RESEARCH ARTICLE

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# Clinicopathological and Prognostic Significance of Ubiquitin-Specific Protease 39 Overexpression in Solid Cancers: A Meta-Analysis

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## Abstract

**Objectives:** This meta-analysis aimed to evaluate the association between USP39 expression, the prognosis of patients with solid cancer, and to identify the clinicopathological characteristics of these patients. **Material and Method:** This study was carried out using PRISMA strategy. Pubmed, ScienceDirect, Google Scholar, Ebsco, Cochrane Library electronic databases were searched for relevant studies published up to April 2022. 14 studies was included in this study. Hazard ratio (HR) and 95% confidence interval (CI) data were collected, including number of samples, detection methods, number of sample with high USP39 expression, and cut-off value. HR and 95% CI was used to evaluate the prognostic value of USP39 expression. Odds ratio (OR) with 95% CI was used to assess the effect of USP39 expression on clinicopathological parameters. **Results:** Qualitative analysis using 14 included studies and quantitative analysis using 7 included studies. We found that USP39 expression has significant risk for histological grade (OR 3.14, CI 95% 2.15-4.58, p<0.001), TNM stage (OR 2.23, CI 95% 1.66-3.00, p<0.001), tumor size (OR 2.17, CI 95% 1.56-3.03, p<0.001), lymph node metastasis (OR 2.31, CI 95% 1.23-4.33, p=0.009), vascular invasion (OR = 1.76, 95% CI = 1.13-2.73, p=0.01). Furthermore, high expression of USP39 protein was associated with worse OS (OR 1.17, CI 95% 1.13-1.21, p<0.001) and DFS (OR 1.39, CI 95% 1.23-1.57, p<0.001) in cancer patients. **Conclusion:** It can be concluded that USP39 has a significant prognostic value in patients with solid cancer and was found to have a significant relationship in the clinicopathology of solid cancer patients.

**Keywords:** Ubiquitin-specific protease 39- solid cancer- survival- prognosis- meta-analysis

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## Introduction

Cancer is a disease that is a burden on health and causes high mortality worldwide. The global cancer burden in 2040 is expected to increase to 28.4 million cases due to changing demographics and increasing risk factors along with globalization (Sung et al., 2020). The high mortality rate in cancer patients, particularly solid cancer, but the low number of survivors, prompts improvements in treatment and screening efforts to identify factors such as stage, grade, tumor size, and metastases early (Oeffinger et al., 2013; Giraldo et al., 2019; Zhang et al., 2019). However, these clinicopathological factors are not fully a tool to determine the outcome of the condition of cancer patients, including solid cancer (Zhang et al., 2019).

RNA splicing is known to have an important role in the expression of eukaryotic genes so mutations and changes in the activity of splicing elements can affect tumor development and progression (Lee et al., 2015; Pan et al., 2015; Wilkinson et al., 2020). Ubiquitin Specific Protease 39 (USP39) is a deubiquitinating enzyme without protease activity and is involved in the spliceosome assembly. USP39 does not have two amino acid residues, namely histidine and cysteine, so it does not have the activity of deubiquitinating enzymes in general (Singh and Singh, 2016; Julia et al., 2017; Yuan et al., 2020). USP39 is very important in maintaining the mitotic spindle checkpoint and functions as a control on ubiquitin ligase activity. The release of ubiquitin ligase activity is only carried out by USP39 when the entire chromosome is attached to the spindle in the anaphase process (Pan et al., 2015). However, recent studies suggest that overexpression of USP39 may be an oncogenic factor by influencing cell proliferation and apoptosis in various cancers (Cai et al., 2017). USP39 overexpression is found in several cancers, such as breast cancer, hepatocellular carcinoma,

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lung cancer, and medullary thyroid carcinoma (Zhao et al., 2016).

Previous studies have shown that USP39 has the potential to determine the prognosis of patients with solid cancer (Yuan et al., 2017). Liao et al., (2021) showed that the expression of USP39 was increased in hepatocellular carcinoma (HCC) tissue compared to non-tumor tissue and showed a poorer prognosis. This study is in line with Ni et al., (2021) who reported that significantly elevated USP39 gene expression in HCC and high USP39 expression correlated with poor prognosis. Julia et al., (2017) also stated that high USP39 expression significantly associated with poor prognosis in colon and lung cancer.

Several studies have evaluated the role of high USP39 expression on the prognosis and clinicopathological characteristics of patients with solid cancer and found varying results between studies (Zhang et al., 2019; Kisai and Koji, 2021). Different assessment methods certainly show the potential for different biases between studies. Therefore, this meta-analysis aimed to evaluate the association between USP39 expression and the prognosis of patients with solid cancer and to identify the clinicopathological characteristics of patients associated with high expression of USP39. This meta-analysis has used cohort studies, case control studies, previous clinical trials around the world's population that examined USP39 expression in solid cancer tissues and its relationship with cancer prognosis.

## Materials and Methods

This meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page, 2021). This study used previous studies' data, so no ethical approval was required. No prior registration was made for this meta-analysis .

*Identification of relevant literature*

A systematic literature search of databases, such as PubMed, Cochrane, ScienceDirect, and the Cochrane, was performed to identify relevant topics up to March 2022 using the following keywords: "USP39" OR "Ubiquitin Specific Peptidase 39" AND "Prognosis" AND "Clinicopathology". We also inspected the references in identified studies to search for similar and relevant studies. Eligible reports were identified independently by two investigators (IN and K.A.).

*Eligibility criteria*

Eligible studies had to meet the following inclusion criteria: 1) evaluating USP39 expression in solid cancer tissues; 2) evaluating the association between USP39 expression and cancer prognosis; and 3) providing sufficient information about 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.

