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Original Article

Ubiquitin-specific protease 22 as a prognostic biomarker in patients with various cancers: a meta-analysis

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Abstract: Many studies have reported that elevated ubiquitin-specific protease 22 (USP22) expression was association with poor prognosis in various cancer patients. To evaluate the prognostic value of USP22 in cancers, a comprehensive meta-analysis of published studies was conducted. Eligible studies were identified via multiple search strategies through PubMed, Web of Science and Ovid. The literature search was stopped at 19 November 2015. This meta-analysis was performed by Stata statistical software version 12.0. Seventeen eligible articles with a total of 2465 patients were included in this meta-analysis. The results showed that increased USP22 expression was significantly association with poor overall survival (OS), poor disease-free survival (DFS) and poor disease-specific survival (DSS) or relapse-free survival (RFS). The pooled hazard ratio (HR) is 2.47 (95% CI: 1.97-3.11, P = 0.000), 2.66 (95% CI: 2.02-3.50, P = 0.000) and 1.56 (95% CI: 1.12-2.18, P = 0.009), respectively. In the subgroup analysis, elevated USP22 expression was significantly correlation with all variables including publication year, sample size, the type of cancer, the method of survival analysis and Newcastle-Ottawa Quality Assessment Scale (NOS) score. USP22 overexpression was significantly associated with some of clinicopathological parameters, such as histological grade and lymph node metastasis for OS and DFS, tumor stage for OS. However, USP22 overexpression was not significantly associated with gender and tumor stage for OS. Sensitivity analysis showed there was not individual study affecting the pooled HRs. No publication bias was observed in this meta-analysis. This meta-analysis indicates that USP22 may be a potential prognostic biomarker in cancer patients. Elevated USP22 is significantly associated with clinicopathological factors and poorer prognosis in a variety of cancers.

Keywords: USP22, cancer, prognosis, biomarker, meta-analysis

Introduction

Belonging to the cysteine protease family, Deubiquitinating enzymes not only regulate a number of cellular mechanisms, such as preimplantation, growth and differentiation, oncogenesis, cell cycle progression, transcriptional activation, and signal transduction [1], but also catalyze the deconjugation of ubiquitin-tagged substrates [2]. Ubiquitin-specific proteases (USPs), which have highly specific activity and are involved in several human pathologies including cancer, are a subclass of deubiquitinating enzymes with specific targets of therapeutic importance 45 [3-5]. An 11-gene Polycomb/cancer stem cell signature was identified. The stem could powerfully predict the therapeutic outcome of individual cancer patients [6]. Ubiquitin-specific protease 22 (USP22) is a member of Polycomb/cancer stem cell signature identified recently [7]. USP22 is a key subunit of the human Spt-Ada-Gcn5-acetyltransferase (hSAGA) co activator complex. In addition, as an activator for nuclear receptor-mediated transactivation to regulate the expression of genes related to oncogenicity and proliferation, it can function within the hSAGA complex [8-10]. USP22 can interact within the hSAGA complex so as to hydrolyse the ubiquitin conjugated to histones H2A and H2B, which activates target gene transcription as mediated by alterations in levels of histone

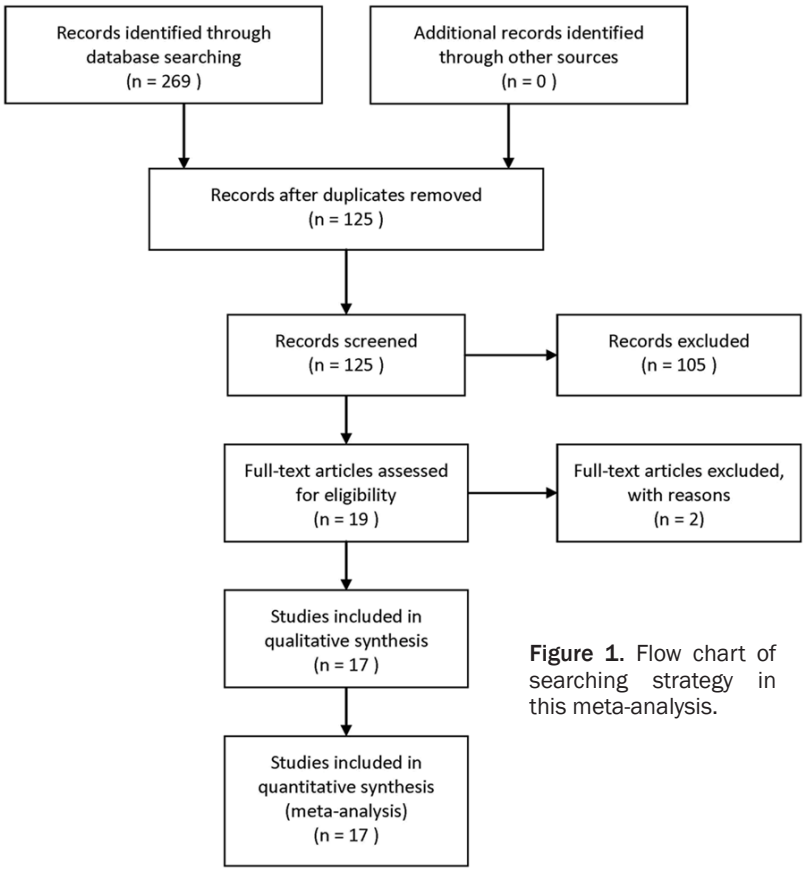

Figure 1. Flow chart of searching strategy in this meta-analysis.

