

Review Article

Clinicopathological and prognostic value of USP22 in patients with digestive system malignancies: a systematic review and meta-analysis

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Abstract: Background and Aim: Recent studies have demonstrated that USP22 was overexpressed in digestive system malignancies. However, the association between positive USP22 expression and clinicopathological and prognostic significance remains controversial. Thus, this meta-analysis was conducted to explore the roles of USP22 in digestive system malignancies. Methods: Articles were selected from PubMed, Cochrane Library, Web of Science, EMBASE database, Chinese CNKI, and Chinese WanFang databases. Relationships between USP22 expression, clinicopathological features, and survival rates were calculated. Pooled odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with STATA14.2. Results: A total of 1,926 patients from 17 articles were enrolled. Positive expression of USP22 was associated with depth of infiltration, tumor size, differentiation, and TNM stage. However, it was not related to gender and age. Positive USP22 expression indicated poor 5-year overall survival rates (disease-specific survival rates) and disease-free survival rates. However, USP22 expression was not related to 3-year overall survival rates and it was not an independent predictive factor for OS in patients with digestive system malignancies. Conclusion: The present meta-analysis indicated that positive USP22 expression was related to depth of infiltration, tumor size, differentiation, and TNM stage in patients with gastrointestinal carcinoma. USP22 may be an unfavorable prognostic biomarker for HCC in a Chinese population. Further research is necessary.

Keywords: Ubiquitin-specific protease 22, USP22, digestive system malignancies, prognosis, meta-analysis

Introduction

Digestive system malignancies seriously endanger human health [1, 2], including esophageal cancer (EC), gastric cancer (GC), colorectal cancer (CRC), pancreatic cancer (PC), hepatocellular carcinoma (HCC), and gallbladder carcinoma (GBC). Gastric cancer is the fourth most common malignancy in the world with the second highest fatality rate [2]. Prognosis of hepatocellular carcinoma is very poor and there are about 630,000 new cases diagnosed of HCC every year, resulting in about 590,000 deaths [3]. Digestive system malignancies have always been in the first place in a variety of malignant tumors in China. With continuous improvement in the diagnosis and treatment of gastrointestinal cancer in recent years, the majority of patients have been diagnosed at middle-late stages, with poor prognosis [4, 5]. Therefore,

exploring the pathogenesis of digestive system malignancies, aiming to find early diagnosis molecular biomarkers, has become a hot spot of research.

Ubiquitin-specific protease 22 (USP22), a subunit of the human SAGA transcriptional co-factor acetylation complex, is an ubiquitin-specific protease belonging to a member of the deubiquitinated DUB gene family that exerts a biological regulatory role by binding to deubiquitinated protein substrates [6]. Studies have shown that USP22 is highly expressed in a variety of tumors, such as cervical cancer [7], papillary thyroid cancer [8], non-small cell lung cancer [9] and glioma [10]. Expression of USP22 has been related to clinicopathological features and prognosis of the tumors. Studies have always indicated that USP22 is over-expressed in gastrointestinal tumors, such as gastric can-

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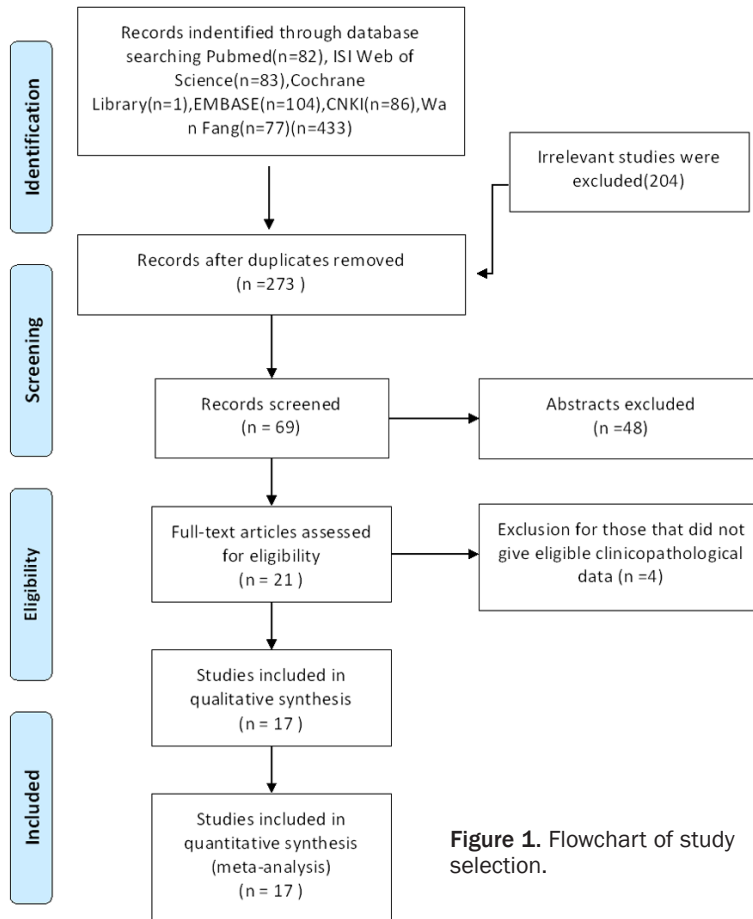


Figure 1. Flowchart of study selection.

patients with colorectal cancer. A recent meta-analysis [18] explored the relationship between overexpression of USP22 and clinicopathological features and prognosis of patients with cancers. Pooled results suggested that high USP22 expression was associated with poor overall survival and disease-free survival rate and that USP22 expression indicated an advanced histological grade, advanced tumor-node-metastasis stage, positive lymph node metastasis, and distant metastasis. However, the included articles and sample sizes of the meta-analysis were limited. There was no analysis of 3-year and 5-year overall survival. Thus, in view of the above controversy, there was an urgent need to conduct a meta-analysis exploring the roles of USP22 in gastrointestinal carcinoma.

Materials and methods

Search strategy

Electronic databases were searched, including PubMed, Cochrane Library, Web of Science, EMBASE database, Chinese CNKI, and Chinese Wanfang database. The search ended on December 1, 2017. The following key words were used: “USP22” or “Ubiquitin-specific protease 22”, combined with “survival” or “prognosis” or “outcome”, combined with “cancer”. In addition, the name of each specific digestive system cancer (for example, colorectal cancer) was used instead of the search term “cancer”, attempting to recognize additional studies. No language limitations were applied. References cited in identified articles were also searched to find other applicable studies.