*Quality assessment*

The methodological quality of the studies was assessed by a modified form of the Newcastle-Ottawa quality assessment scale (NOS) (Kisai and Koji, 2021; Wells, 2000). Generally, this system used three aspects of the study design to assess quality: selection of the subject groups, comparability of subject groups, and ascertainment of the outcome. The total quality score ranged between 0 and 9. Studies scoring ≥ 6 points were regarded as high-quality studies.

*Data Extraction*

The following data were extracted from selected studies, such as: name of the author, year of publication, country, the total number of samples, cancer types, detection method, high USP39 expression, cut-off value, HR Estimation with HR and CI95% for OS, and DFS/RFS/EFS, cancer staging, and prognosis to high USP39 expression. Overexpression of USP39 was defined as higher value than cut off point of USP39 expression that has been determined in each included study. Therefore, in this study, authors didn't determine any particular cut-off point anymore regarding differentiation of overexpression and normal expression of USP39.

The HR was calculated for outcome measure in these selected studies. We included the article that provided HR using multivariate analysis. In these studies, we also used 95% confidence interval (Cis) as one of the components that we used in the calculation. If the data was presented as a graphical survival plot, the HR was calculated from the data reconstructed using the Kaplan-Meier curve (Kanda, 2013).

*Statistical analysis*

The individual HR estimates were combined into an overall HR using the inverse variance method. Heterogeneity among the studies was assessed using Cochran's Q and the I2 statistic. If heterogeneity was found ($P < 0.1$ or $I2 > 50\%$), the random effects model using on the DerSimonian–Laird method will be performed for analysis. While the fixed effects model was applied. Sensitivity analysis was used to identify studies that may generate heterogeneity. Then, the data from each study was extracted and the changes in the pooled HR estimate and its heterogeneity were examined. To explore the sources of heterogeneity, we performed subgroup analysis based on the cancer type and NOS score. The random effects model was applied when at least one subgroup exhibited heterogeneity among the studies. Publication bias was examined through a funnel plot (Kisai and Koji, 2021).

The association between USP39 expression and clinicopathological features was determined using an Odds Ratio (OR). The estimated OR was performed using the Mantel-Haenszel method. The cancer staging was determined in accordance with tumor-node-metastasis (TNM) staging and the International Federation of Gynaecology and Obstetrics (FIGO) stage.

The two-sided statistical analysis with a p-value $<0.05$ was considered significant except for the heterogeneity test in this study. The meta-analysis was performed using Review Manager 5.4.

## Results

*Literature search*

In the literature study search process, 3428 studies were found from online databases (PubMed, ScienceDirect, and Cochrane Library) and 3 studies originated from data sources previously identified by the authors. In the title and abstract screening process, 1,699 studies were obtained that could be assessed for eligibility (eligibility). Furthermore, 1,675 studies were excluded cause by unmatched with the inclusion and exclusion criteria, resulting in qualitative analysis using 14 included studies (systematic study) and quantitative analysis (meta-analysis) using 7 included studies. The entire literature search process follows the PRISMA Guideline 2022 and is summarized through a flowchart as follows (Figure 1) (Page et al., 2021).

*Data Characteristics*

Data characteristics of all studies that meet the inclusion and exclusion criteria are compiled in Table 1. All of the reviewed studies were written in English. Most of the included studies were carried out in China. The total participants were 2,591 cancer patients. The types of cancer found in patients are predominantly lung cancer and hepatocellular carcinoma, with the most detection method used, was immunohistochemistry (IHC). Hazard ratio (HR) estimation values were mostly assessed using Kaplan Meyer (K-M). Moreover, all studies have reported that high USP39 expression is associated with a poor prognosis.

*Outcomes of Studies*

The primary outcomes of all studies included in this systematic review are summarized in Table 2. The outcomes are clinicopathological characteristics of the cancer patients, overall survival (OS), and disease-free survival (DFS)/recurrence-free survival (RFS)/event-free survival (EFS).

*Quality of Studies*

The quality of study and the bias assessment of the included studies using modified NOS for the cross sectional study show that all included studies have high quality (1, 11, 2 studies with very good, good, and satisfactory quality, respectively).

*Quantitative Analysis*

A total of 7 studies were included in the quantitative analysis with a total of 2591 patients. The prognosis of USP39 expression in cancer patients (OS and DFS/RFS/EFS) was assessed using the Hazard Ratio (HR) approach by inverse variance model including 851 patients with high expression of USP39. Our analysis showed a significant

