Systematic Review and Meta-Analysis

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CDC20 overexpression leads to poor prognosis in solid tumors

A system review and meta-analysis

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Abstract

Background: A plenty of previous researches have reported the prognostic value of CDC20 (Cell Division Cycle Protein 20) in solid tumors. Nevertheless, these researches were restricted by the small sample databases and the results were not strongly consistent among them.

Methods: We comprehensively searched these relevant studies by PubMed, Web of Science, and EMBASE, in which publications before March 2017 were included. Pooled HR values for OS were cumulatively pooled and quantitatively analyzed in the meta-analysis.

Results: Hence we composed a meta-analysis based on 8 studies with 1856 patients in order to assess the potential relationship between CDC20 overexpression and OS (overall survival) in human solid tumors. There were a total of 8 studies (n = 1856) assessed in the meta-analysis. What suggested in both univariate and multivariate analysis for survival is that high level of CDC20 expression apparently pointed to poor prognosis. In the univariate analysis, the combined hazard ratio (HR) for OS was 1.75 (95% confidence interval [CI]: 1.07–2.86, $P = .03$). The pooled HR of multivariate analysis for OS was 2.48 (95% confidence interval [CI]: 2.10–2.94, $P < .001$).

Conclusions: The meta-analysis indicated that high level of CDC20 expression is significantly correlated with decreased survival in most case of human solid tumors. In addition, CDC20 shows promise as a meaningful prognostic biomarker and original therapeutic target, on the basis of its expression level in solid tumors.

Abbreviations: APC = anaphase-promoting complex, CDC20 = Cell Division Cycle Protein 20, CI = confidence interval, HR = combined hazard ratio, IHC = immunohistochemistry, IV = inverse variance, M = multivariate analysis, No = number, NOS = Newcastle-Ottawa, NR = not reported, OS = overall survival, SAC = assembly checkpoint, SE = standard error, TMA = transcription-mediated amplification, U = univariate analysis.

Keywords: CDC20, meta-analysis, solid tumor

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1. Introduction

Cancer, existing for decades, is a leading cause of death in the world.[1] And there were a large number of valuable epidemiological data have showed that numerous new cancer cases and cancer deaths occurred in recent years.[2] Although we have payed much efforts to perform better in the diagnostic capabilities and therapeutic methods of cancer, patients all over the world still suffer from pain for the poor prognosis, especially in advanced stages.[3] There were also some limitations in the biomarkers for early diagnosis and curative effect in solid tumor patients. Therefore, it is quite necessary to improve the standard of diagnosis, therapy and prognosis in solid tumors, especially in the detection of biomarkers and the research of molecular mechanisms.

Up to now, researches on special Cell Division Cycle Protein 20 (CDC20) in tumorigenesis and tumor progression is still attached much attention. The CDC20, as a regulatory protein, is a target molecule in the cell-cycle checkpoint.[4] CDC20 is an important spindle assembly checkpoint (SAC) protein and a key component of the mammalian cell cycle mechanism that activates the anaphase-promoting complex (APC).[4,5] It consists of 499 amino acids with C-terminal WD40 domain for protein binding, serving as the substrate recognizing subunit of APC.[6–8] Its expression is

essential for cell division, and its protein activity may be controlled by a balance between ubiquitination and deubiquitination. APC activation is required for anaphase initiation and mitosis exit. An abnormal level or dysfunction of CDC20 may therefore abolish mitotic arrest and thus promote premature anaphase by deregulating APC activation, resulting in aneuploidy in the daughter cells.[9] In addition to regulating cell cycle, recent evidence has demonstrated that CDC20 also plays an important role in carcinogenesis and cancer progression and CDC20 might become a promising therapeutic target.[10] Some microarray studies have already reported overexpression of CDC20 in various tumors. However, the results of these articles were inconclusive and there were no consensus among them. So it is imperative to make it certain whether CDC20 overexpression is a prognostic marker for unfavorable pathologic features and poor outcomes in human solid tumors. Thus, we performed a meta-analysis to evaluate the prognostic role of CDC20 expression in patients with human solid tumors.

