

Prognostic and clinicopathological significance of ubiquitin-specific protease 22 overexpression in cancers: evidence from a meta-analysis

Ning Ao¹
Liang Wang²
Yuqin Liu³

¹Department of Pathology, Beijing Tiantan Hospital, Capital Medical University, ²Department of Pathology, Chinese PLA General Hospital, ³Department of Pathology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, Tsinghua University, Beijing, People's Republic of China

Purpose: This meta-analysis study aimed to reveal the prognostic relevance of ubiquitin-specific protease 22 (USP22) expression in patients with cancers.

Methods: PubMed, Embase, and the Cochrane Library electronic databases were searched for relevant studies published up to April 2017. The prognostic value of USP22 expression was evaluated by hazard ratio with 95% confidence intervals (CIs). Relative risk (RR) with 95% CIs assessed the effects of USP22 expression on clinicopathological parameters. A total of 16 studies of 2,233 Chinese patients were included in the final meta-analysis.

Results: A significant association was found between USP22 overexpression and survival in patients with cancers. The pooled RR indicated that USP22 overexpression was related to histological grade, advanced tumor–node–metastasis stage, positive lymph node metastasis, and distant metastasis.

Conclusion: This meta-analysis demonstrated that USP22 could be a novel biomarker for predicting prognosis in patients with cancers in the Chinese population.

Keywords: ubiquitin-specific protease 22, cancer, survival, prognosis, meta-analysis

Introduction

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. It has a high mortality rate,¹ but the number of survivors has slightly increased because of improvements in treatment modalities and screening programs that identify the grade, stage, and size of the tumor in the last 10 years; however, these clinicopathological factors cannot fully predict individual outcomes.^{2,3} Therefore, to improve clinical care, it is imperative to explore effective biological prognostic markers.

Ubiquitin-specific protease 22 (USP22) is a subunit of the human SAGA transcriptional cofactor acetylation complex that functions to deubiquitinate histones H2B and H2A.⁴ USP22 was identified as one of the 11-gene “death-from-cancer” signatures that predict rapid disease recurrence, distant metastatic sites, and poor response to therapy across multiple solid tumors.^{5,6} Its expression correlates with a stem cell-like expression profile and appears to be driven by the BMI-1 oncogene. Previous studies showed that USP22 enhances cancer cell proliferation through interaction with Rb and p53.^{7–9} USP22 is recruited by the Myc oncoprotein or nuclear receptors and counteracts heterochromatin silencing, thereby transactivating specific target genes in cancer cells.^{10,11} USP22 activation markedly contributes to aberrant cell cycle control and anoikis resistance, and its aberrant expression is associated with cancer progression and poor prognosis.^{8,12,13}

Correspondence: Yuqin Liu
Department of Pathology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, Tsinghua University, #5, Dong Dan San Tiao, Dong Cheng District, Beijing 100005, People's Republic of China
Tel +86 10 6915 6473
Fax +86 10 6527 6098
Email ccc@pumc.edu.cn

Many studies have evaluated the prognostic value of USP22 overexpression in patients with cancer; some other conflicting conclusions were arrived.^{14,15} Therefore, the impact of USP22 expression on cancer prognosis remains controversial. To better understand the relationship between cancer pathogenesis and USP22 overexpression, we performed a meta-analysis to evaluate the effects of USP22 on survival and clinicopathological parameters in patients with cancer.

Methods

Search strategy

A systematic literature search of the databases PubMed, Embase, and the Cochrane Library was performed to identify relevant English language studies published up to April 2017 using the following keywords: “USP22” AND “prognosis” OR “prognostic” OR “survival” OR “outcome” AND “cancer” OR “carcinoma” OR “neoplasm” OR “tumor” OR “malignant”. We also inspected the references listed in identified studies to find additional relevant studies. Eligible reports were identified independently by two investigators (NA and LW).