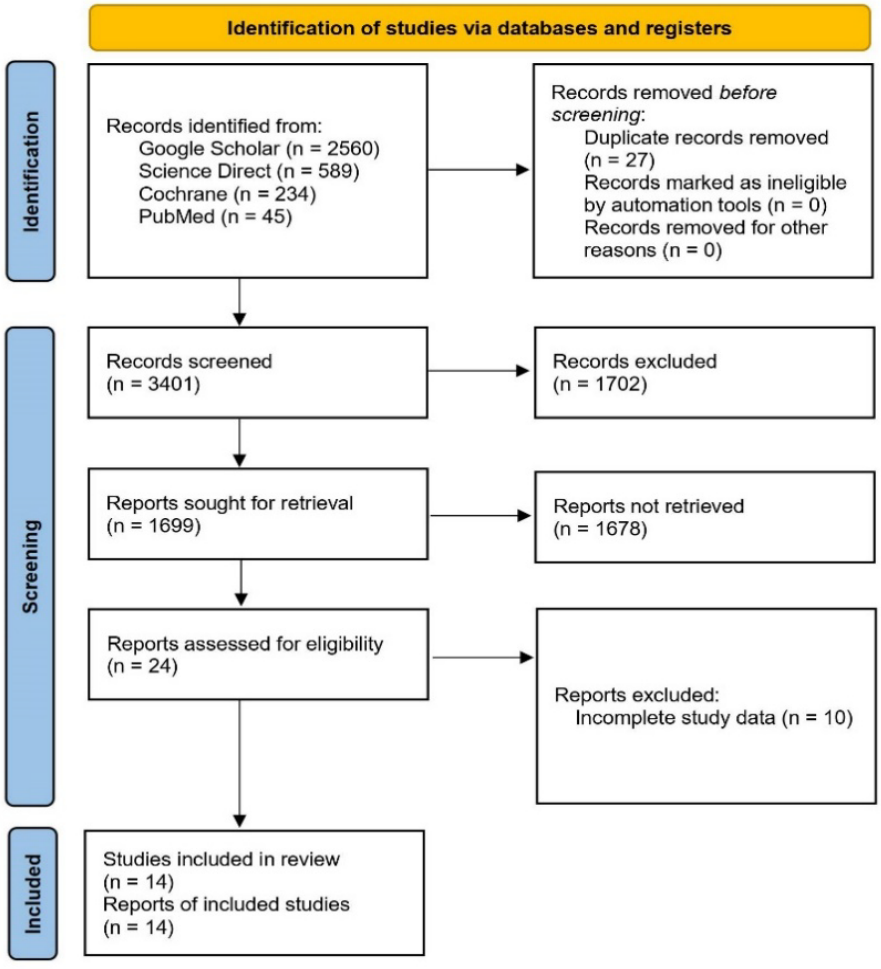



Figure 1. PRISMA Flowchart

Table 1. Data Characteristics

| Author, year | Country | Total population | Cancer type | Detection method | High USP expression (n/N(%)) | Cut-Off Value | Study Quality |
|---|---|---|---|---|---|---|---|
| Cai et al., 2017 | China | 90 | Pancreatic carcinoma | qRT-PCR, WB | 67/90 (74.4) | NA | Good |
| Dong et al., 2021 | China | 40 | Hepatocellular Carcinoma | IHC | 24/40 (60.0) | Mean* | Good |
| Huang et al., 2016 | China | 79 | Prostate carcinoma | qRT-PCR, IHC, WB | 40/79 (50.6) | Score ≥7 | Good |
| Julia et al., 2017 | Spain | 360 | Lung cancer | qRT-PCR, WB. | NA | NA | Good |
| Li et al., 2021 | China | 364 | Hepatocellular Carcinoma | qRT-PCR, WB IHC | 99/364 (27.2) | Score ≥6 | Good |
| Liao et al., 2021 | China | 374 | Hepatocellular Carcinoma | IHC | 187/371 (50.4) | Median* | Good |
| Ni et al., 2021 | China | 374 | Hepatocellular Carcinoma | IHC, WB. | N.A | Score > 4 | Good |
| Pan et al., 2021 | China | 176 | Renal cell carninoma | qRT-PCR, WB | 88/176 (50.0) | N.A | Good |
| Wang et al., 2021 | China | 149 | Ovarian Cancer | IHC, PCR | 53/149 (35,6) | Score ≥7 | Good |
| Wu et al., 2019 | China | 175 | Lung Cancer | IHC | 61/175 (34,9) | NA | Good |
| Yuan et al., 2017 | China | 90 | Colorectal Cancer | qRT-PCR, WB IHC | 89/90 (98.9) | Score ≥2 | Very good |
| Yuan et al., 2020 | China | 80 | Lung Cancer | IHC | NA | Score ≥2 | Good |
| Zhao et al., 2016 | China | 120 | Melanoma | IHC, PCR | 61/120 (50,8) | NA | Satisfactory |
| Zhao et al., 2021 | China | 120 | Esophageal squamous cell carcinoma | qRT-PCR, WB. | 82/120 (68.3) | Score ≥5 | Satisfactory |

*Note: IHC, immunohistochemistry; WB, western blot; PCR, qt-PCR; N/A, not assessed

difference in prognostic values between high and low expression of USP39 based on the overall effect on both groups with CKD, which indicates that those values were affected by the prebiotic intervention. The pooled HR for OS and DFS/RFS/EFS was 1.17 (95% CI 1.13 – 1.21; p<0.001) and 1.39 (95% CI 1.23 – 1.57; p<0.001), which is described in Figure 2.

We also assessed the correlation of clinicopathological characteristics and high expression of USP39 using odds ratio (OR) with fixed model analysis that described in Table 3.

*Gender*

The results of the analysis showed that gender was not significantly associated with high USP39 expression. Females are at 1.02 times higher risk for having high USP39 expression compared to males (OR 1.02; CI 95% 0.78 – 1.35; p=0.86) (Figure 3).

*Histological grade*

The results of the analysis showed that histological grade was not significantly associated with high USP39 expression. Patient with poor histological grade are at 3.14 times higher risk for having high USP39 expression compared to patient with moderate-well histological grade (OR 3.14; CI 95% 2.15 – 4.58; p<0.001) (Figure 3).

*TNM stage*

The results of the analysis showed that TNM stage was not significantly associated with high USP39 expression. Patient with TNM stage III-IV are at 2.23 times higher risk for having high USP39 expression compared to patient

