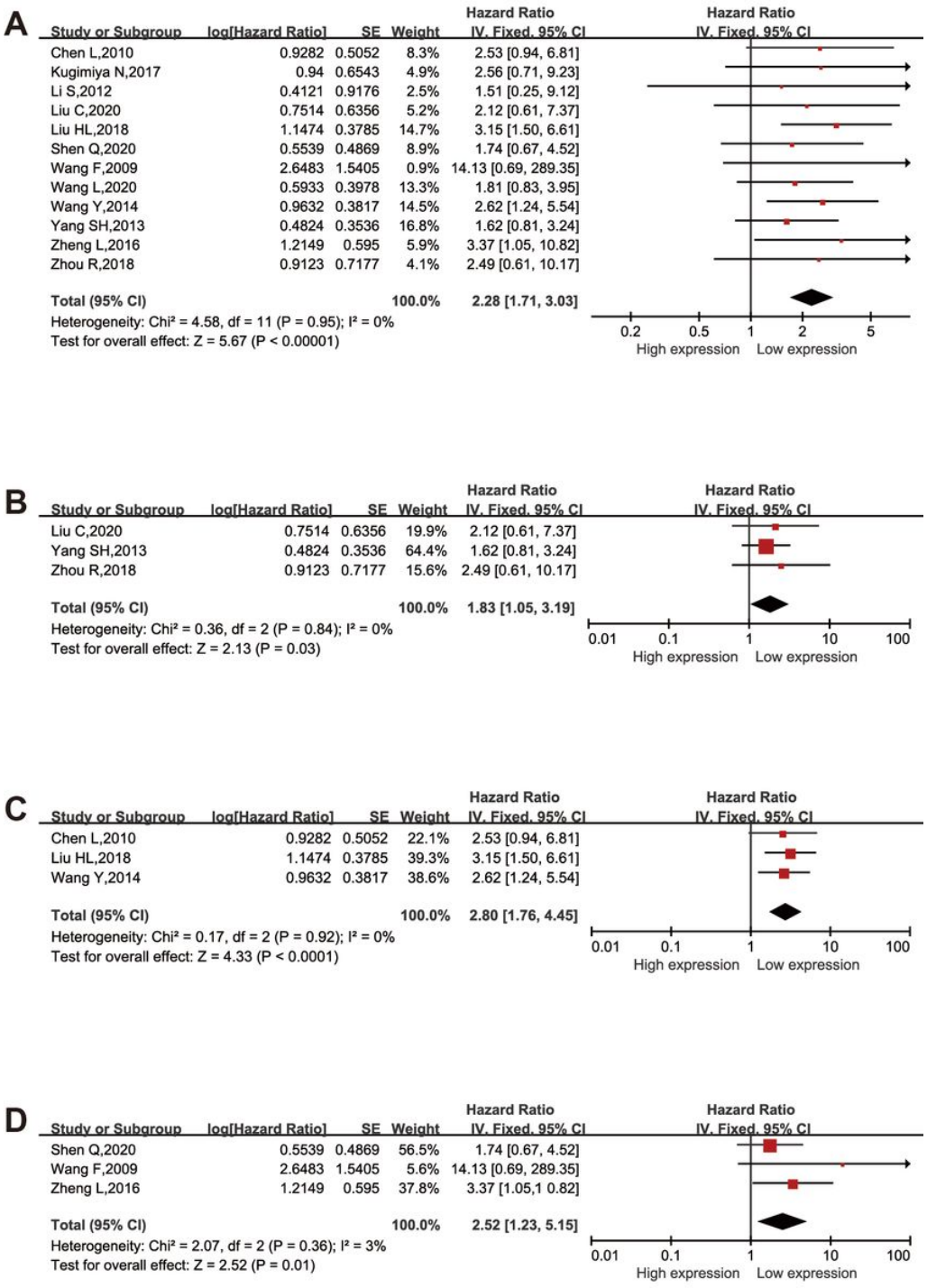

Figure 2

Forrest plot of HR. (A) OS of all digestive system cancer; (B) OS of CRC; (C) OS of HCC; (D) OS of ESCC.