ubiquitylation [10]. More importantly, knockdown of USP22 reduces transcriptional activation of all c-myc and most p53 target genes as well as compromises cell cycle progression and anchorage-independent growth, strengthening the link with cancerous growth [10-12].

USP22 plays a key role in many aspects, including cell cycle regulation, embryo development, telomere homeostasis, therapy resistance, tumor progression and tumor metastasis [10, 13-16]. The elevated expression of USP22 has been found in various human cancers, including head and neck cancers, ovarian cancer, cervical cancer, breast cancers, lung cancer and digestive system cancers, while normal tissues express low levels of USP22 [7]. Recently, many studies have reported that the cancer patients with elevated USP22 expression had poor survival outcome [24-40]. USP22 may be used as a potential and new biomarker for the diagnosis, treatment and prognosis of cancers. Because of the limitation of the single study and small sample size, and in order to understand the relationship between USP22 expression and the prognosis of patients suffered cancers deeply, a comprehensive and quantitative meta-analysis to evaluate the published literatures is necessary. We first evaluate the relationship between USP22 expression and the prognostic value to cancer patients in this systematic meta-analysis.

Materials and methods

Literature search strategy

This meta-analysis was carried out following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and the systematic reviews and meta-analysis guidelines of tumor marker prognostic studies (REMARK) criteria [17-19]. Relevant articles that assessed on the prognostic value of USP22 in various cancers were identified through a search in PubMed, Web of Science and Ovid. The literature search was stopped at 19 November 2015. The following keywords and medical subject headings (MeSH) terms: “USP22”, “Ubiquitin-specific protease 22”, “cancer OR carcinoma OR neoplasm OR tumor OR sarcoma”, “prognostic OR prognosis OR outcome OR survival” were used in a comprehensive search. The literatures in English and human studies were restricted in this search. Two investigators (Xia and Guan) performed the search independently and resolved the disagreements by discussions.

Inclusion and exclusion criteria

The eligible articles in this meta-analysis have to meet the following criteria: (1) the population in human studies diagnosed a type of cancer; (2) the method of USP22 detection, such as quantitative real-time PCR (qRT-PCR) or immunohistochemistry (IHC); (3) the relationship of expression USP22 with survival outcome; (4) the follow up period; (5) English articles. The

Table 1. Characteristics of 19 studies included in the meta-analysis

Author	Year	N	Tumor type	Stage	Method	Cutoff	Treatment	Survival outcome	Survival analysis	Hazard ratios	Follow-up (month)	NOS score
Liu	2011	192	CRC	I-IV	IHC	> 10%	Surgery	DSS, DFS	M	Reported	61.05 (4.20-105.93)	8
Yang	2011	219	GC	I-IV	IHC	≥ 20%	Surgery	DSS	U	SC	29.57 (1.9-78.1)	9
Zhang	2011	100	BC	I-III	IHC	IRS ≥ 3	Surgery	OS, DFS	M	Reported	67 (6-81)	9
Li	2012	157	ESCC	I-III	IHC	≥ 3	Surgery	DSS	U	SC	39 (6-73)	9
Ning	2012	86	NSCLC	I-II	IHC	IRS ≥ 3	Surgery	OS	U + M	Reported	51.9 (26-67)	9
Piao	2012	319	OSCC	I-IV	IHC	≥ 20%	Surgery	OS, DFS	M	Reported	41 (3.9-87.1)	9
Wang	2013	156	PTC	I-IV	IHC	EI > 3	Surgery	OS	U + M	Reported	NR	8
Dai	2014	135	SACC	NR	IHC	IRS ≥ 3	Surgery	OS, DFS	U + M	Reported	60	9
Ji	2014	86	EOC	I-IV	qRT-PCR	Median	Surgery	OS, RFS	U	SC	45 (median)	9
Liang	2014	68	PC	I-IV	IHC	66.2%	Surgery	OS	U	SC	NR	8
Liang	2014	109	glioma	I-IV	IHC	IRS ≥ 4	Surgery	OS	U	SC	NR	7
Ning	2014	136	PDA	II	IHC	> 50%	Surgery	OS	U + M	Reported	NR	8
Yang	2014	180	CerC	I-II	IHC	IRS ≥ 4	Surgery	OS, DFS	M	Reported	64 (median)	9
Hu	2015	146	NSCLC	I-III	IHC	≥ 20%	Surgery	OS, DFS	U + M	Reported	25.25 (2.33-93.6)	9
Tang	2015	151	HCC	I-IV	IHC	> 20%	Surgery	DFS	U	SC	60	9
Tang	2015	104	HCC	I-IV	IHC	> 20%	Surgery	OS, RFS	M	Reported	> 60	9
Wang	2015	121	CC	I-IV	IHC	IRS ≥ 1	Surgery	DSS	M	Reported	60	9