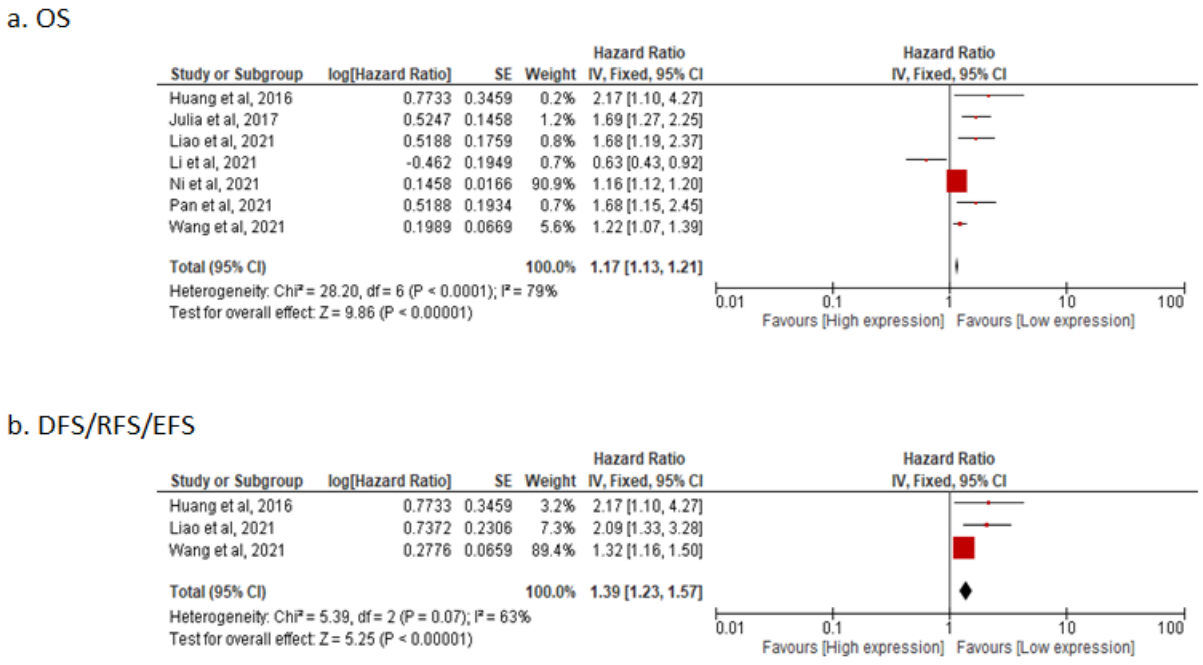



Figure 2. Forest Plot of Hazard Ratio for the Prognostic Value of High USP39 Expression (A, OS; B, DFS/RFS/EFS)

Table 2. Outcomes of the Studies

| Author, year | Outcomes | | | | | | Cancer Stage | Prognosis to high USP39 |
|---|---|---|---|---|---|---|---|---|
| | OS | | | DFS/RFS/EFS | | | | |
| | HR Estimation | HR | CI 95% | HR Estimation | HR | CI 95% | | |
| Yuan et al, 2017 | K-M | N/A | N/A | K-M | N/A | N/A | I-IV | Poor |
| Zhao et al, 2021 | N/A | N/A | N/A | K-M | N/A | N/A | I-IV | Poor |
| Dong et al, 2021 | K-M | N/A | N/A | K-M | N/A | N/A | I-IV | Poor |
| Li et al, 2021 | K-M | 0.63 | 0.43-0.92 | N/A | N/A | N/A | I-IV | Poor |
| Wu et al, 2019 | N/A | N/A | N/A | N/A | N/A | N/A | Cell line | Poor |
| Yuan et al, 2020 | N/A | N/A | N/A | N/A | N/A | N/A | Cell line | Poor |
| Zhao et al, 2016 | N/A | N/A | N/A | N/A | N/A | N/A | Cell line | Poor |
| Julia et al , 2017 | K-M | 1.69 | 1.27-2.25 | N/A | N/A | N/A | N/A | Poor |
| Liao et al , 2021 | K-M | 1.68 | 1.19-2.38 | K-M | 2.09 | 1.33-3.30 | I-IV | Poor |
| Wang et al, 2021 | K-M | 1,22 | 1,07-1,39 | K-M | 1,32 | 1.16-1.50 | N/A | Poor |
| Ni et al , 2021 | K-M | 1.16 | 1.11-1.21 | N/A | N/A | N/A | I-IV | Poor |
| Cai et al, 2017 | K-M | N/A | N/A | K-M | N/A | N/A | I-IV | Poor |
| Huang et al, 2016 | directly (univariate) | 2.17 | 1.10-4.27 | K-M | 2.167 | 1.10-4.27 | I-IV | Poor |
| Pan et al , 2021 | directly (univariate) | 1.68 | 1.15-2.46 | N/A | N/A | N/A | I-IV | Poor |

with TNM stage I-II (OR 2.23; CI 95% 1.66 – 3.00; p=0.86) (Figure 3).

*T/Tumor size/depth of invasion*

The results of the analysis showed that T/Tumor size/depth of invasion was significantly associated with high USP39 expression. Patient with T/Tumor size/depth of invasion (III-IV) are at 2.17 times higher risk for having high USP39 expression compared to patient with T/Tumor size/depth of invasion (I-II) (OR 2.17; CI 95% 1.56 – 3.03; p<0.001) (Figure 3).

*N-stage*

The results of the analysis showed that N stage was not significantly associated with high USP39 expression. Patient with N stage III-IV are at 4.21 times higher risk for having high USP39 expression compared to patient with N stage I-II (OR 4.21; CI 95% 0.71 – 25.04; p=0.11) (Figure 3).

*Lymph node metastasis*

The results of the analysis showed that lymph node metastasis was significantly associated with high USP39 expression. Patient with lymph node metastasis are at 2.31 times higher risk for having high USP39 expression compared to patient without lymph node metastasis (OR 2.31; CI 95% 1.23 – 4.33; p=0.009) (Figure 3).

*Vascular invasion*

The results of the analysis showed that vascular invasion was significantly associated with high USP39 expression. Patient with vascular invasion are at 1.76 times higher risk for having high USP39 expression compared to patient without vascular invasion (OR 1.76; CI 95% 1.13 – 2.73; p=0.01) (Figure 3).