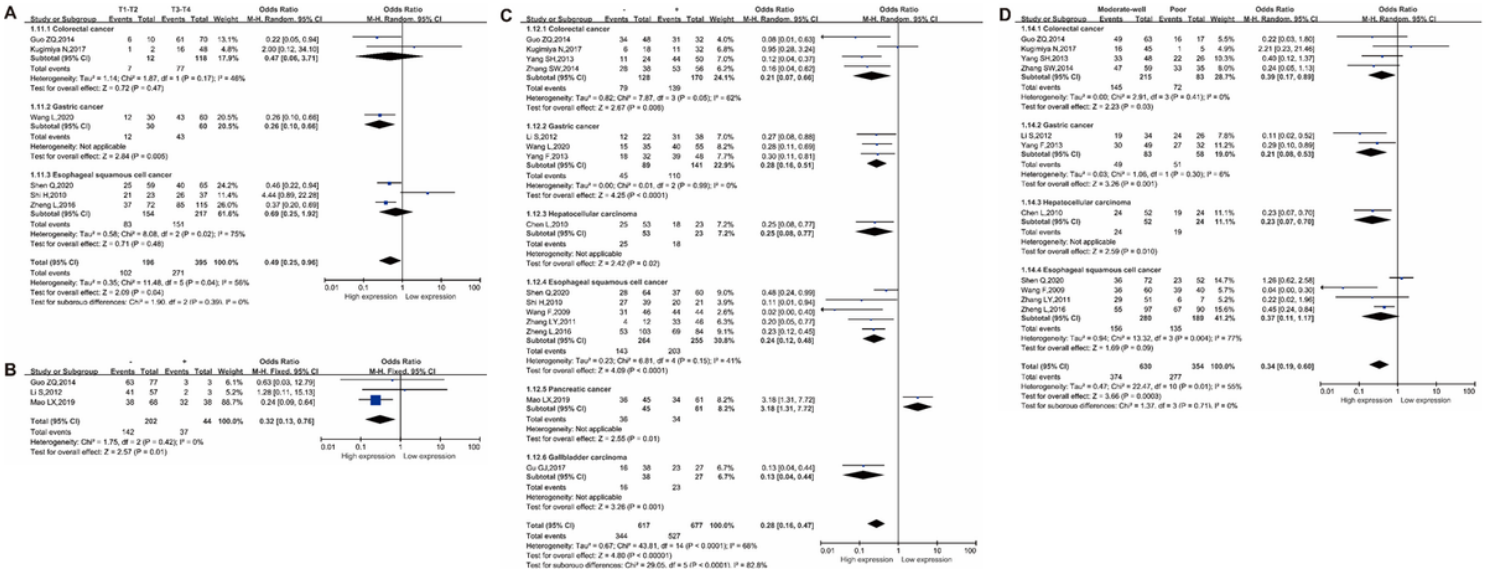

Figure 3

Forrest plot of OR. (A) invasion depth; (B) lymphatic metastasis; (C) distant metastasis; (D) differentiation degree. (To be continued) Forrest plot of OR. (A) invasion depth; (B) lymphatic metastasis; (C) distant metastasis; (D) differentiation degree. (To be continued) Forrest plot of OR. (A) invasion depth; (B) lymphatic metastasis; (C) distant metastasis; (D) differentiation degree.