Inclusion criteria and exclusion criteria

If studies met all of the following inclusion criteria, they were included: (1) Study was available for full text; (2) Patients were diagnosed clearly with gastrointestinal cancer and directly examined USP22 expression status, tested by immu-

cer [11], hepatocellular carcinoma [12], and colorectal cancer [13]. However, relationships between positive USP22 expression and clinicopathological features and prognosis remain controversial. Zhang et al. [14] demonstrated that positive USP22 expression was related to tumor size, tumor differentiation, and TNM stage of HCC and that USP22 predicted a poor prognosis. Li et al. [15] indicated that positive USP22 expression was correlated with depth of infiltration, TNM stage, and poor prognosis, but not related to tumor size and differentiation of patients with colorectal cancer. Zhai et al. [12] found that positive expression of USP22 in HCC was not related to TNM stage. Tang et al. [16] indicated that USP22 in HCC was not associated with tumor size, with multivariate analysis showing that USP22 was not an independent risk for disease-free survival. Wang et al. [17] found that USP22 was not an independent risk factor for postoperative disease-specific survival in colon cancer. Interestingly, Liu et al. [13] suggested that positive USP22 expression was correlated with tumor size, depth of infiltration, and TNM stage, but not with differentiation in

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

Author	Year	Country	Kind	No. of patients	Larbotory method	Antibody	Antibody concentration	IHC Positive Cut-off	Age > 60 (+/-) < 60 (+/-)	Gender male (+/-) female (+/-)	Depth of infiltration T1/2 (+/-) T3/4 (+/-)	Tumor size ≤ 5 cm (+/-) > 5 cm (+/-)	Differentiation low (+/-) high and moderate (+/-)	UICC stage I, II (+/-) III, IV (+/-)	Survival information	Quality score
Liu YL	2010	China	CRC	51	qRT-PCR	NA	NA	NA	NA	NA	NA	NA	NA	NA	DFS	7
Liu YL	2011	China	CRC	192	IHC	Abcam	1:320	≥ 10%	48/56 56/47	68/44 36/44	40/64 64/24	31/45 73/43	27/14 77/74	42/56 62/32	OS DFS	8
Deng MZ	2011	China	GC	100	IHC	Abcam	1:100	≥ 10%	52/14 28/6	54/12 26/8	8/8 72/12	NA	56/6 24/14	16/12 64/8	NA	6
Yang DD	2011	China	GC	219	IHC	Abcam	1:400	≥ 20%	70/52 55/42	88/74 37/20	17/43 51/108	56/49 69/45	88/50 37/44	23/59 102/35	OS	8
Li J	2012	China	ESCC	157	IHC	Abcam	1:400	≥ 15%	48/44 32/33	55/57 25/20	30/41 50/36	38/48 42/29	12/8 68/69	18/33 62/44	OS	8
Zhou F	2012	China	CRC	126	IHC	Abcam	1:250	≥ 20%	25/24 36/41	45/33 25/23	25/60 20/21	20/17 49/40	20/6 37/63	17/67 21/21	NA	6
Jia YY	2013	China	CRC	80	IHC	Abgent	1:50	≥ 10%	24/17 20/19	26/20 18/16	7/16 37/20	NA	34/20 10/16	NA	NA	6
Zheng WF	2013	China	ESCC	44	IHC	Abcam	NA	≥ 10%	16/6 14/8	18/9 12/5	10/11 20/3	NA	NA	8/22 9/5	NA	6
Guo YL	2014	China	ESCC	45	IHC	Abcam	NA	≥ 25%	14/8 13/10	16/12 11/6	7/14 20/4	NA	16/2 11/16	8/11 19/7	NA	6
Liang JX	2014	China	PC	68	IHC	Abcam	1:400	NA	27/14 18/9	27/13 18/10	NA	NA	23/4 22/19	21/19 24/4	OS	8
Ning Z	2014	China	PC	136	IHC	Abcam	1:200	≥ 50%	48/37 26/25	39/35 35/27	NA	NA	36/21 38/41	NA	OS	7
Tang B	2015	China	HCC	104	IHC	Abcam	1:50	≥ 30%	NA	55/39 2/8	NA	18/23 40/23	23/1 35/45	8/22 50/24	OS DFS	8
Wang ZJ	2015	China	CRC	129	IHC	Abgent	NA	≥ 10%	45/18 45/21	39/17 51/22	1/8 40/80	NA	15/21 26/67	13/49 28/39	OS	8
Yu JL	2016	China	GC	125	IHC	Abcam	1:250	≥ 20%	NA	41/41 26/17	9/20 58/38	42/28 25/30	50/31 17/27	14/34 53/24	NA	7
Zhai R	2016	China	HCC	175	IHC	NA	1:100	≥ 30%	NA	25/127 6/17	NA	11/71 22/71	15/28 19/113	3/48 31/93	OS DFS	8
Li YM	2017	China	CRC	123	IHC	Abcam	1:200	NA	33/22 34/34	39/34 28/22	21/28 46/28	27/32 40/24	31/20 36/36	24/30 43/26	OS	8
Zhang J	2017	China	HCC	52	IHC	NA	NA	≥ 30%	NA	34/15 1/1	NA	8/10 28/6	16/13 20/3	18/14 18/2	OS	7

Table 2. USP22 clinicopathological features for gastrointestinal carcinoma

Clinicopathological features	No. of studies	No. of patients	Heterogeneity					Model used
			Pooled OR (95% CI)	PHet	I ² (%)	P value		
Gender	16	1874	1.03 (0.82-1.28)	0.389	5.6	0.930	Fixed	
Age	12	1542	1.04 (0.84-1.28)	0.917	0.0	0.725	Fixed	
Depth of infiltration	11	1340	0.36 (0.28-0.47)	0.059	43.8	0.000	Fixed	
Tumor size	9	1273	0.60 (0.42-0.86)	0.026	54.1	0.005	Random	
Differentiation	14	1779	2.64 (1.75-3.30)	0.086	36.2	0.000	Fixed	
TNM stage	14	1659	0.26 (0.20-0.32)	0.346	9.8	0.000	Fixed	

Random, random-effects model; Fixed, fixed-effects model; OR, odds ratio; CI, confidence interval.

nohistochemistry (IHC) or RT-PCR; (3) Results included clinicopathological characteristics, disease-free (recurrence-free) survival, and overall survival; and (4) Hazard ratios (HRs) for overall survival were reported or could be calculated from the published data.

Exclusion criteria were as follows: (1) Non-eligible trials included ecological studies, case reports, reviews, editorials, letters, conference abstracts, and animal trials; and (2) Repeated studies based on the same database or patients.

Data extraction and quality assessment

Studies were screened, independently, by two investigators (Chaojie Liang and Tuanjie Zhao) to determine if the relevant articles met inclusion criteria. Discrepancies were resolved by discussions, re-extraction, or third-party adjudication. Extracted data included the name of first author, publication year, number of patients, region of origin, patient characteristics, HRs with 95% CI for overall survival, disease-free survival, and disease-specific survival. Newcastle-Ottawa Scale (NOS) was introduced to evaluate the quality of included studies. If NOS ≥ 6, the study was regarded as good quality, otherwise it was considered poor quality. High quality studies were included in this meta-analysis.

Statistical analysis

STATA 14.2 software was used to calculate pooled odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs). Survival data was extracted by Engauge Digitizer 10.0 software from a Kaplan-Meier curve. Association between positive USP22 expression and clinicopathological features, including

gender, age, tumor size, depth of infiltration, differentiation, and TNM stage, was calculated by fixed or random-effects models when I² was < 50% or > 50%. If the HR or OR > 1, this implied a worse prognosis for the group with positive USP22 expression. It was considered statistically significant if the 95% CI did not overlap 1. Potential publication bias was examined by Begg's funnel plot test.

Results

Characteristics of studies

As shown in **Figure 1**, showing details of the selection process, seventeen [11-17, 19-28] studies (3 ESCC, 3 GC, 6 CRC, 2 PC, 3 HCC) with 1,926 patients were included in this meta-analysis. These studies were published from 2010 to 2017, with sample sizes ranging from 44 to 219 patients. All studies were from China. Eleven of these studies were published in English and six articles were in Chinese. All studies scored ≥ 6 in methodological assessment, which implied high quality. Details are shown in **Table 1**.