*Heterogeneity and Publication Bias*

Q-Test was used to evaluate evidence of heterogeneity. Our analysis showed that the correlation between high USP39 expression and the prognostic value of the patient was found to have heterogeneity (OS, p<0.001; DFS/RFS/EFS, p=0.07), which was also supported by the $I^2$ test value <50% (OS, 79%; DFS/RFS/EFS, 63%). We also found that pooled studies for OR between high USP39 expression and histological grade (Q test, p<0.001; $I^2$ test, 66%), TNM stage (Q test, p<0.01; $I^2$ test, 60%) were found to have heterogeneity. Publication bias was also assessed by assessing the symmetry of the funnel plot described in Figure 4.

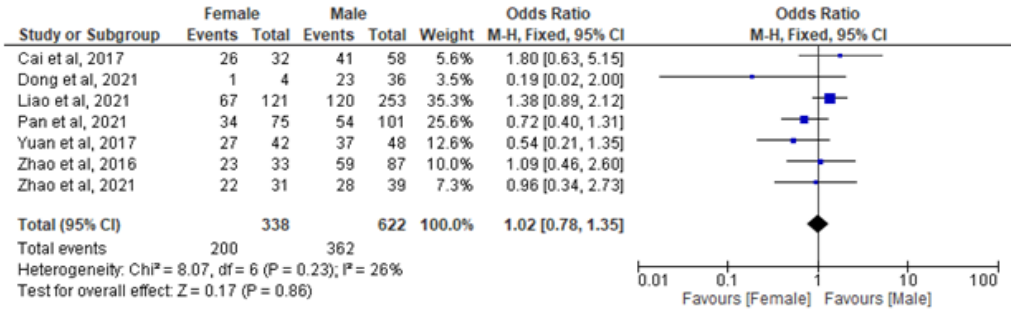
## Discussion

For the last few years, several studies regarding the role of USP39 as a prognosis predictor in several cancers have been conducted, but variable results have been reported. USP39 is a deubiquitinating enzyme essential for pre-mRNA splicing but does not have protease activity (Yuan et al., 2017). USP39 is a member of the deubiquitylation family. Based on various studies, increased expression of USP39 is associated with carcinogenesis through upregulation of proliferative activity and cell migration in various types of cancer by various pathways, such as through the epithelial-to-mesenchymal transition (EMT) process (Li et al., 2021).

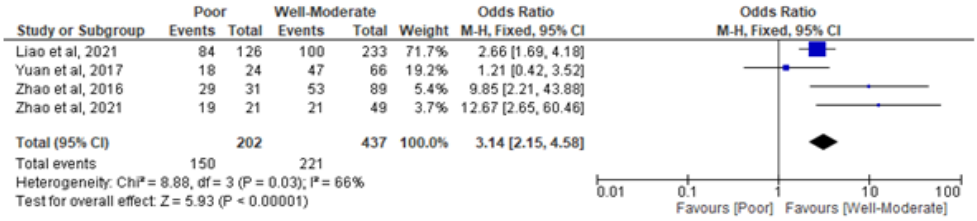
Basen on modified form-Newcastle-Ottawa quality assessment scale, we assessed each article by each point of the assessment scale. As shown on Table 1, most of the articles were categorized as good quality and eligible to be included in this study with low risk of bias as well. These included studies were the result of of PRISMA flowchart searching strategy. Excluded articles were eliminated from the searching process due to duplicated title of the article, not using English, or due to incomplete study data.

In our meta-analysis, we included seven studies discussing the prognosis of USP39 in overall survival and 3 studies on disease-free survival and the odds ratio

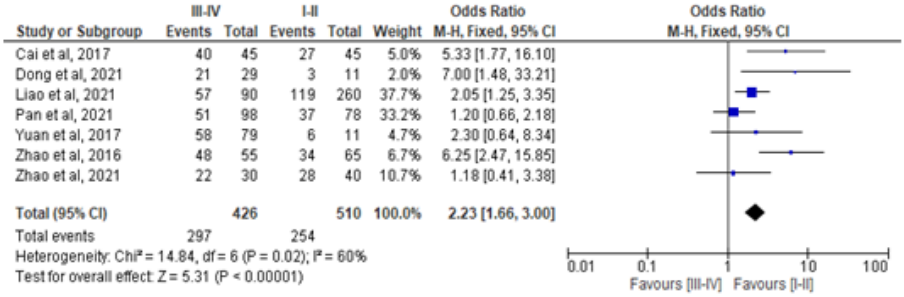
a. Gender



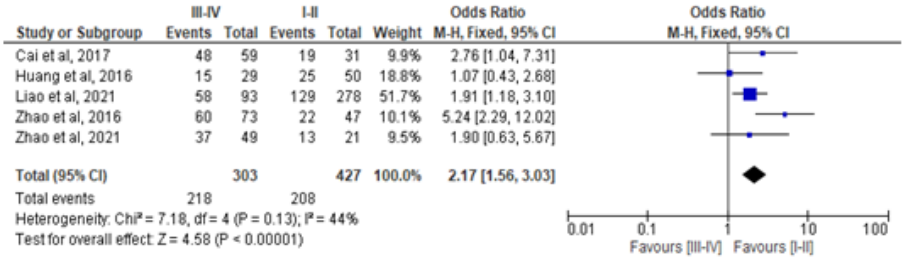

b. Histological Grade




c. TNM Stage




d. T/Tumor Size/Depth of Invasion




e. N Stage

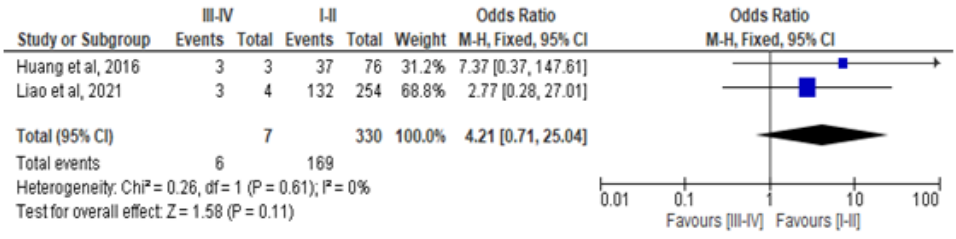



Figure 3. Forest Plot of Odd ratios for Correlation between High USP39 Expression and Clinicopathological Characteristics