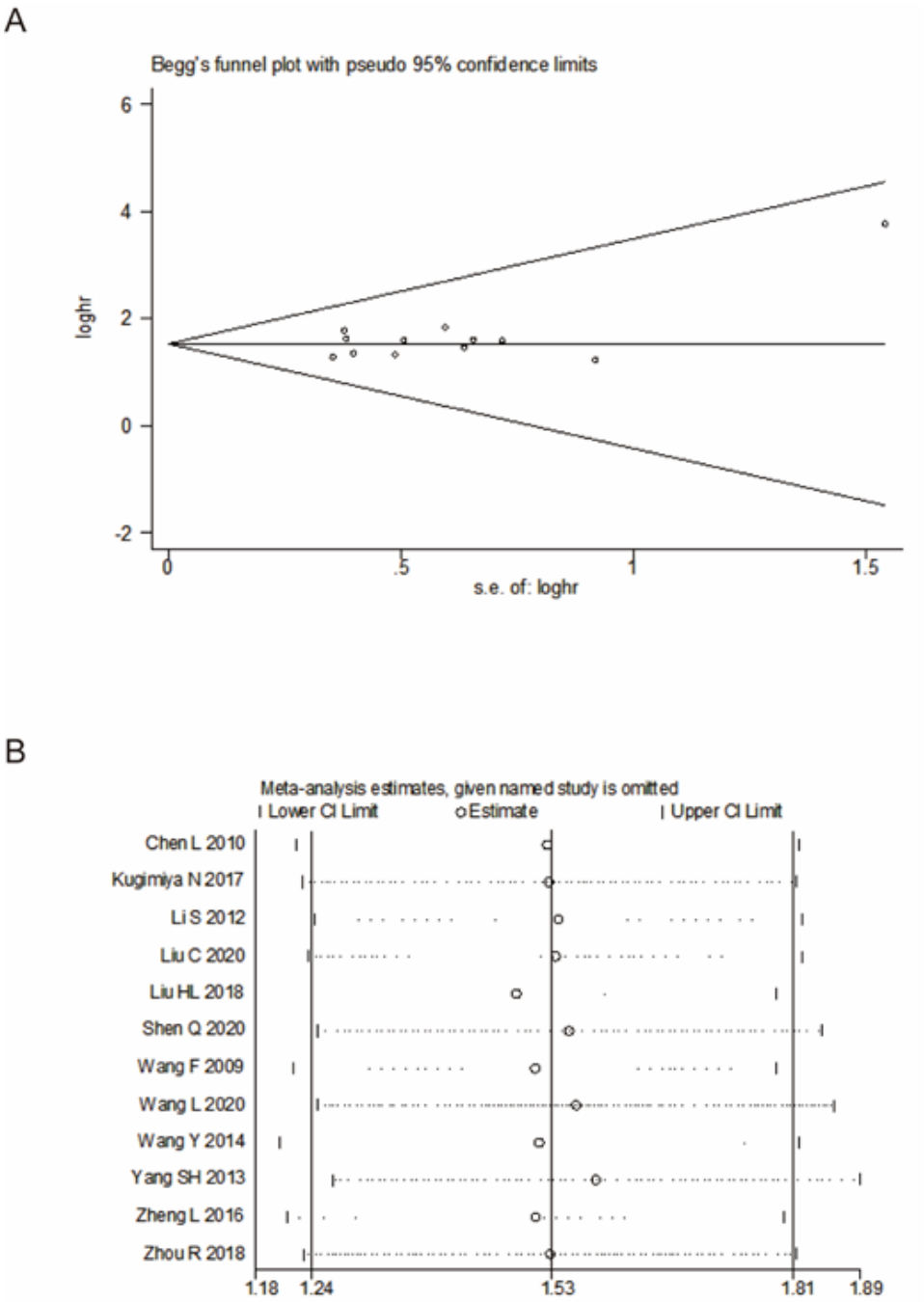

Figure 4

(A) Begg's funnel plot for publication bias tests of OS; (B) Sensitivity analysis of OS.