Relationship between USP22 expression and clinicopathological features in patients with digestive system malignancies

As shown in **Table 2**, the association between positive USP22 expression and clinicopathological features in patients with gastrointestinal carcinoma was calculated. Seventeen studies with 1,874 patients were enrolled to evaluate the relationship between positive USP22 expression and gender. Pooled results showed no statistical significance (OR = 1.03, 95% CI = 0.82-1.24, P = 0.930, I² = 5.6%, **Figure 2B**), while 12 studies with 1,542 patients showed no statistically significant relationship between

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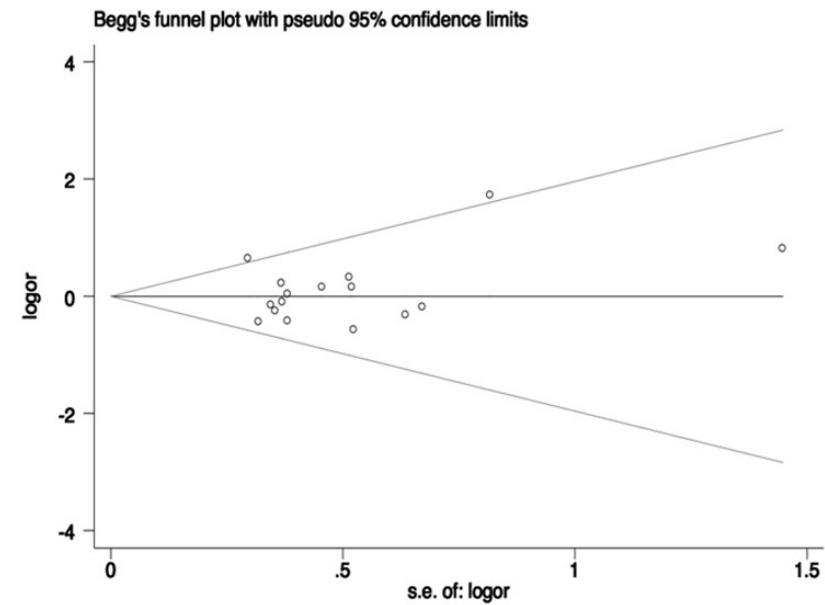
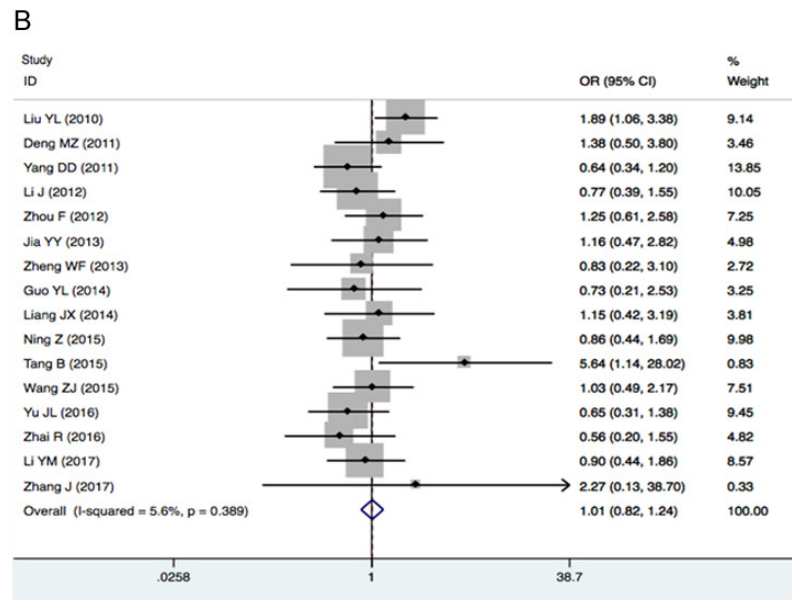
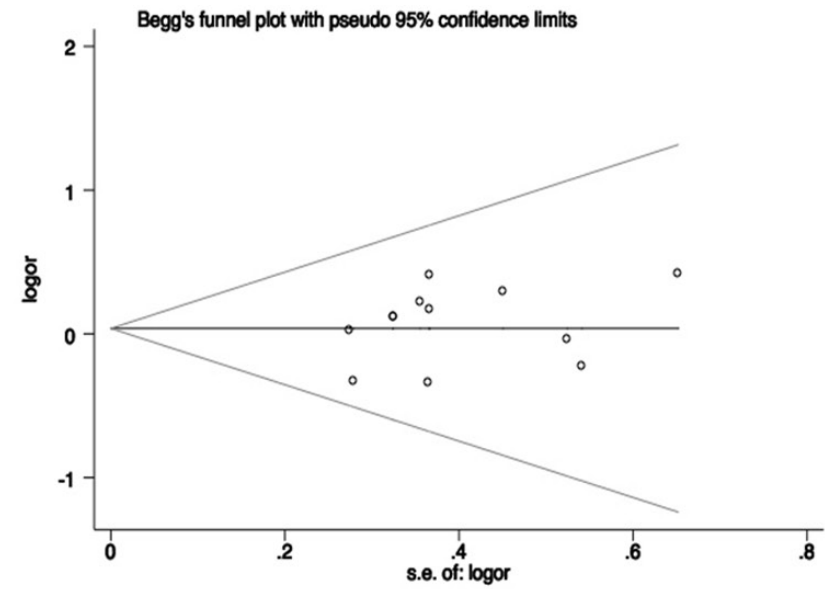
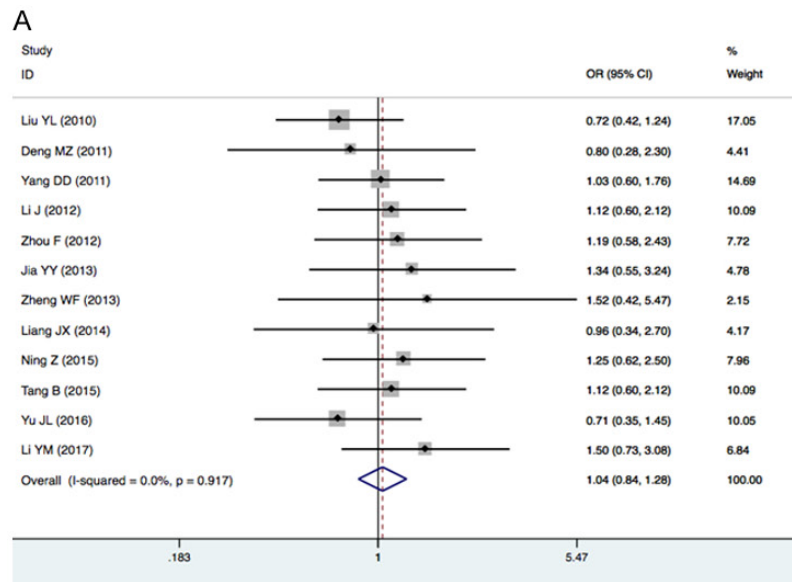
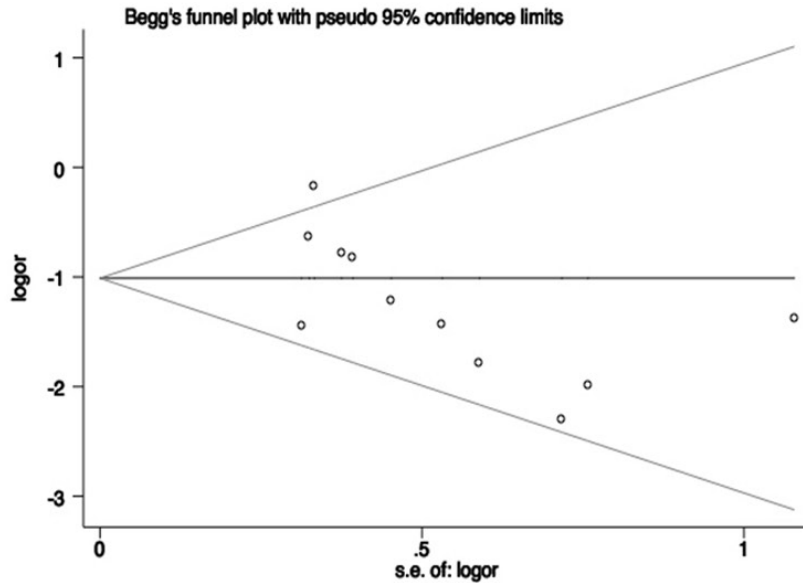
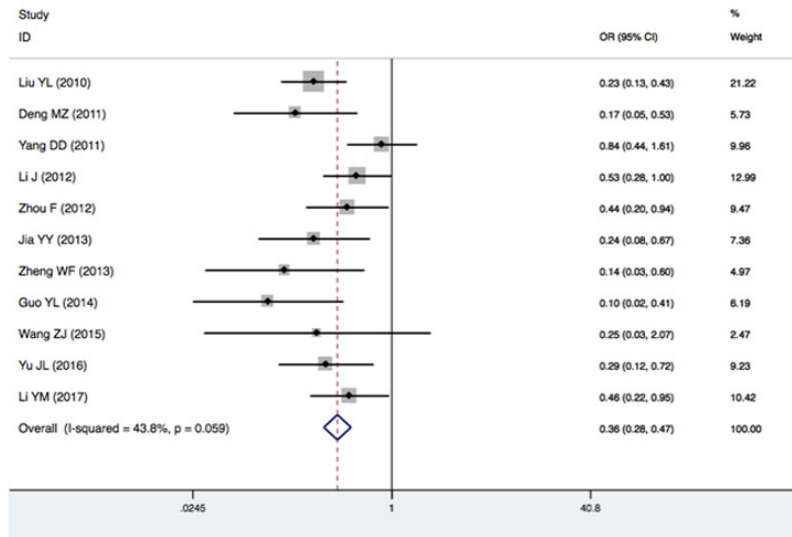