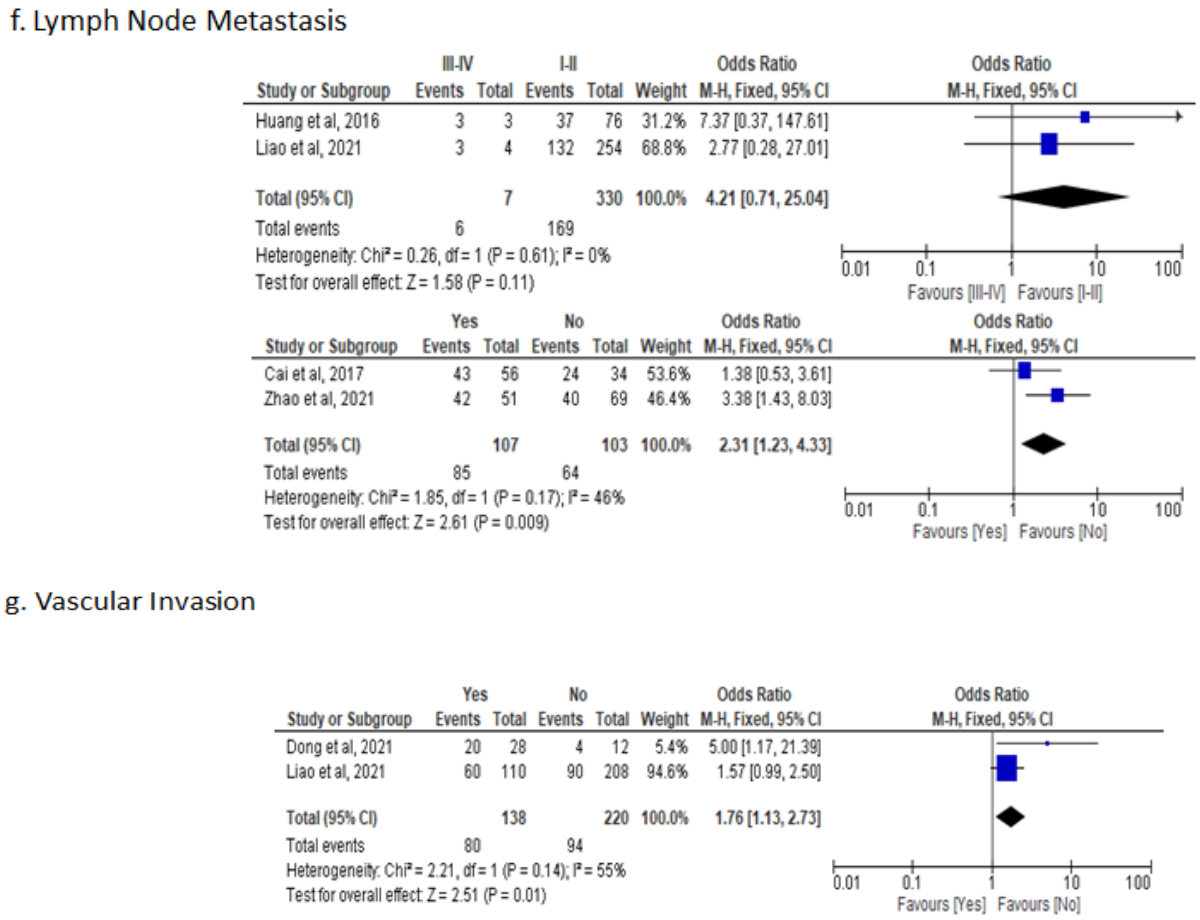



Figure 3. Continued, Forest Plot of Odd ratios for Correlation between High USP39 Expression and Clinicopathological Characteristics

value on USP39 expression for sex, histological grade, TNM stage, T-tumor, size or depth of invasion, lymph node metastasis, and vascular invasion based on forest plot analysis it was found that variables other than gender and N stage had significant analysis results ($p<0.05$). Our analysis found that high expression of USP39 protein was

Table 3. Modified New Ottawa Castle Scale for Cross Sectional Studies

| Author, years | Selection | | | | Comparability | Outcomes | | Overall score | Quality of study |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the sample | Sample size | Non-respondents | Ascertainment of the exposure (risk factor) | Comparability of subjects in different outcome groups | Assessment of outcome | Statistical test | | |
| Cai et al., 2017 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 | Good |
| Dong et al., 2021 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 | Good |
| Huang et al.,2016 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 | Good |
| Julia et al., 2017 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 | Good |
| Li et al., 2021 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 | Good |
| Liao et al., 2021 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 7 | Good |
| Ni et al., 2021 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 | Good |
| Pan et al., 2021 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 | Good |
| Wang et al., 2021 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 8 | Good |
| Wu et al., 2019 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 8 | Good |
| Yuan et al., 2017 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 9 | Very good |
| Yuan et al., 2020 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 | Good |
| Zhao et al., 2016 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 6 | Satisfactory |
| Zhao et al., 2021 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6 | Satisfactory |

Note: Very Good Studies: 9-10 points; Good Studies: 7-8 points; Satisfactory Studies: 5-6 points; Unsatisfactory Studies: 0 to 4 points; This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to provide quality assessment of cross sectional studies