2. Methods

2.1. Literature search strategy

PubMed, EMBASE, and Web of Science, as an electronic database search, were conducted to assess CDC20 expression and clinical results in solid tumors update to March 2017. The search terms included "cell division cycle protein 20" or "CDC20" and "tumor" or "cancer" or "prognosis" or "survival." Only human studies of solid tumors were taken into account to be accepted. So entries amount to 855 were identified. We set an inclusion criteria including measuring CDC20 by IHC, publishing in English and survival data for at least 5 years. The relevant studies showed in the list of reference were scanned and there were further analysis on other articles of possible interest. The Cohen's kappa coefficient is used to reach an Inter-reviewer agreement. We would go all the way to reach a consensus if there was any disagreement between assessors.

2.2. Study selection

A study to be qualified for inclusion in this meta-analysis must meet the following criteria: measure the expression of CDC20 by immunohistochemistry (IHC) in the primary cancer tissue; investigate the association between CDC20 with patients' prognosis (OS); have a follow-up period no less than 5 years; only English-language studies were included; the most complete report or the most recent was included when the same results author reported from the same patient population. All candidate manuscripts were carefully checked and approved by 2 independent authors (Wang and Huang). Disagreements on conflicting results were resolved between the 2 authors to obtain a consensus.

2.3. Data collection process and quality assessment

There were 2 investigators (Wang and Liu) assessing all the studies independently including patient number, gender, age or median age, country, cancer type, follow-up duration, cut-off definition, cut-off value for CDC20 positivity, references, HR for OS and with corresponding 95% CIs. The OS data were acquired from the tables or Kaplan–Meier curves which contained the negative and positive groups of CDC20. The studies were entire cohort studies in this meta-analysis. Each publication was scored based on the Newcastle-Ottawa (NOS) system to identify high-quality studies.[11] Each study showed a score ≥6 is abled to be methodologically sound. Each item was achieved for a consensus NOS score by discussion.

2.4. Statistical analysis

Data were acquired from the original articles and analyzed by the software of RevMan 5.3. The Mantel–Haenszel random-effect model was used for the weighted and pooled HR estimates, while Cochran's Q and I^2 statistics were used for the heterogeneity statistics.[12,13] According to the Cochrane Handbook for Systematic Reviews of interventions, differences appearing in the subgroups were assessed. It was considered statistically significant in the case of 2-sided $P < .05$. Publication bias was estimated qualitatively using funnel plots with the standard error, and evaluated by Begg and Egger test.[14]

3. Results

3.1. Search results and study characteristics

Eight studies with entire 1856 patients were showed in this meta-analysis (Fig. 1). The included studies are summarized in Table 1. Two studies evaluated lung cancer,[5,15] and one each evaluated breast cancer,[16] colorectal cancer,[17] gastric cancer,[18] oral squamous cell carcinoma,[19] pancreatic ductal adenocarcinoma,[20] prostate cancer,[21] urothelial bladder cancer.[22] The studies were performed in 5 countries (China, Finland, Japan, Gandra, and the Korea) and published update to March 2017.

3.2. Association of CDC20 with OS

There were 8 studies that reported OS data with multivariate analysis. Relevant results showed that CDC20 overexpression in the tumor tissue of human was associated with survival decreasing on solid tumor patients (HR = 2.48; 95% CI: 2.10–2.94, $P < .001$) (Fig. 2). There was no evidence of heterogeneity among the 8 studies mentioned ($P = .18$, $I^2 = 31\%$). There were 2 studies reporting OS data with univariate analysis. Relevant results showed that CDC20 overexpression in the human tumor tissue was relevant to a decrease in survival among solid tumor patients (HR = 1.75; 95% CI: 1.07–2.86, $P = .03$) (Fig. 3). Among the 2 studies involved, there was no significant heterogeneity ($P = .39$, $I^2 = 0\%$). Pooled HR for OS according to subgroup analysis included studies are shown in Table 2. We further conducted a subgroup analysis to assess different cancer types OS data with multivariate analysis. As is shown in a stratified analysis on solid tumor type, CDC20 overexpression was connected with negative clinical outcome in Chinese (HR = 2.43; 95% CI: 1.99–2.96, $P < .001$) (Fig. 4A), other country people (HR = 2.14; 95% CI: 1.51–3.04, $P < .001$) (Fig. 4B). A stratified analysis of solid tumor type, CDC20 overexpression was connected with negative clinical outcome in digestive system neoplasm (HR = 2.52; 95% CI: 1.81–3.52, $P < .001$) (Fig. 5A), and other system neoplasm (HR = 2.47; 95% CI: 2.03–2.99, $P < .001$) (Fig. 5B).