Inclusion criteria

Eligible studies had to meet the following inclusion criteria: 1) evaluating USP22 expression in human cancer tissues; 2) evaluating the association between USP22 expression and cancer prognosis; and 3) providing sufficient information to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). The exclusion criteria were as follows: 1) reviews, case reports, letters, and conference abstracts and 2) overlapping data. A flow diagram of the study selection process is shown in Figure 1. Because immunohistochemistry (IHC) is the

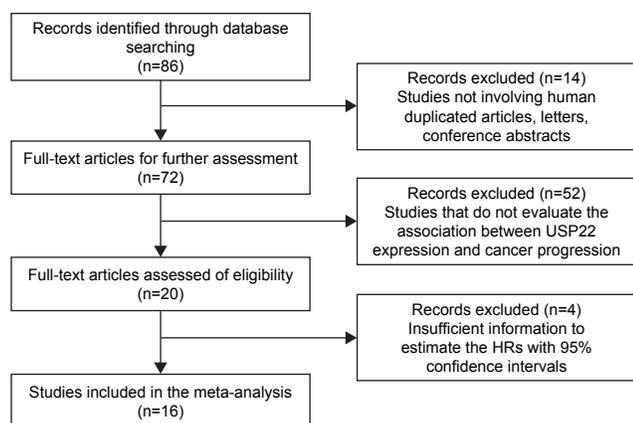


Figure 1 PRISMA flow diagram of study selection.

Abbreviations: HRs, hazard ratios; PRISMA, preferred reporting items for systematic review and meta-analysis; USP22, ubiquitin-specific protease 22.

most common method used to detect USP22 expression in tumors, and as mRNA expression levels were analyzed by reverse transcription polymerase chain reaction in cancer tissues than in paired adjacent normal tissues,^{16–23} we did not include studies reporting relationship of USP22 mRNA expression and clinicopathological parameters of patients in our current meta-analysis.

Data extraction

Data from eligible studies were extracted independently by two investigators (NA and LW). The following items were collected: first author’s name, year of publication, nationality, number of cases, cancer type, method of detection, cutoff value of USP22 positivity, HRs with corresponding 95% CIs for disease-free survival (DFS) and overall survival (OS) analyses, and clinicopathological parameters. Any disagreements were settled by a third investigator (NA).

Quality assessment

The quality of included studies was assessed by two independent investigators (NA and LW) on the basis of the Newcastle–Ottawa scale (NOS) 9-point scoring system.²⁴ Studies with an NOS score of ≥ 6 were regarded as high quality.

Statistical analysis

HRs with their 95% CIs were used to evaluate the association between USP22 expression levels and survival. If available, we obtained the data directly from the article. Alternatively, we reviewed the data from Kaplan–Meier survival curves using the Engauge Digitizer version 4.1 software. All included HRs derived from univariable models. Then, we stratified the variables by clinicopathological parameters of patients shown to contribute to poor survival, including lymph invasion, M stage, tumor–node–metastasis (TNM) stage, and histodifferentiation. The impact of USP22 expression on clinicopathological parameters was assessed by relative risks (RRs) with their 95% CIs. Heterogeneity among the included studies was checked by the chi-squared Q test.²⁵ If the studies were heterogeneous ($P < 0.10$ or $I^2 > 50\%$), the random effects model was used; otherwise, the fixed effects model was used.²⁶ A sensitivity analysis was carried out to evaluate whether any single study affected the pooled univariable HRs by sequentially discarding individual studies. Egger’s test and Begg’s funnel plots were applied to assess publication bias.²⁷ All statistical analyses were performed using the R 3.2.0 meta-analysis software. P -values < 0.05 were considered statistically significant.

Results

Study characteristics

A total of 86 studies were selected following an initial search, of which 16 eligible studies from 2011 to 2015 met the inclusion and exclusion criteria and were included in this meta-analysis. The articles from January 2016 to April 2017 do not meet the inclusion criteria that we mentioned. The main characteristics of the eligible studies are summarized in Table 1. All studies were performed exclusively in patients from China. Seven of the studies were of patients with digestive system cancers (colorectal cancer, hepatocellular cancer, esophageal cancer, gastric cancer, and pancreatic cancer),^{16,18,23,28–31} two of the studies were of patients with salivary carcinoma,^{20,22} and seven of the studies were of patients with other cancer types (oral squamous cell carcinoma, lung cancer, glioma cancer, breast cancer, epithelial ovarian cancer, and papillary thyroid carcinoma).^{17,19,21,32–35} IHC was the main method used to detect USP22 expression in these studies.