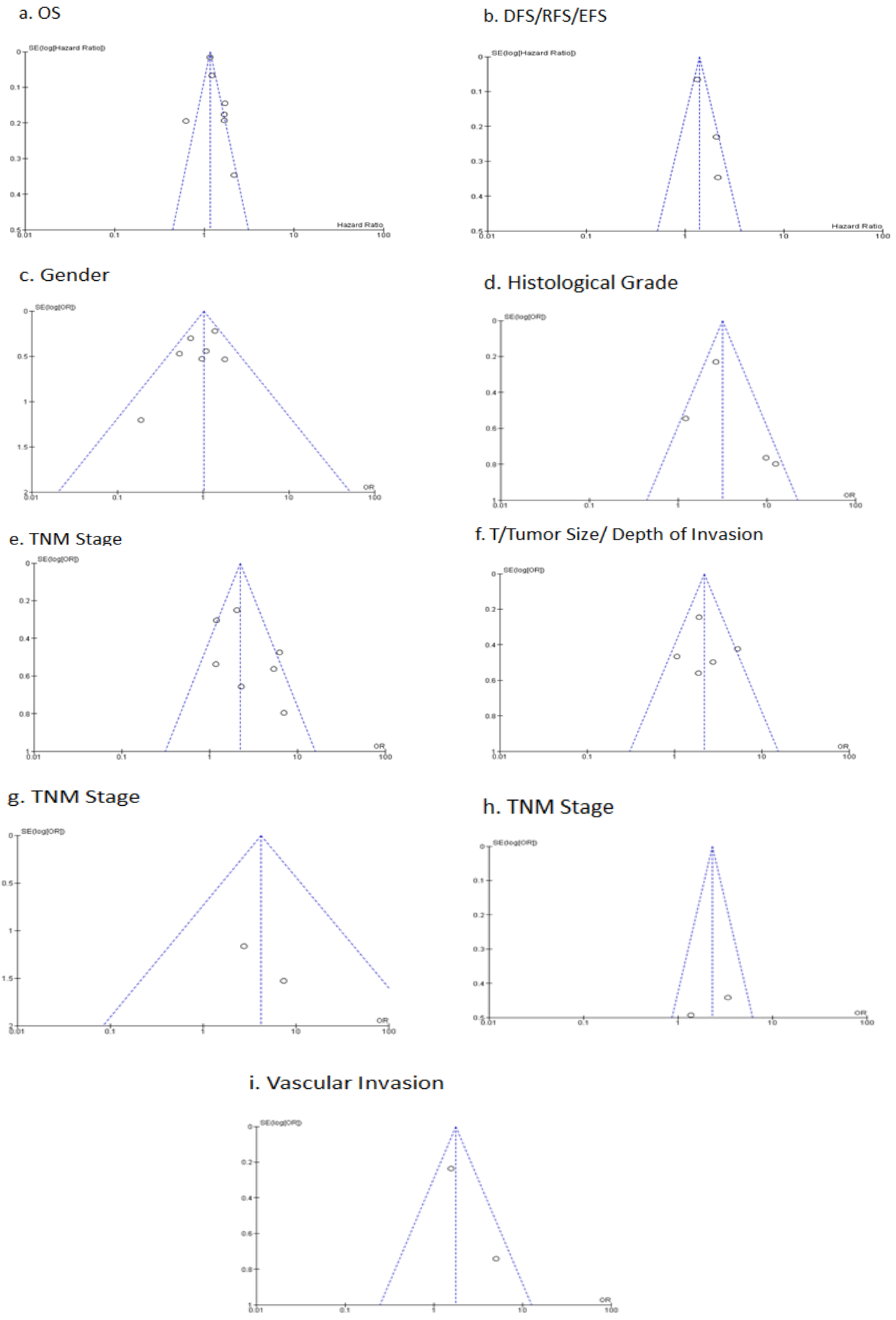



Figure 4. Funnel Plot for Publication Bias Analysis of the Correlation between High USP39 Expression and Prognostic Value (A-B); and clinicopathological characteristic (C-I)

associated with 1.17-fold worse OS in cancer patients compared to the group with low USP39 expression. Corresponding results were also found in the analysis of DFS, where we found that the high-expression USP39 had a 1.39-fold worse DFS in cancer patients than the low USP39-expression group. Based on our literature searching, this is the first meta-analysis that demonstrated to assess the prognostic significance of USP39 in solid cancer.

When viewed from the relationship of high expression of USP39 to clinicopathology, significant results were found, such as the histological grade found that patients with high expression of USP39 had a 3.14-fold poor histological grade, 2.23-fold worse TNM stage, 2.17-fold worse tumor size, 2.31-fold lymph node metastasis, and 1.76-fold vascular invasion odd ratio when compared with the total number of cases. Based on our literature review, this is the first meta-analysis study conducted to determine the relationship between the high expression of USP39 and solid tumor clinicopathology.

Based on various studies, it was found that USP39 plays a role in various pathways involved in carcinogenesis and tumor development, such as proliferation, angiogenesis, and tumor cell invasion. When viewed from the role of USP39 in the aspect of proliferation, one of the pathways known to be associated with increased expression of USP39 is Wnt/β-catenin. This pathway starts when β -catenin, the oncoprotein, binds to members of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family genes as its nuclear factor (Cheng et al., 2019). β-catenin also activates the transcription of peroxisome-proliferator-activated receptor delta (PPARd), c-myc, and cyclin D1, all of which partake in the proliferation of cells. β-catenin is an integral part of the pathophysiology of colorectal cancer as it takes part in the most prominent pathway of colorectal cancer pathogenesis. It also takes part in the Wnt pathway, which has also been shown to worsen cancer conditions by inversely correlating to CD8+ T cell activities, increasing the activity of the XPNPEP3 gene that promotes the tumorigenic attribute of colorectal cancer cells and has been shown to worsen the prognosis of colorectal cancer in patients (Cheng et al., 2019; Yuan et al., 2021).