N, number; CRC, colorectal cancer; GC, gastric carcinoma; BC, breast cancer; ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; PTC, papillary thyroid carcinoma; SACC, salivary adenoid cystic carcinoma; EOC, epithelial ovarian cancer; PC, pancreatic cancer; PDA, pancreatic ductal adenocarcinoma; CerC, cervical cancer; HCC, hepatocellular carcinoma; CC, colon cancer; NR, not reported; IHC, immunohistochemistry; qRT-PCR, quantitative real-time PCR; IRS, immunoreactive scores; EI, extent (E) × intensity (I); DSS, disease-specific survival; DFS, disease-free survival; OS, overall survival; RFS, relapse-free survival; M, Multivariate; U, Univariate; U + M, Univariate and Multivariate; SC, survival curve.

exclusion criteria was as follows: (1) review articles, letters, conference abstract, or laboratory articles; (2) non-human studies; (3) non-English articles; (4) overlapping studies; (5) lacking key information for calculation using methods as previously reported [20-22]. The most recent studies with larger sample size were selected if the same patient cohort was utilized in different articles. The two authors reached an agreement on all items. A flow diagram of the study selection process is presented in **Figure 1**.

Data extraction and quality assessment

Two reviewers (Xia and Guan) extracted the data from all eligible studies according to the before-mentioned selection criteria independently. The primary information including hazard ratios (HR), 95% confidence interval (CI), *P* value, univariate analysis, multivariate analysis and Kaplan-Meier survival curve were extracted by two investigators (Xia and Guan). Subsequently, more data were extracted from the studies. The following information was collected: first author's name, publication year, sample size of the study population, type of cancer, TNM stage, method of detecting USP22, cutoff value, treatment of the patients, survival outcome, and duration of follow up. Clinicopathological features data including gender, tumor stage, histological grade and lymph node metastasis were reviewed. The HRs were obtained by two methods. HRs were extracted from the publications directly or the survival curves using the described method [20]. Newcastle-Ottawa Quality Assessment Scale (NOS) was used for assessing the quality of the primary studies [23]. NOS score ≥ 7 indicates good quality in this study. Disagreements were resolved by discussion. All the data were subject to consensus.

Statistical analysis

The HRs were calculated from Kaplan-Meier survival curves using software designed by Matthew Sydes and Jayne Tierney [21], when the statistical variables were not described in the publications. The effect of USP22 expression on survival outcome (OS, DFS, DSS/RFS) were estimated using forest plots. Heterogeneity among these studies was assessed using Chi-square based Q test. There is significant heterogeneity when I^2 > 50% or P < 0.1. Pooled