Meta-analysis results

USP22 expression and survival

As shown in Figures 2 and 3, USP22 overexpression was significantly associated with poor DFS (HR =0.86, 95% CI: 0.53–1.38) and OS (HR =0.78, 95% CI: 0.37–1.64) in cancers. Owing to the heterogeneity detected in these studies, the random effects model was applied.

USP22 expression and clinicopathological parameters

As shown in Figure 4 and Table 2, increased USP22 was significantly associated with histological grade (RR =0.72, 95% CI: 0.66–0.78, $P=0.002$), advanced TNM stage (RR =0.55, 95% CI: 0.49–0.61, $P=0.000$), positive lymph node metastasis (RR =0.69, 95% CI: 0.64–0.75, $P=0.000$), and positive distant metastasis (RR =0.66, 95% CI: 0.61–0.72, $P=0.017$) but not with gender ($P=0.748$). Owing to insufficient data, we did not detect a relationship between USP22 overexpression and other clinicopathological parameters.

Sensitivity analysis

Sensitivity analysis revealed no significant changes in HRs when any individual study was discarded (Figure 5). The investigation of the impact of USP22 overexpression on survival gave a Begg's test score of $P=0.533$ and an Egger's test score of $P=0.368$, reflecting no evidence of publication bias in the analysis.

Discussion

The *USP22* gene is located on human chromosome 17 and consists of 14 exons. Its 1,578 bp open reading frame encodes a 525 amino acid polypeptide with a molecular weight of ~66 kDa, containing a C-terminal peptidase domain of the C19 family and an N-terminal zinc finger motif that

Table 1 Main characteristics of the studies included in this meta-analysis

| First author | Year | Case number | Patient source | Cancer type | Method | Cutoff | Outcome measures | HR estimation | HR (95% CI) for survival | NOS score |
|------------------------------|------|-------------|----------------|------------------------------------|--------|----------------|------------------|---------------|--------------------------|-----------|
| Wang et al ²⁸ | 2015 | 129 | China | Colon carcinoma | IHC | Score ≥ 6 | DFS | Sur-curve | 0.71 (0.35–1.43) | 8 |
| Tang et al ¹⁶ | 2015 | 151 | China | Hepatocellular carcinoma | IHC | 20% | DFS | Sur-curve | 0.26 (0.15–0.44) | 7 |
| Hu et al ³² | 2015 | 146 | China | Lung adenocarcinoma | IHC | Score ≥ 2 | DFS | HR | 2.47 (1.45–4.22) | 7 |
| Ji et al ¹⁷ | 2015 | 86 | China | Ovarian cancer | IHC | Median | DFS | Sur-curve | 0.74 (0.41–1.35) | 8 |
| Liang et al ^{31,33} | 2014 | 109 | China | Glioma | IHC | Score ≥ 4 | OS | Sur-curve | 0.29 (0.15–0.55) | 7 |
| Ning et al ¹⁸ | 2014 | 136 | China | Pancreatic ductal adenocarcinoma | IHC | Score ≥ 3 | OS | HR | 3.23 (1.88–6.98) | 8 |
| Liang et al ^{31,33} | 2014 | 68 | China | Pancreatic cancer | IHC | Median | OS | Sur-curve | 0.61 (0.35–1.08) | 6 |
| Dai et al ²⁰ | 2014 | 135 | China | Salivary adenoid cystic carcinoma | IHC | Score ≥ 3 | DFS | HR | 3.62 (1.06–5.72) | 7 |
| Wang et al ²¹ | 2013 | 156 | China | Papillary thyroid carcinoma | IHC | Score ≥ 4 | OS | Sur-curve | 0.50 (0.28–0.89) | 7 |
| Piao et al ²² | 2013 | 44 | China | Salivary duct carcinoma | IHC | Score ≥ 2 | DFS | Sur-curve | 0.61 (0.27–1.38) | 8 |
| Li et al ²⁹ | 2012 | 157 | China | Esophageal squamous cell carcinoma | IHC | Score ≥ 3 | DFS | Sur-curve | 1.64 (1.10–2.45) | 6 |
| Piao et al ³⁵ | 2012 | 319 | China | Oral squamous cell carcinoma | IHC | Score ≥ 2 | DFS | Sur-curve | 0.61 (0.44–0.84) | 8 |
| Ning et al ¹⁹ | 2012 | 86 | China | Non-small-cell lung cancer | IHC | Score ≥ 3 | OS | HR | 2.16 (1.23–3.80) | 8 |
| Liu et al ²³ | 2011 | 192 | China | Colorectal cancer | IHC | 10% | DFS | Sur-curve | 0.54 (0.35–0.81) | 7 |
| Yang et al ³⁰ | 2011 | 219 | China | Gastric carcinoma | IHC | 20% | OS | Sur-curve | 0.38 (0.25–0.57) | 8 |
| Zhang et al ³⁴ | 2011 | 100 | China | Breast cancer | IHC | Score ≥ 3 | DFS | Sur-curve | 0.50 (0.12–2.03) | 7 |