Based on a study conducted by Xing et al., (2018) on colorectal cancer cell lines SW1116 and HCT116, it was found that knockdown of USP39 could inhibit cell viability and colony formation of cell lines significantly in the group of cells treated with USP39 knockdown compared to the negative control group (<0.001). In addition, this study found that USP39 knockdown could inhibit cell cycle progression through an increase in the proportion of cells in the G2/M phase and a decrease in the proportion of cells in the G0/G and S phases. This finding was also associated with an increase in the number of cells undergoing apoptosis in the sub-G1 phase, with findings in the form of increased expression of apoptotic cell markers, such as PARP, p53, and caspase-3 in the group of cells subjected to USP39 knockdown (Xing et al., 2018). USP39 knockdown on cell lines A549 and HCC827 indicated that cell apoptosis is a cell death process that is highly dependent on the role of caspase function (caspase-dependent), where a decrease in the number and function of caspases here will result in the failure of cells to perform apoptosis when failure or abnormality occurs. Apoptosis is one of the physiological abilities of cells that requires several signaling cascades that are carried out to get rid of damaged or dysfunctional cells so that they will not cause further damage (Fraile et al., 2017). Apoptosis can be triggered by various physiological and pathological stimuli, such as viral infections, the influence of cytotoxic drugs, growth factor deficits, DNA damage, and others. In normal cells, apoptosis can occur properly so that damaged cells are immediately eliminated and replaced with new cells. However, in pathological conditions, such as cancer, apoptosis becomes an outcome that can be avoided from existing defects (Lin et al., 2016; Luke et al., 2019). This can occur due to regulation or processes that should not exist in normal cells that cause these cells to avoid death. For example, in normal cells apoptosis can occur in the absence of adequate growth factors or under conditions of an unfavorable cellular environment. However, under pathological conditions, cells will be able to avoid apoptosis by producing their own growth factors or by engineering factors that can cause apoptosis to occur such as downregulation of BAX protein and upregulation of Bcl-2 protein (Salvesen and Dixit, 1997; Zhang et al., 2022).

The findings in the study conducted by Xing et al., 2018 are in line with the research conducted by Yaun et al., 2020. Based on research conducted by Yuan et al., 2020 it was found that knocking down USP39 will cause the accumulation of p53, thereby increasing p53-responsive transcriptional reporter activity and an increase the mRNA and protein level of the p53 target gene p21, so it can be concluded that the expression USP39 has an important role in the regulation of DNA repair. In addition, this study also found that knocking down USP39 affects the downregulation of CDC2, cyclinB1, MMP2, and MMP9, which play a role in tumor progression and metastasis (Yuan et al., 2020). In addition, this study found that there were morphological changes in cells where USP39 knockdown cells showed changes in the form of smaller, rounder and wrinkled cell sizes than in the negative control group, which was a sign of cell apoptosis. This finding supports previous findings that USP39 has a role in the regulation of DNA repair based on the AipuFu database (http://www.aipufu.com/index.html). It is known that USP39 has a negative correlation with TP53 through the p53 pre-mRNA splicing reaction process facilitated by USP39 and several other proteins involved in the splicing process, so that increased expression of USP39 in pathological conditions, such as cancer, will cause a decrease in the expression of p53 which further reduces the antioncogenic function of the cells (Yuan et al., 2020; Zhao et al., 2016). In addition, based on research conducted by Wu et al., (2018) found that USP39 is associated with the function of the response to DNA damage and chemotherapy resistance through the process of deubiquitinating and stabilizing checkpoint kinase 2 (CHK2), a serine/threonine kinase, whose activity is influenced by post-translational modification (Wu et al., 2019). In healthy cells, certain conditions that can cause

DNA damage will cause CHK2 to be activated through ATM-mediated phosphorylation of Thr68, which in turn causes phosphorylation of multiple downstream targets to cause various cellular responses, such as cell cycle arrest, apoptosis and DNA repairs (Huang et al., 2016; McGowan, 2002; Wu et al., 2019). One of the downstream of CHK2 is p53 which then becomes a pathway that is related to each other related to the role of USP39 in regulating various signaling pathways related to cancer development (Perona et al., 2008; Smith et al., 2010).

The results of this meta-analysis study have various weaknesses, so further assessment is needed regarding the role of USP39 in solid cancer. First, this study is the first one that discusses the prognostic value and the relationship to the clinicopathology of USP39 with a limited number of studies. Second, almost all of the studies used in this research are conducted in China, so their generalization should be performed carefully.

In conclusion, based on the meta-analysis studies conducted, it can be concluded that USP39 has a significant prognostic value in patients with solid cancer and was found to have a significant relationship with the clinicopathology of solid cancer patients. However, considering that this study is the first to discuss the prognostic value of USP39 with a relatively small number of included studies, it is necessary to validate it through further studies with a more comprehensive design to produce more representative conclusions.

## Author Contribution Statement

NPSIR, IGWWW, and IGASS for study conception and design; IGKAS, IGPS, and DMW searched the database, screened titles, abstracts, and full text studies included. NPSIR, IGKAS, IGPS, performed study quality assessments, data analyses, and data interpretations. IGWWW, DMW, and IGASS drafted the manuscript for publication. The final version of the manuscript was approved by all authors after they made significant edits to it.

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*Ethical Declaration*

No ethical approval was required for this study because it was a meta-analysis of studies and grey literatures found in medical databases.

*Data Availability*

The corresponding author will provide the datasets used and/or analyzed during the current work upon reasonable request.

*Study Registration*

No prior registration was made for this meta-analysis.

*Conflict of Interest*

All authors declare there was no any conflict of interest regarding this study.

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