3.3. Publication bias

The funnel plots presented no evidence of publication bias in the studies of outcome. No evidence for significant

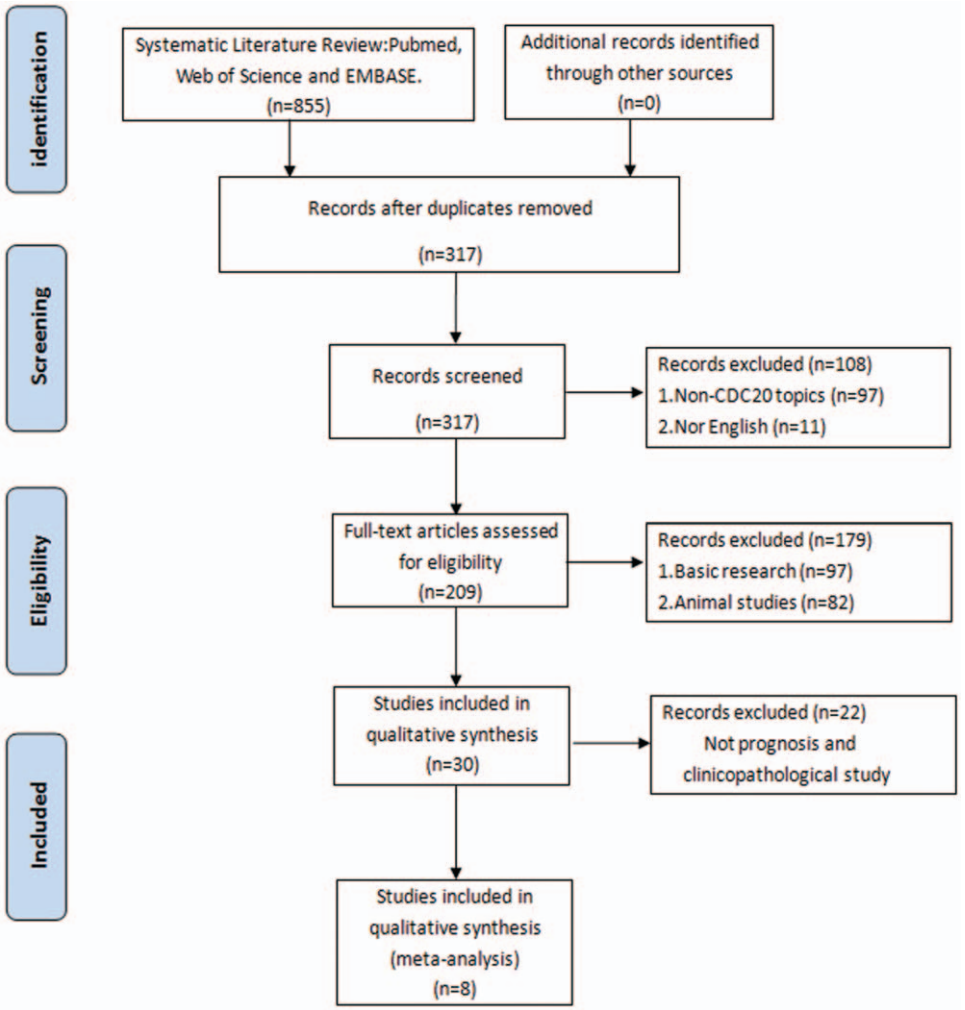

Figure 1. Flow diagram of the meta-analysis process.

publication bias was found in OS with multivariate analysis (Fig. 6).