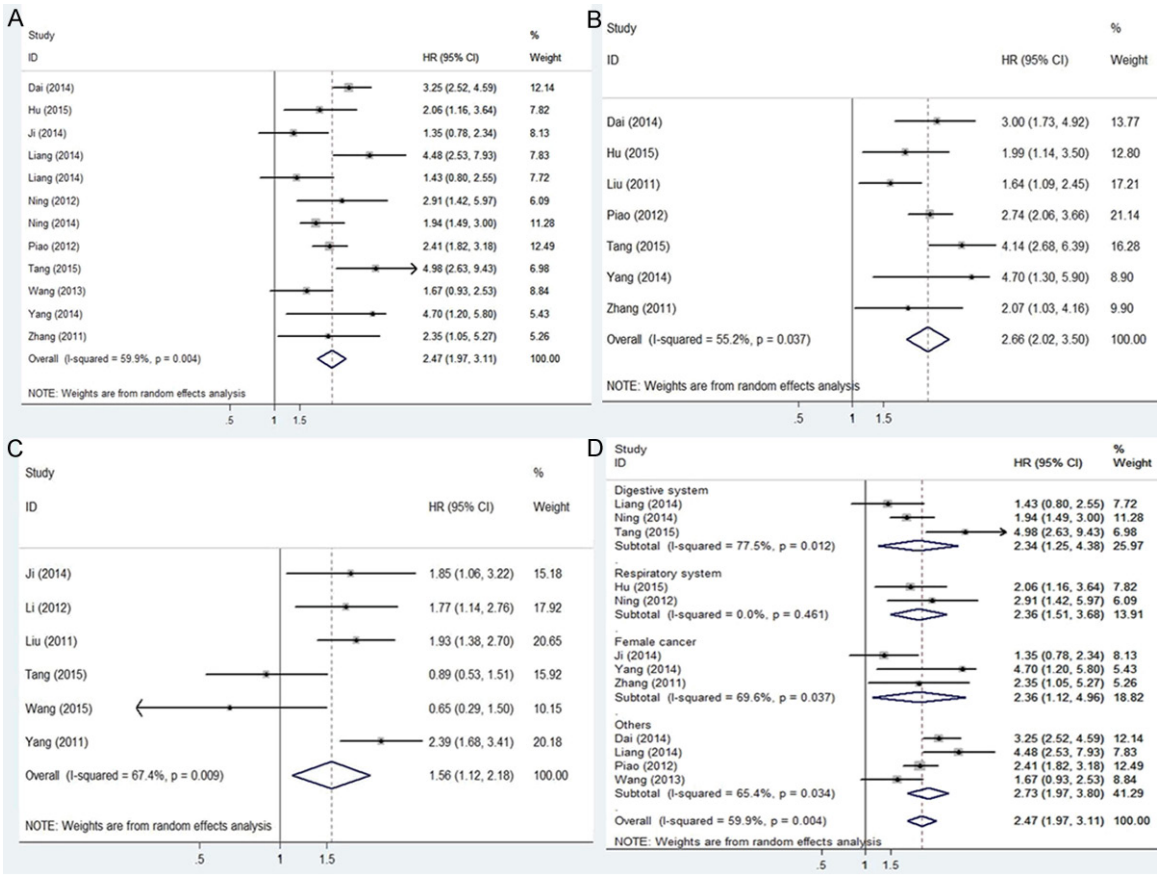

Figure 2. Forest plot of correlation between elevated USP22 expression and OS (A), DFS (B), DSS/RFS (C), and the type of cancer (D) in the different types of cancer.

HRs were calculated using a fixed-effects model if there was no significant heterogeneity. Otherwise, the random effects model was applied. Generally, pooled HR of > 1 was assumed to indicate poor prognosis for the groups with elevated USP22 expression and was interpreted as statistically significant if the 95% CI for the pooled HR did not overlap one. Meta analysis of pooled hazard ratios of cancer patients with elevated USP22 expression were examined with respect to gender (Female vs. Male), tumor stage (III/IV vs. I/II), histological grade (Well vs. Poor/Moderate) and lymph node metastasis (Positive vs. Negative). Sub-group analyses were carried out to explore the source of heterogeneity among variables, such as publication year, sample size, cancer types, the type of COX regression analysis and NOS score. Sensitivity analysis was performed by omitting individual studies to identify the effect of data from each study on pooled HRs. Begg's test and Egger's test were used to detect publication bias quantitatively and funnel plots were performed qualitatively. There is no publication bias when $P > 0.05$. All statistical tests were performed with STATA software version 12.0 (STATA Corporation, College Station, TX, USA) and two sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of eligible studies

A total of 269 relevant articles were indentified based on the study design, our search with key terms. After the primary screen, 144 studies were excluded because of being duplicate or irrelevant. Totally, 19 full text literatures were assessed for the eligibility after the evaluation of the titles and abstracts. Because of containing the same study population, 2 studies were excluded. At last, 17 eligible articles were included in this meta-analysis with a total of 2465 patients (ranged from 68 to 319 per study) and a mean number of 145 patients per

Table 2. Subgroup analysis of the pooled hazard ratios of overall survival with overexpressed USP22 in patients with cancer

Subgroup	No. of studies	No. of patients	Model	Pooled HR (95% CI)	*P* value	Heterogeneity (I^2, *P*-value)	Publication bias	
							Begg's test (*P* value)	Egger's test (*P* value)
Overall	12	1625	REM	2.47 (1.97-3.11)	0.000	59.9%, 0.004	0.583	0.859
Publication Year								
≥ 2014	8	964	REM	2.61 (1.86-3.64)	0.000	71.6%, 0.001	0.621	0.868
< 2014	4	661	FEM	2.28 (1.83-2.84)	0.000	0.0%, 0.554	1.000	0.932
Sample size								
≥ 100	9	1385	REM	2.73 (2.15-3.47)	0.000	56.5%, 0.018	0.404	0.470
< 100	3	240	FEM	1.65 (1.17-2.34)	0.005	36.4%, 0.207	0.117	0.076
Type of cancer								
Digestive system	3	308	REM	2.34 (1.25-4.38)	0.008	77.5%, 0.012	0.602	0.708
Respiratory system	2	232	FEM	2.36 (1.51-3.68)	0.000	0.0%, 0.461	0.317	NA
Female cancer	3	366	REM	2.36 (1.12-4.96)	0.023	69.6%, 0.037	0.602	0.345
Others	4	719	REM	2.73 (1.97-3.80)	0.000	65.4%, 0.034	0.497	0.935
Survival analysis								
Univariate	8	922	REM	2.25 (1.63-3.12)	0.000	58.2%, 0.019	0.216	0.245
Multivariate	9	1462	FEM	2.56 (2.21-2.96)	0.000	46.7%, 0.059	0.532	0.603
NOS score								
= 9	8	1156	REM	2.70 (2.07-3.52)	0.000	52.3%, 0.040	0.621	0.871
< 9	4	469	REM	2.11 (1.37-3.26)	0.001	68.1%, 0.024	0.497	0.771