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IHC, immunohistochemistry; NOS, Newcastle–Ottawa scale; OS, overall survival.

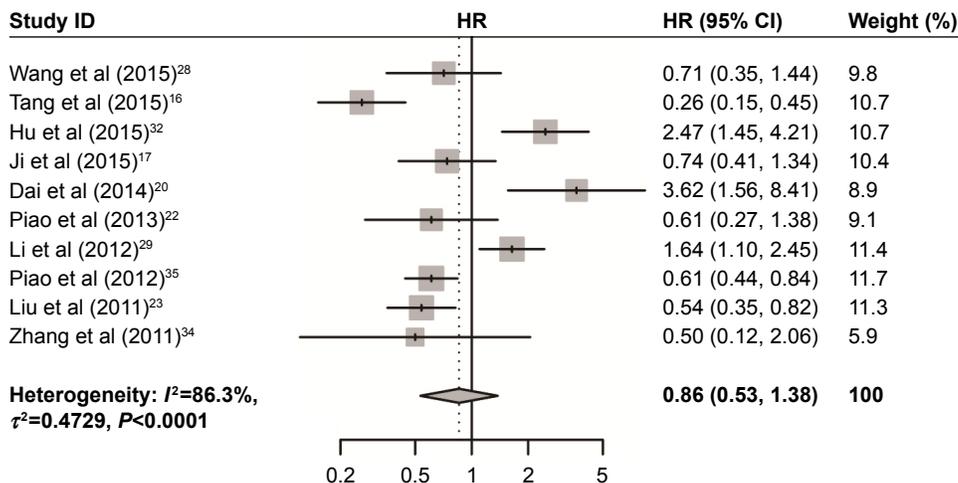


Figure 2 Forest plot of HR for the relationship between high USP22 expression and disease-free survival.

Note: Weights are from random effects analysis.

Abbreviations: CI, confidence interval; HR, hazard ratio; USP22, ubiquitin-specific peptidase 22.

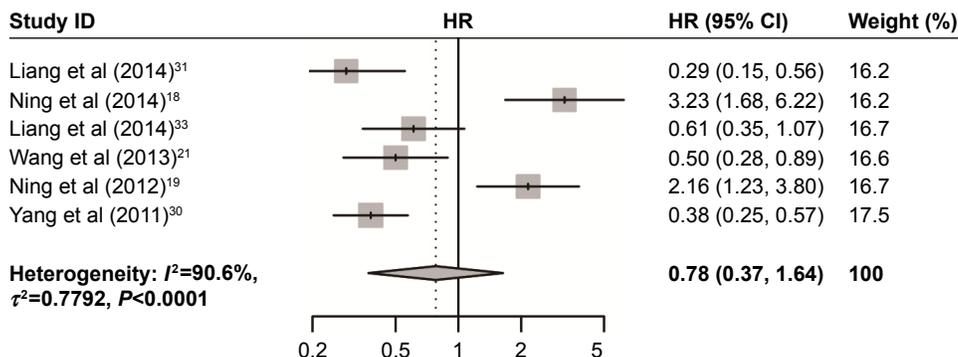


Figure 3 Forest plot of HR for the relationship between high USP22 expression and overall survival.