Figure 2. Forest plot and Begg's publication bias plot of studies evaluating the relationship between USP22 expression and clinicopathological features: (A) Gender; (B) Age.

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A



B

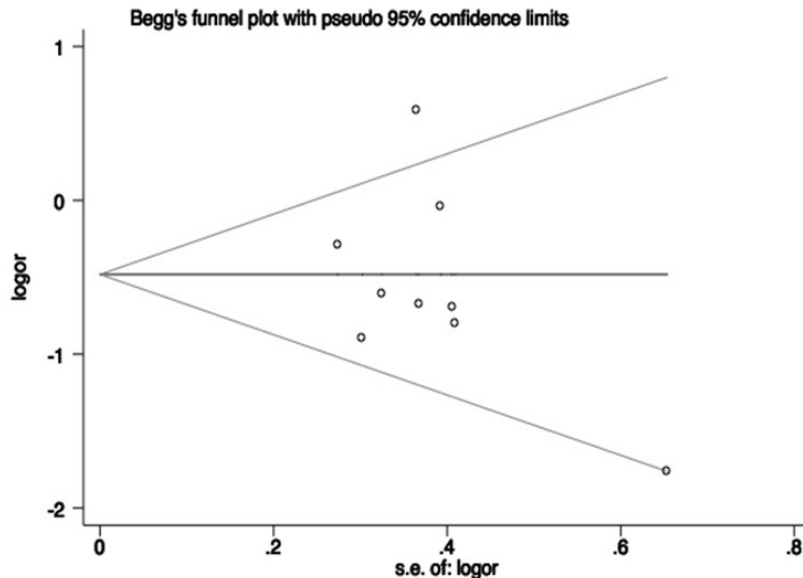
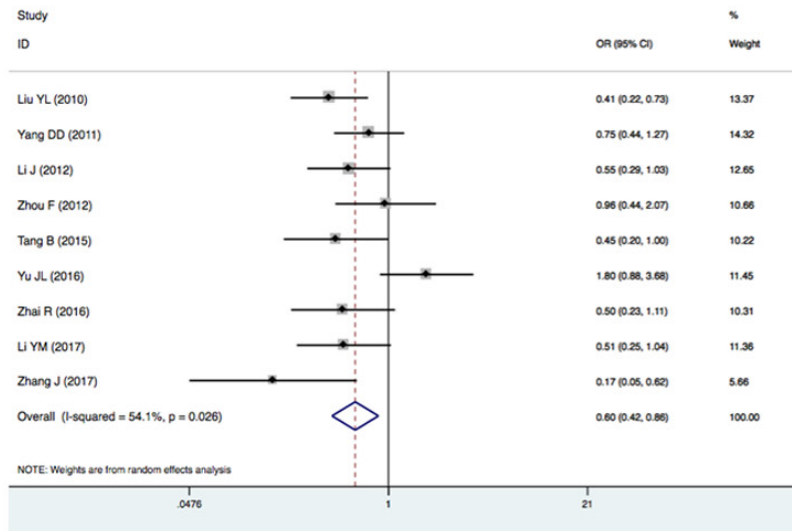
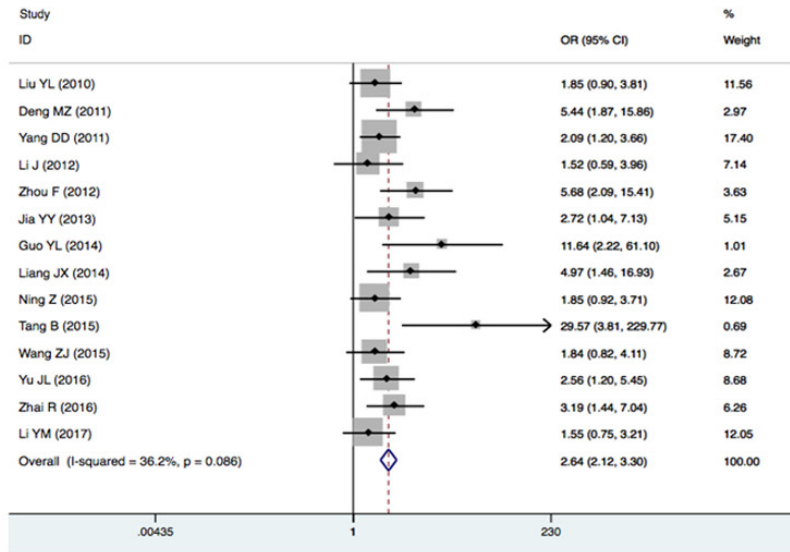


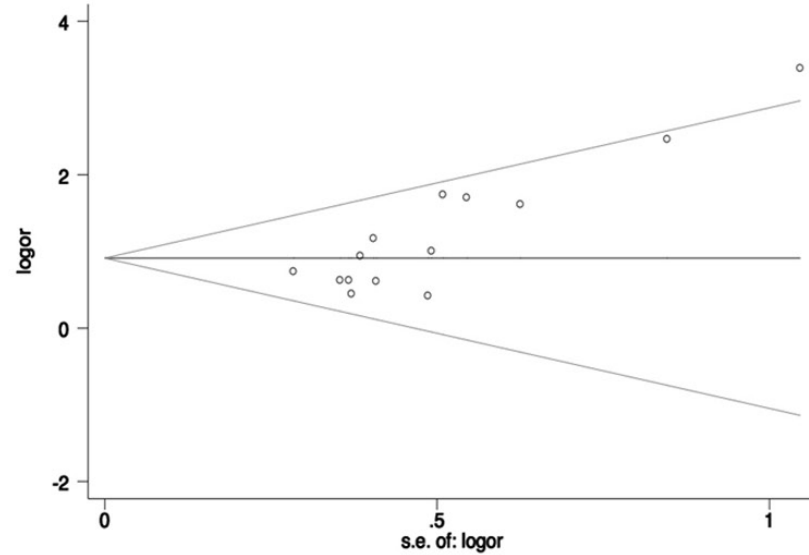
Figure 3. Forest plot and Begg's publication bias plot of studies evaluating the relationship between USP22 expression and clinicopathological features: (A) Depth of infiltration; (B) Tumor size.