HR, hazard ratio; CI, confidence interval; FEM, fixed-effects model; REM, random-effects model; NA, not available.

study [24-40]. These studies were published from 2011 to 2015 and conducted all in Chinese cancer population after surgery. Various cancers were assessed in these studies, including 8 for digestive system cancer [24, 25, 27, 33, 35, 38-40], 2 for lung cancer [28, 37], 3 for female cancer [26, 32, 36] and 5 for others [29-31, 34, 35]. The methods of USP22 detection were IHC and qRT-PCR. The cutoff values were not uniform in these studies because of the different methods and researchers. In all of the studies, 6 studies were not given the HRs and 95% CI directly [25, 27, 32-34, 39]. The main characteristics of the included studies are shown in **Table 1**.

Mata-analysis results

The relationship between elevated USP22 expression and various cancers patients survival outcome is shown in **Figure 2**. The patients with elevated USP22 expression level had a worse survival outcome, with the pooled HRs of OS (**Figure 2A**), DFS (**Figure 2B**), and DSS/RFS (**Figure 2C**) by a random-effects model because of the significant heterogeneity (I^2 = 59.9%, P = 0.004; I^2 = 55.2%, P = 0.037, I^2 = 67.4%, P = 0.009, respectively). Because of the existence of heterogeneity, subgroup analysis for OS was conducted by publication year, sample size, cancer types, the methods of survival analysis and NOS score. The main results of the subgroup analysis for prognostic role of USP22 in various tumors are shown in **Table 2** and **Figure 2D**. The elevated USP22 expression predicts various cancers patients' poor prognosis at any subgroup variable in this subgroup analysis. The pooled HRs were 2.61 (95% CI: 1.86-3.64, P = 0.000) for publication Year (≥ 2014), 2.28 (95% CI: 1.83-2.84, P = 0.000) for publication year (< 2014), 2.73 (95% CI: 2.15-3.47, P = 0.000) for sample size (≥ 100) and 1.65 (95% CI: 1.17-2.34, P = 0.005) for sample size (< 100). In the stratified analyses according to the type of cancer, over-expression of USP22 led a worse survival outcome in digestive system cancers (pooled HR = 2.34, 95% CI: 1.25-4.38, P = 0.008), respiratory system cancers (pooled HR = 2.36, 95% CI: 1.51-3.68, P = 0.000), female cancers (pooled HR = 2.36, 95% CI: 1.12-4.96, P = 0.023) and other cancers (pooled HR = 2.73, 95% CI: 1.97-3.80, P = 0.000). In the studies conducted by multivariate survival analysis, the pooled HR is 2.56 (95% CI: 2.21-2.96, P = 0.000), while the pooled HR is 2.25 (95% CI: 1.63-3.12, P = 0.000) in

Table 3. Meta-analysis of USP22 expression and clinicopathological parameters in cancer patients

Subgroup	No. of studies	No. of patients	Model	Pooled HR (95% CI)	*P* value	Hetero-geneity (I^2, *P*-value)	Publication bias	
							Begg's test (*P* value)	Egger's test (*P* value)
OS								
Gender (Female vs. Male)	3	346	FEM	1.15 (0.75-1.77)	0.527	0.0%, 0.745	0.602	0.536
Tumor stage (III/IV vs. I/II)	2	250	REM	2.06 (0.81-5.25)	0.131	78.9%, 0.029	0.317	NA
Histological grade (Well vs. Poor/ Moderate)	4	501	REM	2.70 (1.94-3.77)	0.000	53.2%, 0.093	1.000	0.643
Lymph node metastasis (Positive vs. Negative)	5	693	REM	2.46 (1.96-3.09)	0.000	67.0%, 0.017	1.000	0.520
DFS								
Tumor stage (III/IV vs. I/II)	2	338	REM	1.74 (1.45-2.10)	0.000	90.1%, 0.001	0.317	NA
Histological grade (Well vs. Poor/ Moderate)	3	415	REM	3.45 (2.24-5.30)	0.000	71.0%, 0.032	0.117	0.118
Lymph node metastasis (Positive vs. Negative)	2	315	FEM	3.10 (1.87-5.13)	0.000	0.0%, 0.586	0.317	NA

HR, hazard ratio; CI, confidence interval; OS, overall survival; DFS, disease-free survival; FEM, fixed-effects model; REM, random-effects model; NA, not available.