4. Discussion

Over the past several decades, much research has focused on identifying new prognostic markers in order to make better clinical decisions and improve therapy and outcomes. As we all know, despite extensive investigation in a variety of cancers, CDC20 expression's prognostic significance is still uncertain. Through the findings of many published studies, we intended to systematically evaluate the relationship between CDC20 and human solid tumors to provide valuable information for clinical decision-making.

This meta-analysis was the first systematic review to investigate in depth the relationships between CDC20 overexpression and

Table 1

Characteristics of the included studies.

References	Country	Cancer type	Case No.	Male/ female	Age (years)	Detect method (cut-off)	Increased CDC20 (%)	Follow-up (months)	Survival analysis	HR (95% CI)	NOS (scores)
Karra et al[16]	Finland	Breast cancer	445	0/445	Mean 61.0	IHC (Score ≥ 3)	165 (37.1%)	240	OS (M)	6.91 (3.20–14.9)	9
Wu et al[17]	China	Colorectal cancer	244	158/86	85/159 (<50y/>50y)	IHC (Score ≥ 2)	114 (46.7%)	91	OS (M)	2.95 (1.94–4.46)	9
Ding et al[18]	China	Gastric cancer	131	77/54	47/84 (<60y/>60y)	IHC (Score ≥ 2)	68 (51.9%)	60	OS (M) OS (U)	1.51 (0.67–2.30) 1.47 (0.79–2.76)	8
Shi et al[5]	China	Lung cancer	104	59/45	26/78 (<60y/>60y)	TMA (strongly staining)	107 (99.1%)	240	OS (M)	2.39 (1.87–3.05)	6
Kato et al[15]	Japan	Lung cancer	362	236/126	123/239 (<60y/>60y)	IHC (Score > 3)	71 (19.6%)	60	OS (M)	2.46 (1.28–4.70)	8
Mao et al[21]	China	Prostate cancer	166	166/0	53/53 (<69y/>69y)	TMA (strongly staining)	40 (24.1%)	90	OS (M) OS (U)	2.29 (1.09–4.81) 2.29 (1.04–5.04)	8
Choi et al[22]	Korea	Bladder cancer	339	293/46	152/187 (<68y/>68y)	IHC (Score ≥ 2)	200 (59.0%)	180	OS (M)	1.91 (1.17–3.12)	8
Moura et al[19]	Gandra	Oral cancer	65	51/14	32/33 (<62y/>62y)	IHC (Score ≥ 2)	37 (56.9%)	120	OS (M)	2.36 (1.08–5.17)	7

HR = hazard ratios, IHC = immunohistochemistry, M = multivariate analysis, No. = number, NOS = Newcastle-Ottawa Scale, NR = not reported, OS = overall survival, TMA = transcription-mediated amplification, U = univariate analysis.

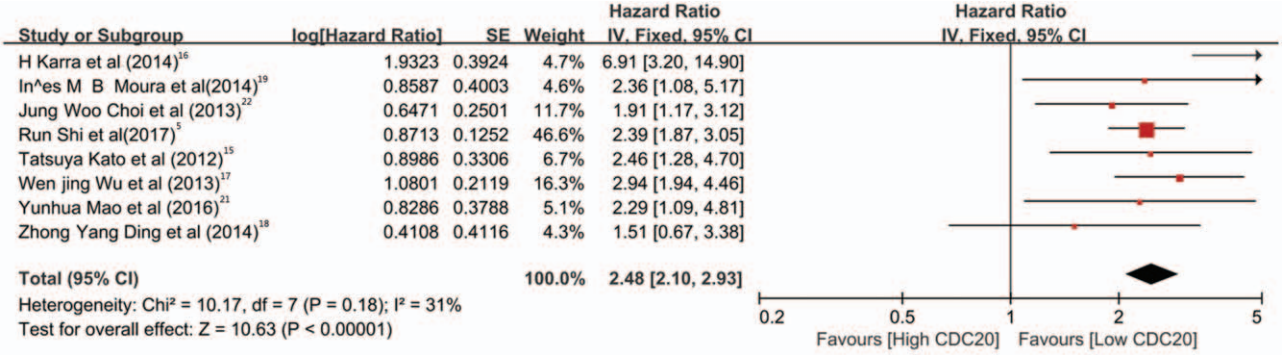

Figure 2. Meta-analysis of the association between CDC20 and OS (multivariate analysis) in patients with solid tumors.