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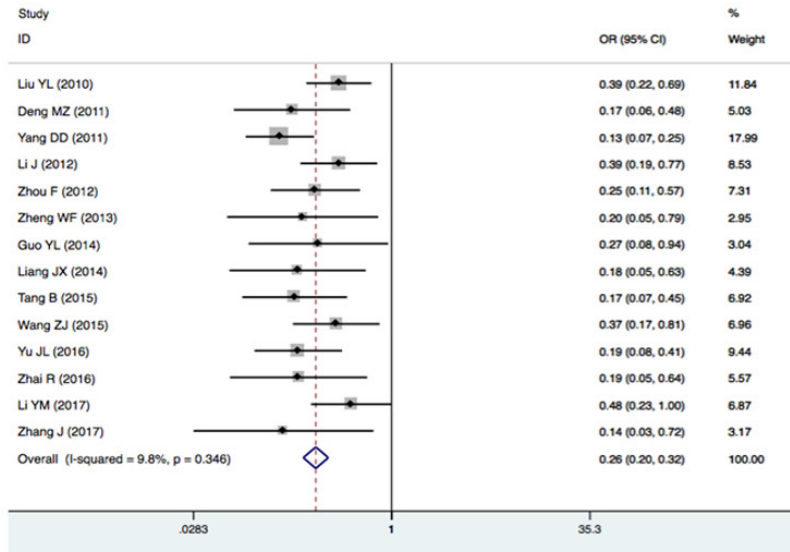
A



Begg's funnel plot with pseudo 95% confidence limits



B



Begg's funnel plot with pseudo 95% confidence limits

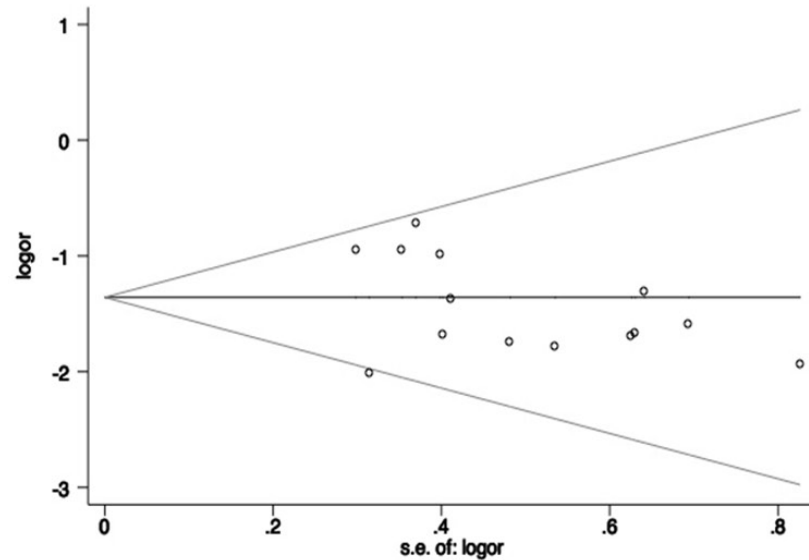
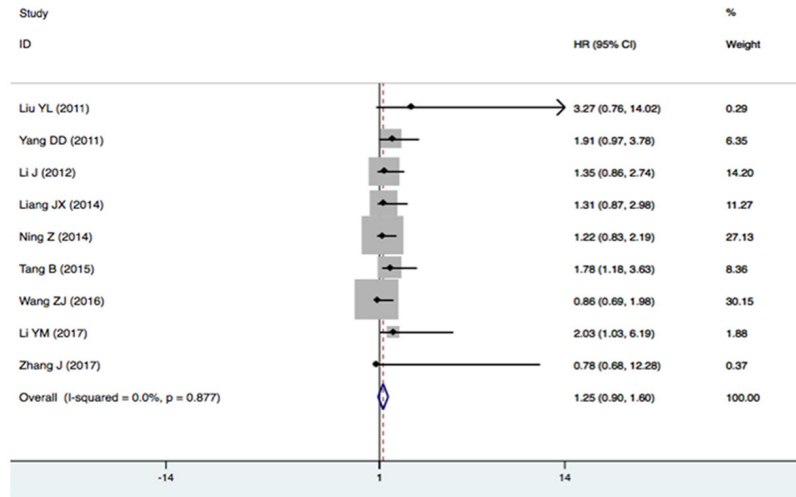


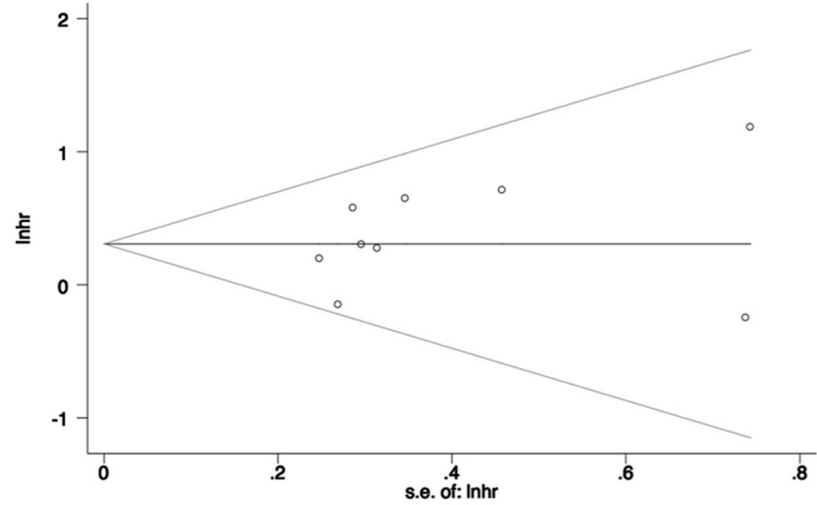
Figure 4. Forest plot and Begg's publication bias plot of studies evaluating the relationship between USP22 expression and clinicopathological features: (A) Differentiation; (B) TNM stage.