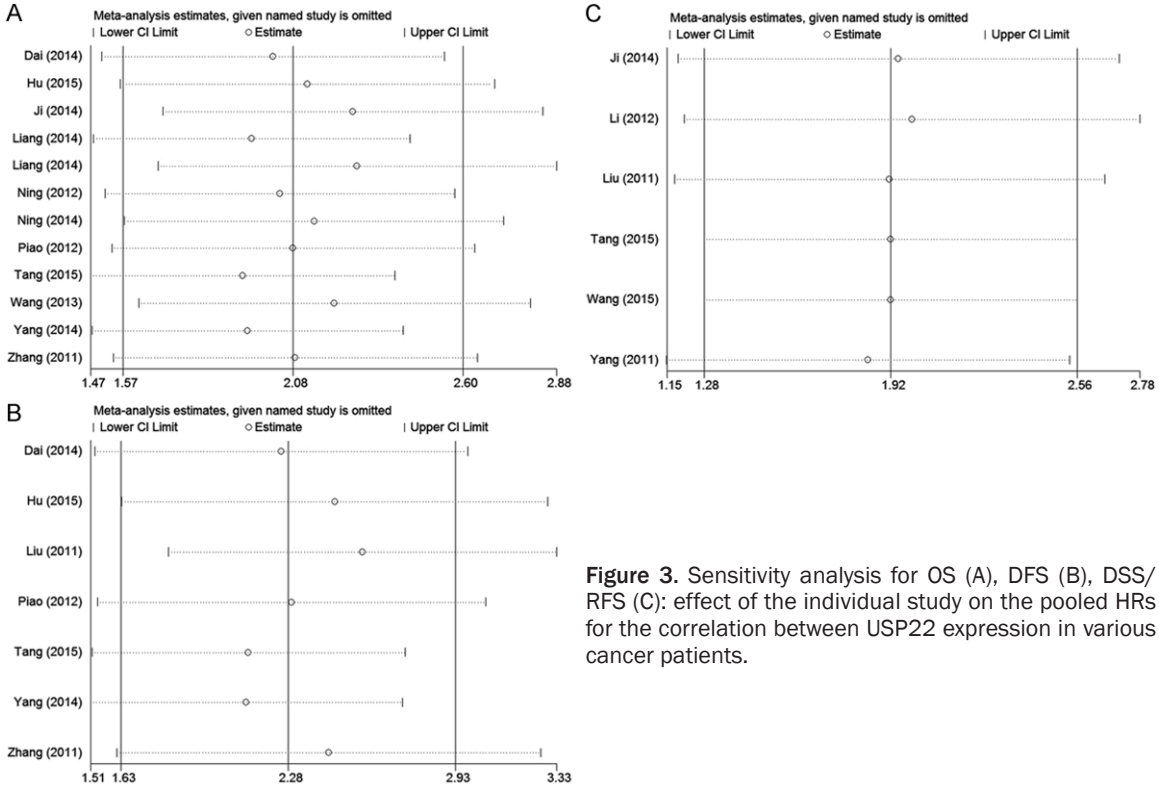

Figure 3. Sensitivity analysis for OS (A), DFS (B), DSS/ RFS (C): effect of the individual study on the pooled HRs for the correlation between USP22 expression in various cancer patients.

the studies by unvariate survival analysis. The pooled HR of the NOS score = 9 and < 9 is 2.70 (95% CI: 2.075-3.52, P = 0.000) and 2.11 (95% CI: 1.37-3.26, P = 0.001), respectively. The random-effects model were conducted in the variable of publication year (≥ 2014), sample size (≥ 100), cancer types (digestive system, female cancer and others), survival analysis (univariate) and NOS score (= 9, < 9) with the significant heterogeneity (I^2 > 50%). The variables with the absence of heterogeneity were calculated by the fixed-effects model. Additionally, we also performed meta-analyses of USP22 expression and clinicopathological parameters including gender, tumor stage, histological grade and lymph node metastasis for OS and DFS. The over-expression of USP22 was not found the relationship with patients' poor prognosis in gender (Female vs. Male) for OS (pooled HR = 1.15, 95% CI: 0.75-1.77, P = 0.527, fixed-effects model). Elevated USP22 predicted worse outcome in patients' stage (III/IV vs. I/II) for DFS (pooled HR = 1.74, 95% CI: 1.45-2.10, P = 0.000) but not for OS (pooled HR = 2.06, 95% CI: 0.81-5.25, P = 0.131) by random-effects model. As shown in **Table 3**, over-