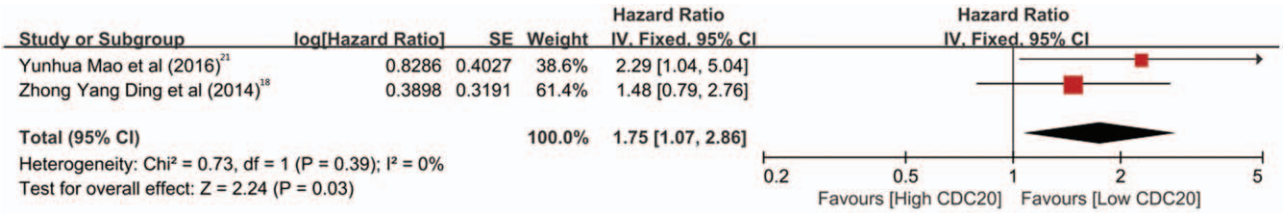

Figure 3. Meta-analysis of the association between CDC20 and OS (univariate analysis) in patients with solid tumors.

Table 2

Pooled HR for OS according to subgroup analysis.

References			Fixed-effect model		Heterogeneity	
Analysis type	**No. of studies**	**No. of patients**	**HR (95% CI)**	***P***	**I^2 (%)**	***P***
Univariate	2	292	1.75 (1.07–2.86)	=.03	0	.39
Multivariate	8	1856	2.48 (2.10–2.94)	<.001	31	.18
Tumor type (multivariate)						
Digestive system neoplasm	3	440	2.52 (1.81–3.52)	<.001	6	.35
Other system neoplasm	5	1416	2.47 (2.03–2.99)	<.001	50	.09
Country (multivariate)						
China	4	645	2.43 (1.99–2.96)	<.001	0	.53
Others	4	1211	2.14 (1.51–3.04)	<.001	0	.80

CI = confidence interval, HR = hazard ratios, No. = number.