Note: Weights are from random effects analysis.

Abbreviations: USP22, ubiquitin-specific peptidase 22; HR, hazard ratio; CI, confidence interval.

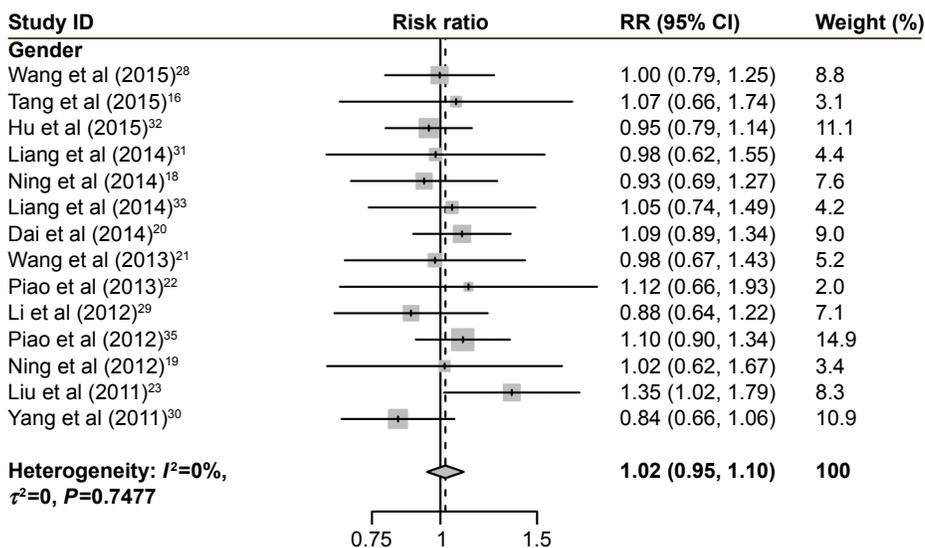


Figure 4 (Continued)