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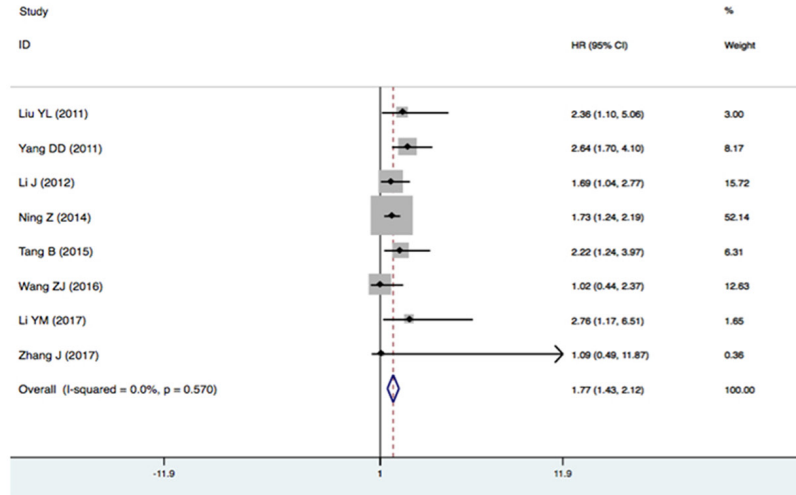
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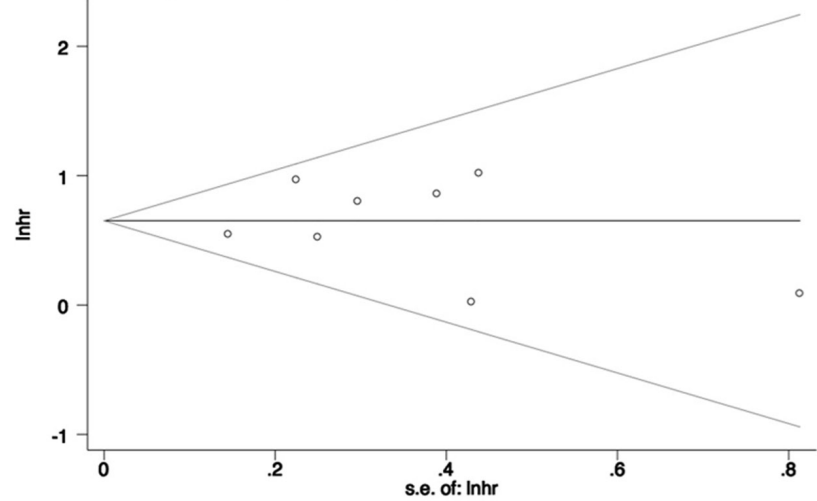
Begg's funnel plot with pseudo 95% confidence limits



B



Begg's funnel plot with pseudo 95% confidence limits



USP22 and digestive system carcinoma

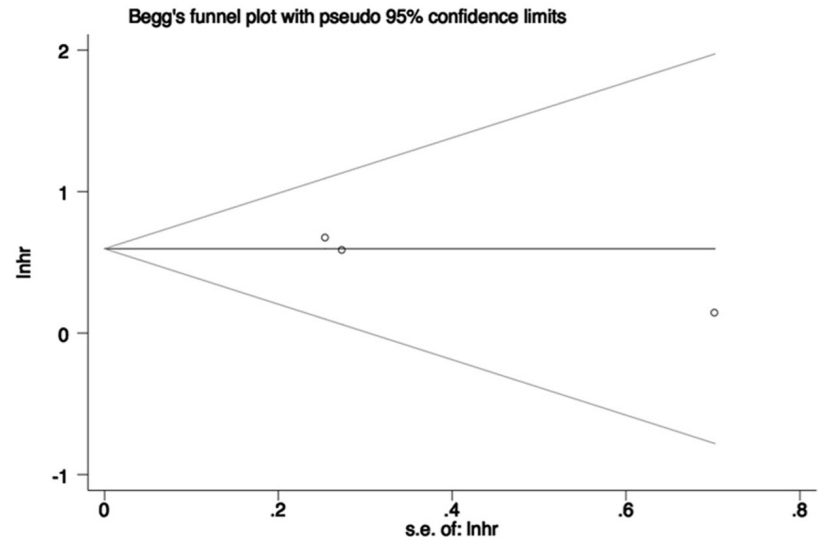
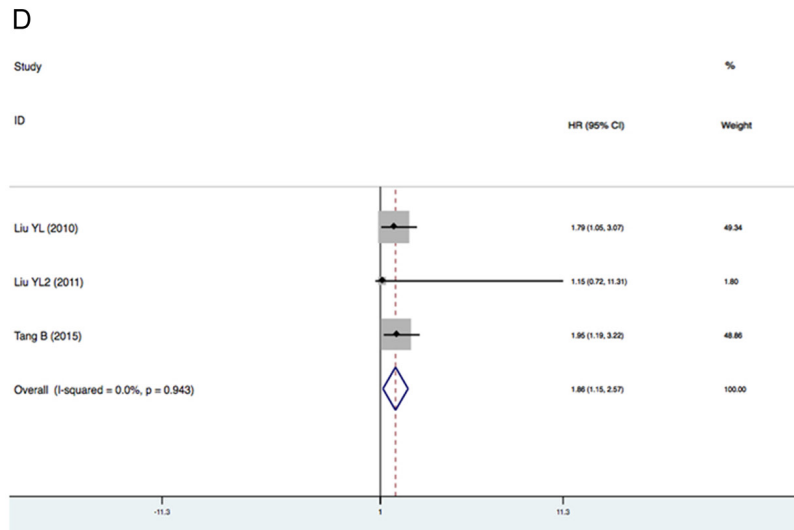
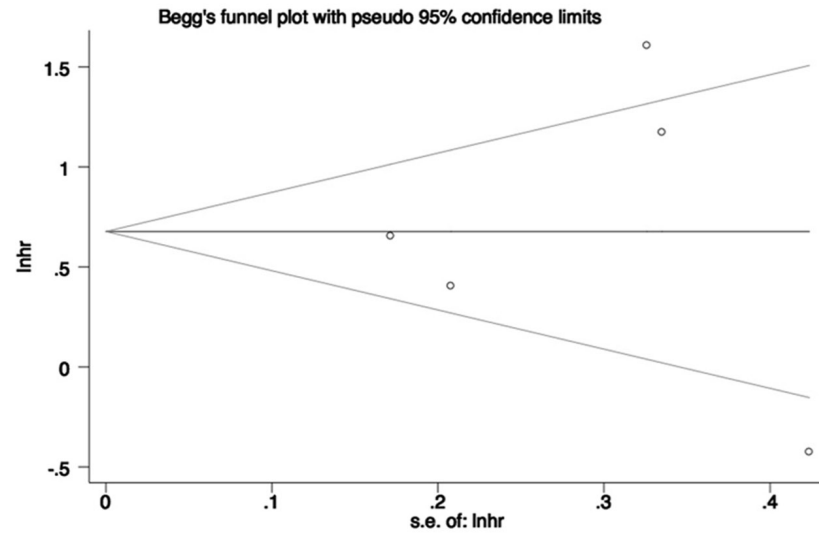
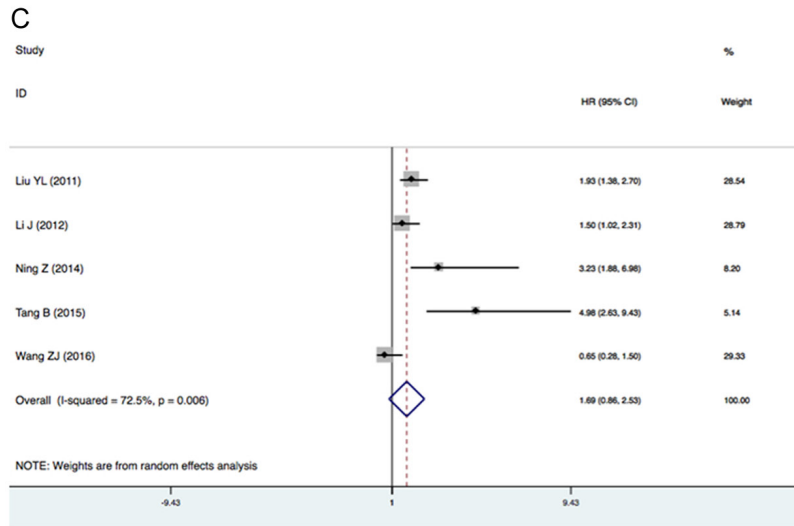


Figure 5. Forest plot of studies evaluating the relationship between USP22 expression and prognosis: (A) 3-year overall survival; (B) 5-year overall survival; (C) Independent role for overall survival; (D) Disease-free survival.