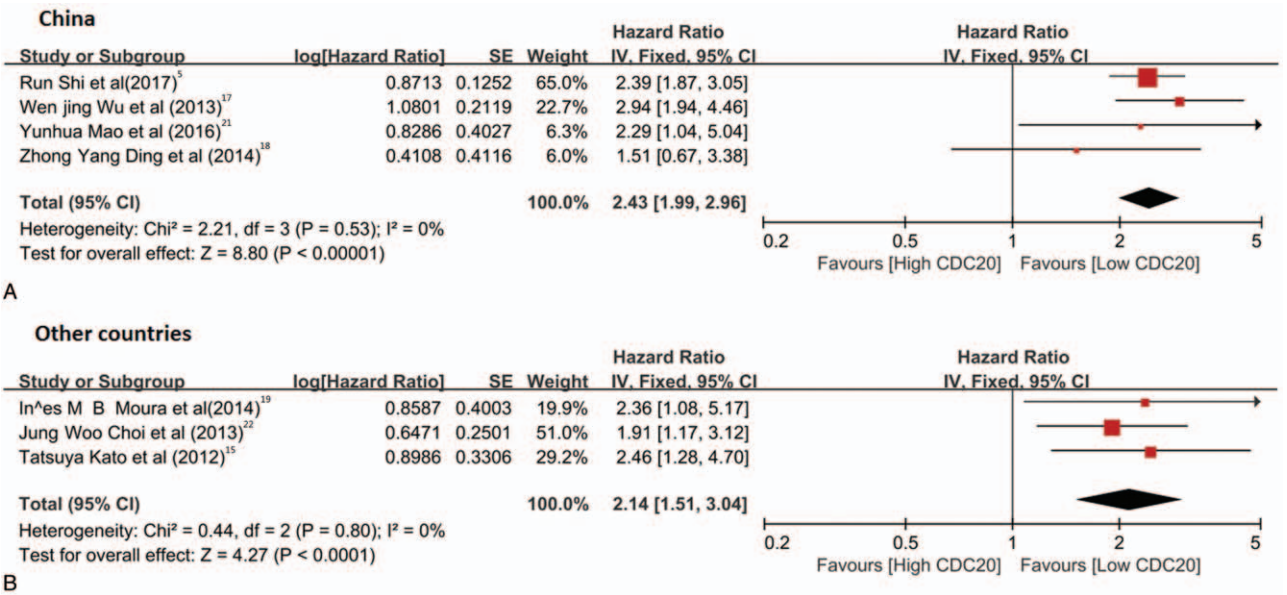

Figure 4. Subgroup analysis of OS (multivariate analysis) by CDC20 expression in various tumor types. (A) China, (B) other countries.

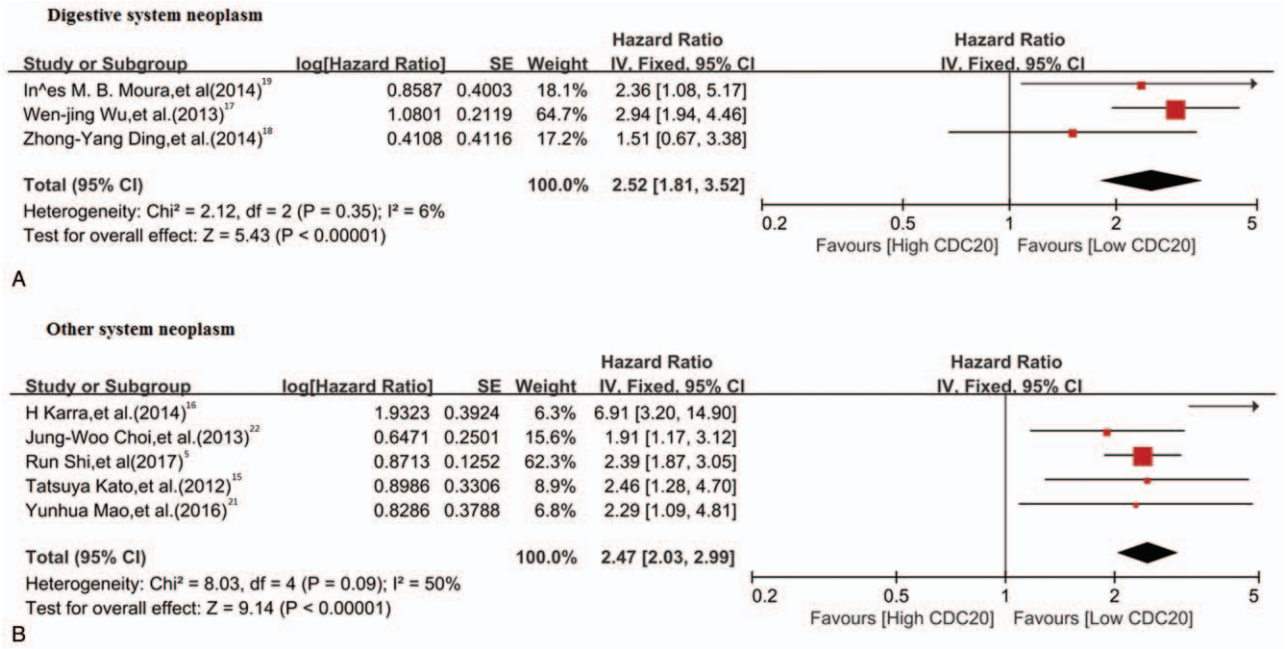

Figure 5. Subgroup analysis of OS (multivariate analysis) by CDC20 expression in various tumor types. (A) Digestive system neoplasm, (B) other system neoplasm.