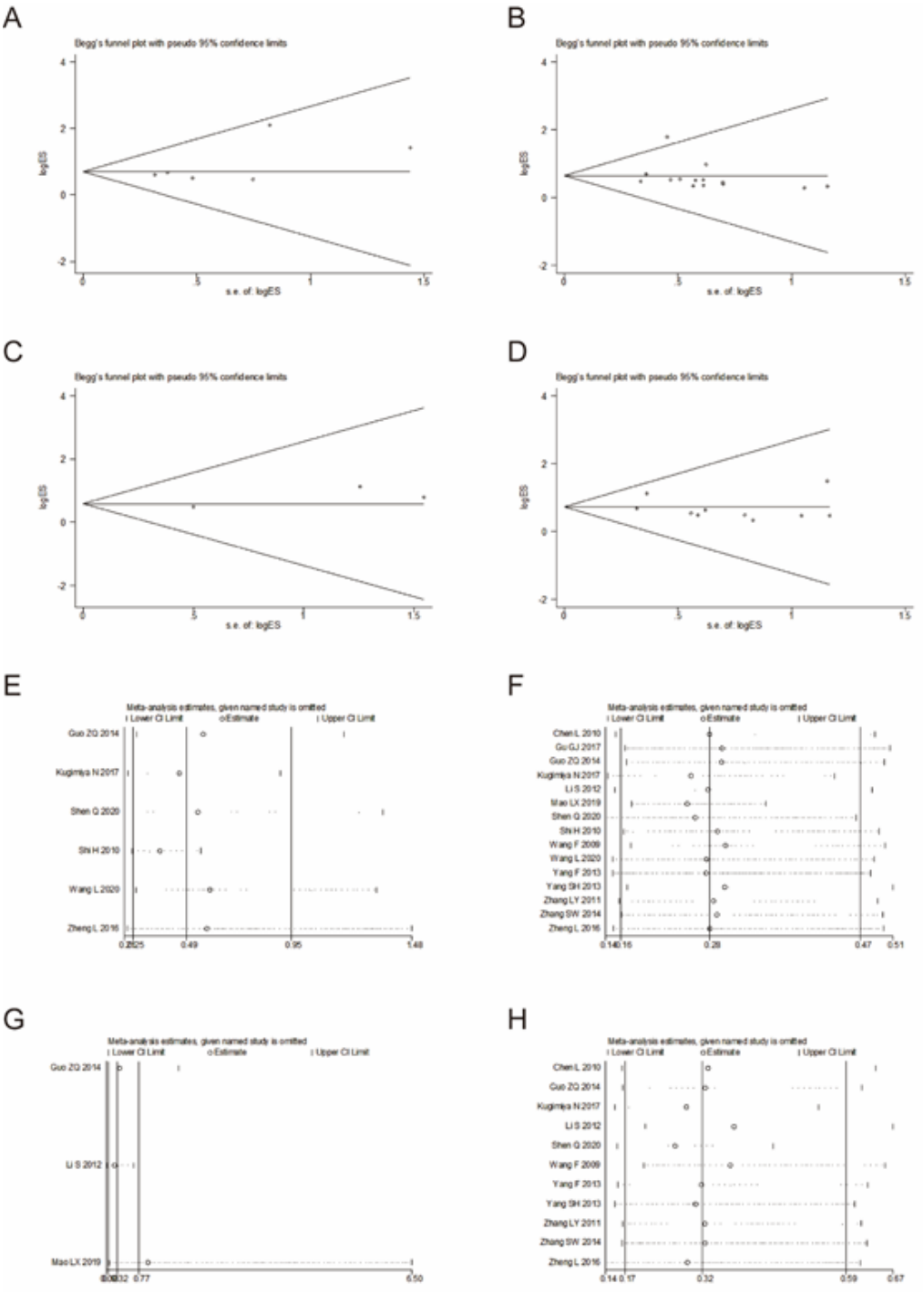

Figure 5

Begg's funnel plot for publication bias tests of (A) invasion depth, (B) lymphatic metastasis, (C) distant metastasis and (D) differentiation degree. Sensitivity analysis of (E) invasion depth, (F) lymphatic metastasis, (G)distant metastasis and (H) differentiation degree.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FIGURES1.jpg
- FIGURES3.jpg
- FIGURES2.jpg