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Table 3. Subgroup analysis of overall survival by tumor type, NOS score, sample size

Subgroups	No. of studies	No. of patients	Pooled HR (95% CI)	PHet	I ² (%)	P value
3-year overall survival						
<i>Tumor type</i>						
Gastrointestinal tract	5	820	1.17 (0.69, 1.66)	0.574	0.0	> 0.05
Digestive gland	4	360	1.34 (0.82, 1.85)	0.884	0.0	> 0.05
<i>Sample size</i>						
≤ 125	4	347	1.17 (0.77, 1.57)	0.645	0.0	> 0.05
> 125	5	833	2.26 (0.79, 2.30)	0.911	0.0	> 0.05
<i>NOS score</i>						
≤ 7	3	256	1.24 (0.67, 1.81)	0.978	0.0	> 0.05
> 7	6	924	1.26 (0.80, 1.71)	0.590	0.0	> 0.05
5-year overall survival						
<i>Tumor type</i>						
Gastrointestinal tract	5	820	1.76 (1.23, 2.30)	0.263	23.7	< 0.01
Digestive gland	3	292	1.78 (1.33, 2.23)	0.780	0.0	< 0.01
<i>Sample size</i>						
≤ 125	3	279	2.28 (1.09, 3.47)	0.861	0.0	< 0.05
> 125	5	833	1.73 (1.37, 2.09)	0.321	14.6	< 0.01
<i>NOS score</i>						
≤ 7	2	188	1.83 (1.33, 2.32)	0.346	0.0	< 0.01
> 7	6	924	1.73 (1.25, 2.20)	0.570	10.9	< 0.01

Abbreviations: OR = hazard ratio, CI = confidence interval, n = number of sample size.

positive USP22 and age (OR = 1.04, 95% CI = 0.84-1.28, $P = 0.917$, $I^2 = 0.0\%$, **Figure 2A**). ORs for depth of infiltration were included in 11 studies, including 1,340 patients. Results indicated a significant association between USP22 expression and depth of infiltration (T1 + 2: T3 + 4: OR = 0.36, 95% CI = 0.28-0.47, $P < 0.001$, $I^2 = 43.8\%$, **Figure 3A**). Positive USP22 expression was related to tumor size (≤ 5 cm: > 5 cm: OR = 0.60, 95% CI = 0.42-0.86, $P = 0.005$, **Figure 3B**), differentiation (low: high + moderate: OR = 2.64, 95% CI = 1.75-3.30, $P < 0.001$, **Figure 4A**), and TNM stage (I + II: III + IV: OR = 0.26, 95% CI = 0.20-0.32, $P < 0.001$, **Figure 4B**).

Association between USP22 expression and overall survival

HRs for overall survival rates (disease-specific survival rates) were calculated in 10 studies. However, sensitivity analysis indicated Zhao et al. [12] as the main reason of heterogeneity (data not shown). Thus, this study was deleted. A total of 9 studies and 1,180 patients included 679 positive USP22 expression cases and 501 negative cases. Pooled results demonstrated that expression of USP22 was not associated

with poor 3-year overall survival (positive: negative HR = 1.25, 95% CI = 0.90-1.60, **Figure 5A**). A total of 8 studies and 1,120 patients indicated that high expression of USP22 was significantly related to 5-year overall survival (positive: negative HR = 1.77, 95% CI = 1.43-2.12, **Figure 5B**). Cox multivariate analysis was calculated in three studies for OS in five studies. Pooled HRs indicated that USP22 was not an independent prognostic factor for OS (HR = 1.69, 95% CI = 1.43-2.12, **Figure 5C**).

In addition, subgroup analysis was conducted of 3-year and 5-year overall survival, according to tumor type, sample size, and NOS score. As shown in **Table 3**, subgroup analysis of 3-year overall survival rates indicated that overexpression of USP22 was not related to poor survival in each group. Subgroup analysis of 5-year overall survival rates suggested that positive USP22 was associated with poor 5-year OS.

Sensitivity analysis was conducted to explore the robustness of pooled results. Results (**Figure 6**) were not significantly impacted if any individual study was removed, indicated that results were reliable.

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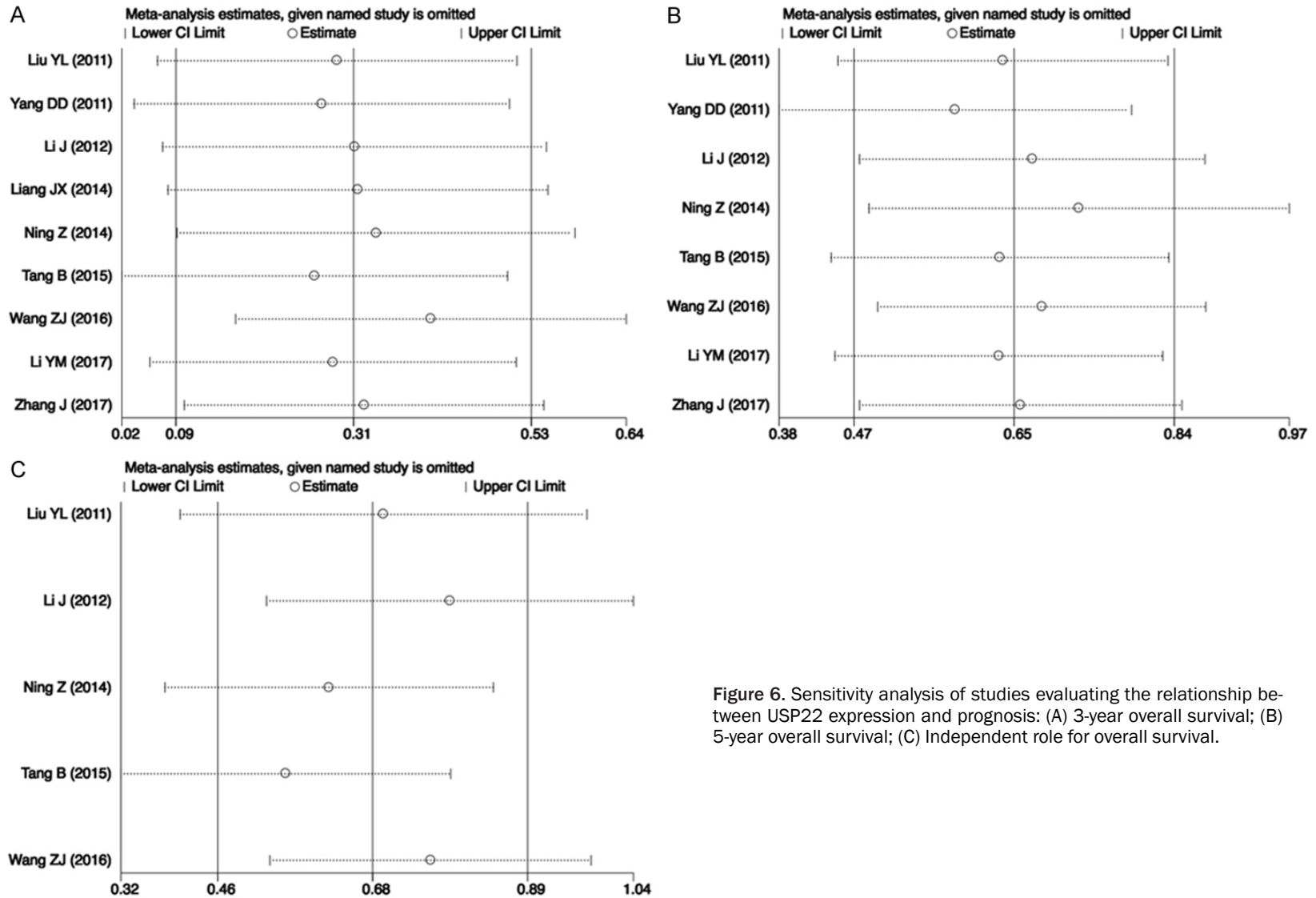


Figure 6. Sensitivity analysis of studies evaluating the relationship between USP22 expression and prognosis: (A) 3-year overall survival; (B) 5-year overall survival; (C) Independent role for overall survival.