OS of patients with solid tumors until now. Survival data for 1856 solid tumor patients in 8 different studies were systematically analyzed. In this meta-analysis, the overexpression of CDC20 was a biomarker causing poor prognosis in human solid tumors, with similar OS results with multivariate analysis and univariate analysis. Concerning solid tumor sites, high CDC20 expression was associated with poor OS in digestive system neoplasms and other system neoplasms. In summary, these findings showed that high CDC20 expression is correlated with poor survival in solid tumors. Further studies are required to verify the potential mechanism and impact of CDC20 in the pathogenesis of human solid tumors, in addition to its prognostic value.

At the same time, there are several significant conclusions revealed in this meta-analysis. First, CDC20 expression is associated with adverse outcomes in various human solid tumors, which indicating that CDC20 may be of use as a new therapeutic target. Second, in a subgroup of tumors, tumor tissues with high CDC20 expression were shown to have worse OS, including lung cancer, gastric cancer, colorectal carcinoma,

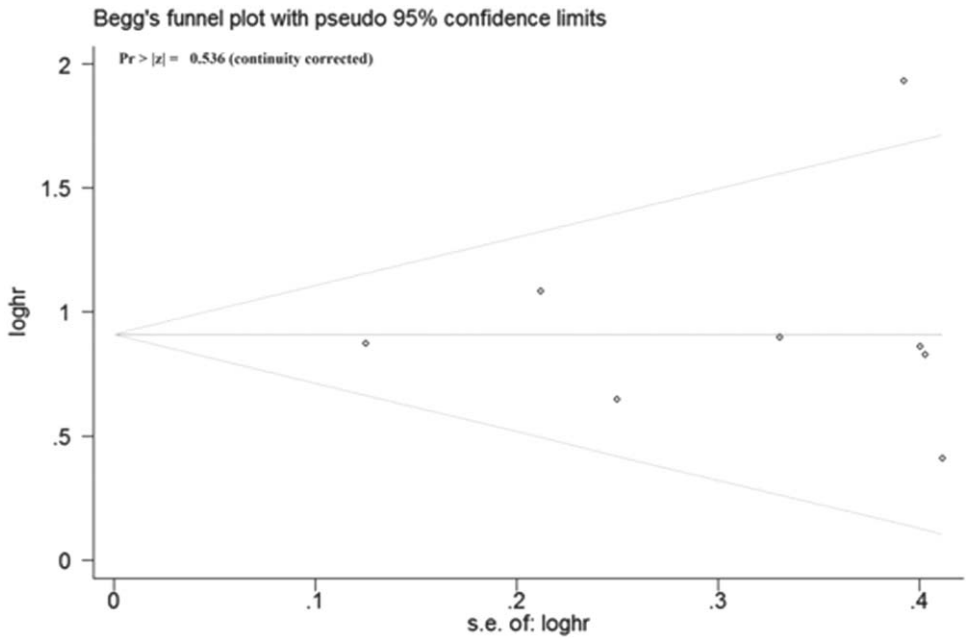

Figure 6. Begg's funnel plot estimated the publication bias of the included literature for OS with multivariate analysis.

and prostate cancer. Finally, this study emphasis a valuable prognostic biomarker-CDC20, which would reflect value in potential clinical application.

However, there are some limitations in this meta-analysis. First, although the results show no significant publication bias, there are a few small sample studies have not been published or the author has not included in the data which may cause bias. So there was a risk of publication bias. Second, there may be inconsistent data in the included reports, as they used different cut-off values and analysis methods for evaluating CDC20 overexpression. Finally, it may not be completely interpreted for substantial heterogeneity among studies although appropriate analytical methods with random effects-models were used.

In summary, toward the case of most human solid tumors, this meta-analysis makes it clear that CDC20 overexpression is related to poor OS. It also suggests that CDC20 is both a new prognostic indicator and a therapeutic target for human solid tumors.

Author contributions

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Supervision: Qi Luo.
Validation: Shengjie Wang, Zhengjie Huang.
Visualization: Gang Liu, Disheng Xiong.
Writing – original draft: Zhipeng Zhu, Junjie Zeng.
Writing – review & editing: Shengjie Wang, Zhengjie Huang.

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