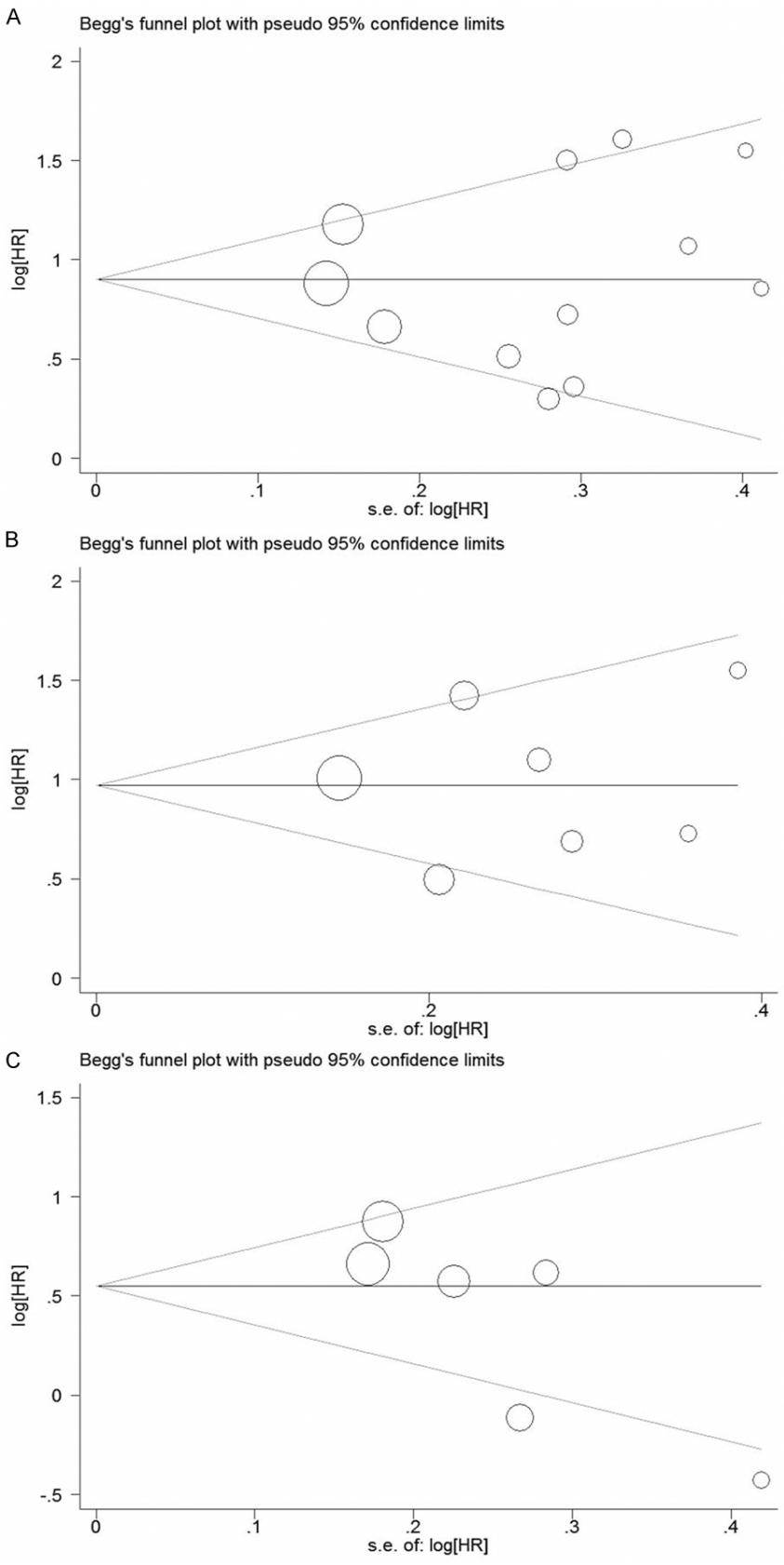

Figure 4. Begg's funnel plot showed no publication bias for OS (A), DFS (B), DSS/RFS (C) in this meta-analysis.

expression of USP22 was significantly associated with histological grade (Well vs. Poor/Moderate) for OS (pooled HR = 2.70, 95% CI: 1.94-3.77, P = 0.000) and DFS (pooled HR = 3.45, 95% CI: 2.24-5.30, P = 0.000), lymph node metastasis (Positive vs. Negative) for OS (pooled HR = 2.46, 95% CI: 1.96-3.09, P = 0.000) and DFS (pooled HR = 3.10, 95% CI: 1.87-5.13, P = 0.000).

Sensitivity analysis and publication bias

To measure the effects of each individual study on the pooled HRs for OS (**Figure 3A**), DFS (**Figure 3B**) or DSS/RFS (**Figure 3C**) by omitting one study respectively, the sensitivity analysis was performed. The results showed that pooled HRs were not influenced which suggested that no individual study significantly affected the pooled results. Publication bias was evaluated using funnel plots, Begg's tests and Egger's tests for OS (**Figure 4A**), DFS (**Figure 4B**) and DSS/RFS (**Figure 4C**). The *P* value for OS, DFS and DSS/RFS were 0.583, 0.652, 0.188 by Begg's tests and 0.859, 0.845, 0.057 by Egger's tests, respectively. No significant publication biases were observed in this meta-analysis and subgroup analysis (**Tables 2**, **3**).