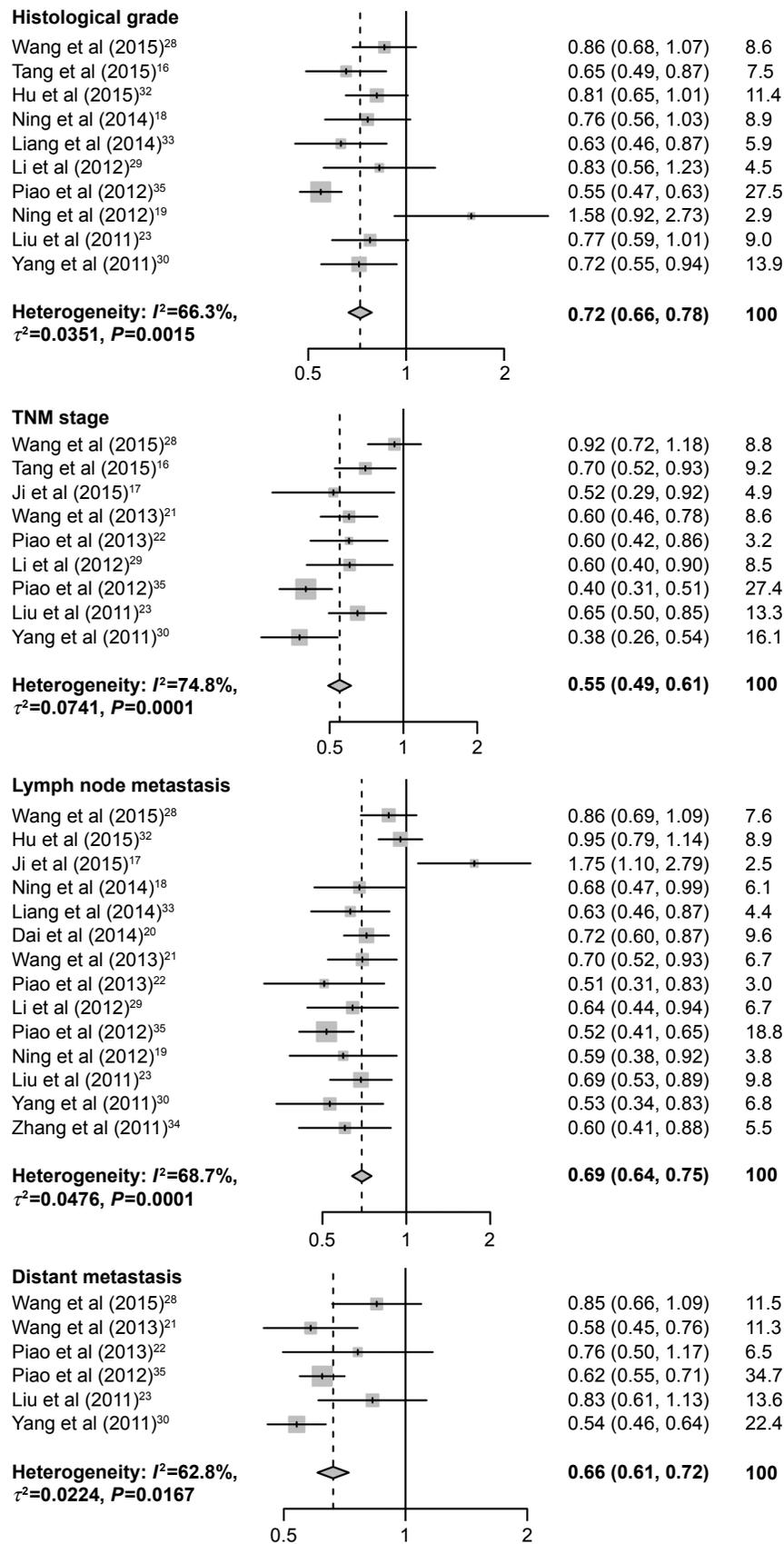


Figure 4 Forest plot of the relationship between high USP22 expression and patient clinicopathological parameters.
Abbreviations: CI, confidence interval; RR, relative risk; TNM, tumor–node–metastasis; USP22, ubiquitin-specific peptidase 22.

Table 2 Meta-analysis: RR value and 95% CI of clinicopathological parameters

| Categories | Studies (n) | Case number | RR (95% CI) | Heterogeneity | | |
|------------------------------|-------------|-------------|------------------|--------------------|---------|----------------|
| | | | | I ² (%) | P-value | Model |
| Gender | | | | | | |
| Male vs female | 14 | 2,047 | 1.02 (0.95–1.10) | 0 | 0.748 | Fixed effects |
| Histological grade | | | | | | |
| Well, moderate, vs poor | 10 | 1,603 | 0.72 (0.66–0.78) | 66.3 | 0.002 | Random effects |
| TNM stage | | | | | | |
| I and II vs III and IV | 9 | 1,453 | 0.55 (0.49–0.61) | 74.8 | 0.000 | Random effects |
| Lymph node metastasis | | | | | | |
| + vs – | 14 | 1,973 | 0.69 (0.64–0.75) | 68.7 | 0.000 | Random effects |
| Distant metastasis | | | | | | |
| + vs – | 6 | 991 | 0.66 (0.61–0.75) | 63.8 | 0.017 | Random effects |

Abbreviations: CI, confidence interval; RR, relative risk; TNM, tumor–node–metastasis.

mediates the association between the enzyme and other proteins.^{8,12} USP22 was previously shown to be weakly expressed or absent in normal tissues but highly expressed in various cancers.³⁶ Although the focus area of much USP22 research is digestive system cancers, the role of USP22 in other malignant tumors has received increasing attention in recent years. Several studies reported that USP22 could be considered as an important prognostic marker for malignant cancers.^{19,23,29,32,33,37,38} However, because only some reports correlated USP22 expression with prognosis, no pooled analysis has previously been performed. Our study conducted a pooled analysis of the prognostic value of USP22

expression relevant to 2,233 patients with cancers in China. Some independent prognostic factors are indicated via pooled analysis in general.