Association between USP22 expression and disease-free survival in patients with digestive system malignancies

HRs for disease-free survival rates were calculated in 3 studies, including 201 positive USP22 expression cases and 145 negative cases. Pooled results indicated that positive USP22 was related to poor DFS (positive: negative HR = 1.86, 95% CI = 1.15-2.57, **Figure 5D**).

Publication bias and sensitivity analysis

There was no publication bias for gender ($P = 0.392$), age ($P = 0.908$), depth of infiltration ($P = 0.119$), tumor size ($P = 0.251$), differentiation ($P = 0.022$), TNM stage ($P = 0.443$), 3-year overall survival rates ($P = 0.251$), 5-year overall survival rates ($P = 1$), and disease-free survival rates ($P = 0.806$), according to Begg's test. However, publication bias existed for differentiation ($P = 0.022$). Therefore, sensitivity analysis was conducted to evaluate whether individual studies influenced pooled OR. Results indicated that no studies substantially influenced pooled OR, indicating that more studies should be included in future research.

Discussion

USP22 is a member of the deubiquitinated USP subfamily. Its gene is located at 17p 11.2 and encoded proteins consist of 525 amino acids. USP22 protein has a highly conserved region located at the carboxyl terminus which can remove ubiquitin molecules from some large protein molecules that have been ubiquitinated. However, if USP22 does not have the Cys box and His box in the carboxy terminus, USP22 will lose the function of de-ubiquitination [29, 30]. Studies have found that USP22 can participate in the regulation of many cellular activities *in vivo*, which is closely related to its downstream target genes. First, USP22 maintains mitosis in normal eukaryotic cells, while silencing expression of USP22 results in G1/S arrest in cells [31]. This effect may be achieved through the regulation of multiple target genes. USP22 can assist c-myc in transcriptional activation of downstream target genes and moreover deubiquitinate the transcription factor FUBP1 [32], thereby inhibiting the transcription of cell cycle inhibitor p21 or promoting mitosis by activating JAK-STAT1 pathways [33]. Second, USP22 can maintain the normal function of

telomeres by stabilizing the telomere protection complex TRF1, such as DNA damage repair [34]. In addition, USP22 also exerts immunomodulatory effects by stabilizing NFATc2 and RCAN1 [35, 36]. As a stem cell-associated molecule, USP22 is also involved in regulating the development of embryonic stem cells and neural stem cells [37].

In recent years, studies have found that USP22 is overexpressed in many tumors and that positive USP22 expression was related to clinicopathological features of tumors. However, the relationship between positive expression of USP22 and clinicopathological features of gastrointestinal tumors remains controversial. This meta-analysis included 17 studies, with 1,926 patients enrolled. Pooled results indicated that positive USP22 expression was associated with depth of infiltration, larger tumor size, lower differentiation, and advanced TNM stage. However, it was not related to gender and age, indicating that USP22 may be involved in the progression of tumors.

The present meta-analysis found 11 articles and 1,340 patients addressing the relationship between USP22 expression and depth of infiltration, with three articles showing that positive USP22 was not related to depth of infiltration. However, pooled results indicated statistical significance. Similarly, six of nine studies showed that positive expression of USP22 was not associated with tumor size, but pooled results indicated that USP22 was related to tumor size and differentiation. In the study of correlation between USP22 and TNM stage, all 14 articles demonstrated that positive USP22 expression predicted advanced TNM stage.

This meta-analysis not only analyzed the correlation between USP22 and clinicopathological features, but also explored the relationship between USP22 and prognosis of patients with gastrointestinal carcinoma. This study analyzed the relationship between positive USP22 expression and 3- and 5-year overall survival rates (disease-specific survival rates). Pooled results showed that positive USP22 expression indicated a poor 5-years OS. However, it was not related to 3-year overall survival rates and USP22 expression could not be an independent risk factor for OS in patients with gastrointestinal carcinoma. This study examined

the relationship between USP22 and disease-free survival. Pooled results suggested a poor DFS. Heterogeneity of the meta-analysis of OS independent factors was large. The source of heterogeneity may be caused by different tumor types, different antibodies, and different cut-off values. Thus, large samples of high-quality studies are necessary to support the results. Despite this, USP22 may be a potential novel biomarker for the prognosis of GICs.

Studies have also indicated that USP22 was closely related to the malignant biological behavior of tumors and may be one of the molecular targets of tumor targeted therapy. One study found that USP22 was involved in tumor progression through multiple signaling pathways, such as STAT, TGF- β , and Wnt/ β -catenin. Ao et al. [38] found that USP22 can form a protein complex with SIRT1 and STAT3 to inhibit the invasion ability of colon cancer. Hu et al. [39] indicated that the sh-USP22 lung adenocarcinoma cells group grew slower than the control group. Expression of TGF- β was decreased. Otherwise, tumor cell growth accelerated and TGF- β expression increased, indicating that USP22 may induce epithelial-mesenchymal transition by altering levels of TGF- β . Ning et al. [27] indicated that USP22 upregulated FoxM1 expression through Wnt/ β -catenin signaling pathways in pancreatic cancer cell line PANC-1 and promoted G1/S phase transition, cell proliferation, invasion, and metastasis of PANC-1.

In recent years, anti-tumor drugs based on ubiquitin-protease have gradually increased. Targeting USP22 anti-tumor drugs will also become a research hot spot. However, there are no small-molecular drugs specific to USP22. Many researchers have achieved anti-tumor effects by inhibiting the expression of USP22 by other means. Xiong et al. [40] found that p38/MAPK negatively regulates the transcription of USP22 in Hela cells and that expression of USP22 mRNA was reduced by about 40% when p38/MAPK was activated, suggesting that the effects are achieved through inhibiting expression of USP22 by activating P38/MAPK. Trichostatin A [41], which is a histone deacetylase inhibitor, interferes with the attachment of RNA polymerase II to the USP22 promoter in Hela cells, thereby reducing the expression of USP22 and inhibiting cell proliferation.

There were some limitations to this meta-analysis. 1) There may be different results for some unpublished articles. This may have caused publication bias and may have impacted heterogeneity; 2) All of the included articles were from China. This result may be only suitable for Chinese or Asian populations; 3) The methods of most studies were immunohistochemistry, a semi-quantitative method that may be affected by antibody quality, antibody concentration, incubate time, and so forth. The positive cut-off values of USP22 were not the same; 4) HRs about 3-year, 5-year OS, or DFS were obtained by survival curves, which may have impacted the results.

Conclusion

Despite these limitations, this meta-analysis indicated that positive USP22 expression was related to larger tumor size, depth of infiltration, lower differentiation, and advanced TNM stage in patients with digestive tumors. Moreover, USP22 may be a potential biomarker for prognosis of gastrointestinal carcinoma.

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Disclosure of conflict of interest

None.

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