Discussion

To nowadays, cancer is still most important problem of public health in the world. There were about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 all over the world [41]. A total of 1,658,370 new cancer cases and 589,430 cancer deaths are projected to occur in the United States in 2015. 1.6 million new cancer patients will be diagnosed and approximate 600 thousand cancer individuals will pass away in the United States in 2015 [42]. Although much progress in treating cancer, there is not a certain prognostic biomarker to estimate the effect of treatment.

Recently, many studies have reported that USP22 might a potential biomarker with prognostic value in cancer patients [24-40]. Cell proliferation was inhibited when knock-down of USP22 protein expression by miRNA. Tumor growth was suppressed by injecting the USP22 miRNA silencing vector in mice model. The study suggested that USP22 plays an important role in tumor formation and progression in human colorectal cancer cell line [43]. USP22 was also indentified to play a key role in the growth of human brain glioma cells by affecting cell apoptosis and the cell cycle [44]. Schrecengost et al. demonstrated that USP22 is a critical promoter of lethal tumor phenotypes by modulating nuclear receptor and oncogenic signaling [45]. Overexpression of USP22 in pancreatic cancer cells promoted tumor invasion and metastasis by epithelial-mesenchymal transition [46]. Meanwhile, USP22 promotes tumorigenesis in vitro and in vivo through upregulation of MDMX and subsequent p53 inhibition and possesses oncogenic role by regulating the stability of cyclooxygenase-2 in non-small cell lung cancer [47-48]. Knock down USP22 expression affected cellular proliferation, growth, and cell cycle in nasopharyngeal carcinoma by inhibiting AKT/GSK-3/Cyclin signaling pathway [49]. Numerous studies have assessed the correlation of high USP22 expression and poor prognosis in cancer patients so far, such as digestive system cancer [24, 25, 27, 33, 35, 38-40], NSCLC [28, 37], gynecologic cancer [26, 32, 36] and head and neck neoplasm [29-31, 34, 35]. To evaluate the prognostic role of USP22 in cancer patients, we performed this meta-analysis.

This is the first meta-analysis of the relationship between USP22 expression and prognosis in patients with various cancers. Upregulated expression of USP22 was significantly associate with poor OS (HR: 2.47, 95% CI: 1.97-3.11, P = 0.000), DFS (HR: 2.66, 95% CI: 2.02-3.50, P = 0.000) and DSS/RFS (HR: 1.56, 95% CI: 1.12-2.18, P = 0.009). In the subgroup analysis, elevated USP22 expression was significant correlation with the every stratification variables of publication year, sample size, tumor type, method of survival analysis and NOS score. There is no significant relationship between elevated USP22 and patients' gender and tumor stage for OS. However, histological grade and lymph node metastasis showed significantly correlation with poor OS. We also evaluated the relationship of clinicopathological parameters same as OS except gender with increased USP22 expression for DFS. The results suggested that poor DFS was significant correlation with tumor stage, histological grade and lymph node metastasis. Even though we calculated the pooled HRs with random-effects model, significant heterogeneity existed in between studies. The different study population characteristics such as tumor stage, sample size and cutoff value may lead the existence of heterogeneity. To evaluate the influence of heterogeneity, sensitivity analyses were carried out. The results of sensitivity analyses showed no effect in predicting poor survival outcome. Although, Begg's test, Egger's test and funnel plot illustrated no significant publication bias concerning the prognostic value of USP22 in various cancers. Publication bias might exist unavoidable in literature-based analysis because more positive results tend to be published.

There are some limitations need to be considered in this meta-analysis. First, only 17 eligible studies were included. More multicentre and large sample population studies need to be conducted to validate the prognostic value of USP22 in cancers. Second, the peoples are all from China in these studies. There is not study about Caucasian or others up to now. Third, only English literatures were included that might lead the exaggeration of the prognostic role of USP22 in various cancers. Fourth, the criteria of elevated USP22 expression using cutoff values were different in these studies. This can explain the existence of heterogeneity partially. Fifth, we did not gain all the HRs and 95% CI from the articles and some of them calculated from the survival curves. These data

were less reliable than that obtained from the original literatures directly.

In conclusion, this meta-analysis has suggested that the increased USP22 expression is significantly associated with poor survival outcome in various cancer patients. USP22 may be used as a novel potential therapeutic target and an independent prognostic biomarker for cancer. In the future, more multicenter prospective studies with standardization and high quality should be carried out to validate the prognostic value of USP22 in various cancers.

Disclosure of conflict of interest

None.

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