In the present meta-analysis, high USP22 expression was associated with worse survival in patients with cancer. Schrecengost et al³⁹ previously showed that USP22 depletion dramatically downregulated androgen receptor protein levels and abolished androgen receptor activity in both androgen deprivation therapy and castration-resistant prostate adenocarcinoma cells. Xu et al⁷ speculated that the observed increase in USP22 activity in CRC might stabilize major vault protein by rescuing it from proteolysis and thus contributing

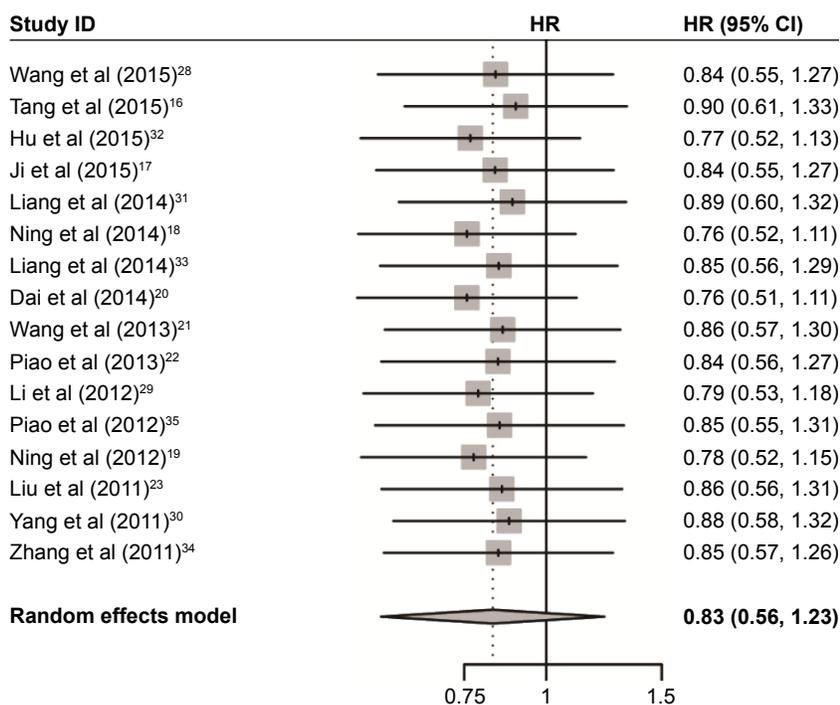


Figure 5 Sensitivity analysis of survival.

Abbreviations: CI, confidence interval; HR, hazard ratio.

to drug resistance. Therefore, the potential use of USP22 as a target for cancer therapy warrants further study.

We stratified the variables by clinicopathological parameters of patients shown to contribute to poor survival, including lymph invasion, M stage, TNM stage, and histodifferentiation. The random effects model was applied because of the significant heterogeneity observed for the association between evaluated USP22 expression and histological grade, TNM stage, and distant metastasis. Our meta-analysis has some limitations that should be acknowledged. First, most of the included studies focused on digestive system cancers and the small number of studies focusing on other cancer types might weaken our conclusions; thus, additional studies of different cancers could be included in a future meta-analysis. Second, all the included studies were of patients from China; hence, our conclusion might not be reliably extrapolated to non-Asian populations. Third, our extraction of data from Kaplan–Meier curves to derive HRs with 95% CIs might not have been reliable. Finally, although all studies detected USP22 expression by IHC, the use of different antibody concentrations and variable cutoff values might have influenced the results.

Conclusion

This meta-analysis indicated that USP22 overexpression was significantly associated with poor prognosis in cancer patients and that it could be used as a biomarker to predict clinical outcomes, especially in patients with cancers of the digestive system. Further clinical research is needed to support our conclusions and to confirm the precise prognostic value of USP22 in cancers.

Acknowledgment

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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