The role of SOX2 overexpression in prognosis of patients with solid tumors
A meta-analysis and system review

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Abstract

Background: Many studies have been done to reported the value of SRY-related HMG-box Gene 2 (SOX2) in prognosis of solid tumors. But results were not particularly consistent among these studies because of the limitations of the small sample data.

Methods: We searched relevant studies published before November 2018 by PubMed, Web of Science and EMBASE. In this meta-analysis, hazard ratio (HR) values for overall survival (OS) were cumulatively pooled and quantitatively analyzed.

Results: A meta-analysis based on 12 studies with 3318 patients was conducted to assess the potential correlation between SOX2 overexpression and OS in human solid tumors. A total of 12 studies (n = 3318) were assessed in the meta-analysis. It suggested that the high expression of SOX2 obviously indicates poor survival and prognosis in both univariate and multivariate analysis. In the univariate analysis, the combined HR for OS was 1.66 (95% confidence interval [CI]: 1.46–1.89, $P < .001$). The pooled HR of multivariate analysis for OS was 1.51 (95% confidence interval [CI]: 1.32–1.71, $P < .001$).

Conclusions: This meta-analysis indicated that the high expression level of SOX2 is significantly associated with a decline in survival of human with solid tumors. On the basis of the expression level in solid tumors, SOX2 is expected to be a meaningful prognostic biomarker and effective therapeutic target.

Abbreviations: CI = confidence interval, HMG = high-mobility-group, HR = combined hazard ratio, IHC = immunohistochemistry, M = multivariate analysis, NE = nuclear expression, No. = number, NOS = New-Castle-Ottawa, OS = overall survival, SE = standard error, SOX2 = SRY-related HMG-box gene 2, SRY = sex-determining region Y, U = univariate analysis.

Keywords: meta-analysis, solid tumor, SOX2

1. Introduction

In recent years, there are millions of new cancers and cancer-related deaths all over the world.[1] Cancer is still a leading cause of mortality worldwide.[2] Although we have tried over and over again to search better methods in the diagnosis and therapy, many solid tumors still lack specific tumor biomarkers and effective treatments. Therefore, it is quite necessary to find novel therapeutic approaches and tumor biomarkers with high specificity and sensitivity, especially in the detection of biomarkers and the research of molecular mechanisms.

Nowadays, researches on SRY-related HMG-box gene 2 (SOX2) in tumorigenesis and tumor progression is still attached much attention. As early as in 1990, a gene called sex-determining region Y (SRY) was found to be located on the sex-determining region of the Y chromosome encoding for a new transcription factor with a distinctive DNA-binding domain.[3,4] The SRY protein binds to specific DNA sequences with its high-mobility-group (HMG) domain. The so-called SRY-related HMG box (SOX) proteins contain an HMG domain with at least 50% sequence similarity to the HMG domain of SRY. Among all SOX genes, SOX2 is probably the most recognized. SOX2, a gene on chromosome 3q26.3-q27 that encodes a member of the SOX family of transcription factors, which regulate embryonic development and determine cell fate.[5] Recently, more and more evidences have revealed the role of SOX2 to tumorigenesis and

suggested many more links between Sox2 and the clinical progression of solid tumors. However, there were no consensuses among them. So making it certain whether SOX2 overexpression is a prognostic marker for unfavorable pathologic features and poor outcomes in human solid tumors is vitally important.

2. Methods

2.1. Literature search strategy

Electronic databases, including PubMed, EMBASE, and Web of Science, were used to search SOX2 expression and clinical results in solid tumors update to November 2018. The search terms included "SRY-related HMG-box Gene 2" or "SOX2" and "tumor" or "cancer" or "prognosis" or "survival." Only human studies of solid tumors were accepted. So entries amount to 3318 were identified. We set a inclusion criteria including measuring SOX2 by immunohistochemistry (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:

1. measure the expression of SOX2 by IHC in the primary cancer tissue;
2. investigate the association between SOX2 with patients' prognosis (OS);
3. have a follow-up period no >5 years;
4. only English-language studies were included;
5. 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 two independent authors (Wang and Liu). Disagreements on conflicting results were resolved between the two authors to obtain a consensus.

2.3. Data collection process and quality assessment

There were two 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 SOX2 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 SOX2. The studies were entire cohort studies in this meta-analysis. Each publication was scored based on the New-Castle-Ottawa (NOS) system to identify high-quality studies.[6] Each study showed a score ≥6 is able 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.[7,8] 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 two-sided $P < .05$. Publication bias was estimated qualitatively using funnel plots with the standard error, and evaluated by Begg's and Egger's test.[9]

3. Results

3.1. Search results and study characteristics

Twelve studies with entire 3318 patients were showed in this meta-analysis (Fig. 1). The included studies are summarized in Table 1. Two studies evaluated esophagus cancer,[10,11] two studies evaluated breast cancer,[12,13] two studies evaluated colorectal cancer[14,15] and one each evaluated glioma,[16] gastric cancer,[17] lung cancer,[18] head and neck carcinoma,[19] cervical cancer,[20] laryngeal carcinoma.[21] The studies were performed in five countries(China, UK, Sweden, Netherland, and Korea) and published update to November 2018.

3.2. Association of SOX2 with OS

There were eight studies that reported OS data with multivariate analysis. Relevant results showed that SOX2 overexpression in the tumor tissue of human was associated with survival decreasing on solid tumor patients (HR = 1.51; 95% CI 1.32–1.71, $P < .001$) (Fig. 2). There was no evidence of heterogeneity among the eight studies mentioned ($P = .77$, $I^2 = 0\%$). There were seven studies reporting OS data with univariate analysis. Relevant results showed that SOX2 overexpression in the human tumor tissue was relevant to a decrease in survival among solid tumor patients (HR = 1.66; 95% CI 1.46–1.89, $P < .001$) (Fig. 3). Among the seven studies involved, there was no significant heterogeneity ($P = .76$, $I^2 = 0\%$). 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 univariate analysis. As is shown in a stratified analysis on solid tumor type, SOX2 overexpression was connected with negative clinical outcome in digestive system neoplasm (HR = 1.61; 95% CI 1.34–1.94, $P < .001$) (Fig. 4A), others (HR = 2.14; 95% CI 1.51–3.04, $P < .001$) (Fig. 4B). In a stratified analysis of country, SOX2 overexpression was connected with negative clinical outcome in China (HR = 1.75; 95% CI 1.39–2.20, $P < .001$) (Fig. 5A), and others (HR = 1.62; 95%CI 1.38–1.90, $P < .001$) (Fig. 5B). 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, SOX2 overexpression was connected with negative clinical outcome in digestive system neoplasm (HR = 1.53; 95% CI 1.28–1.83, $P < .001$) (Fig. 6A), others (HR = 1.48; 95% CI 1.23–1.79, $P < .001$) (Fig. 6B). In a stratified analysis of country, SOX2 overexpression was connected with negative clinical outcome in China (HR = 1.60; 95% CI 1.27–2.01, $P < .001$) (Fig. 7A), and others (HR = 1.46; 95%CI 1.25–1.71, $P < .001$) (Fig. 7B). In a stratified analysis of ethnicity, SOX2 overexpression was connected with negative clinical outcome in Asian (HR = 1.54; 95% CI 1.29–1.84, $P < .001$) (Fig. 8A), and others (HR = 1.47; 95%CI 1.22–1.78, $P < .001$) (Fig. 8B).

3.3. Publication bias

The funnel plots presented no evidence of publication bias in the studies of outcome. No evidence for significant publication bias was found in OS with univariate (Fig. 9A) and multivariate analysis (Fig. 9B).
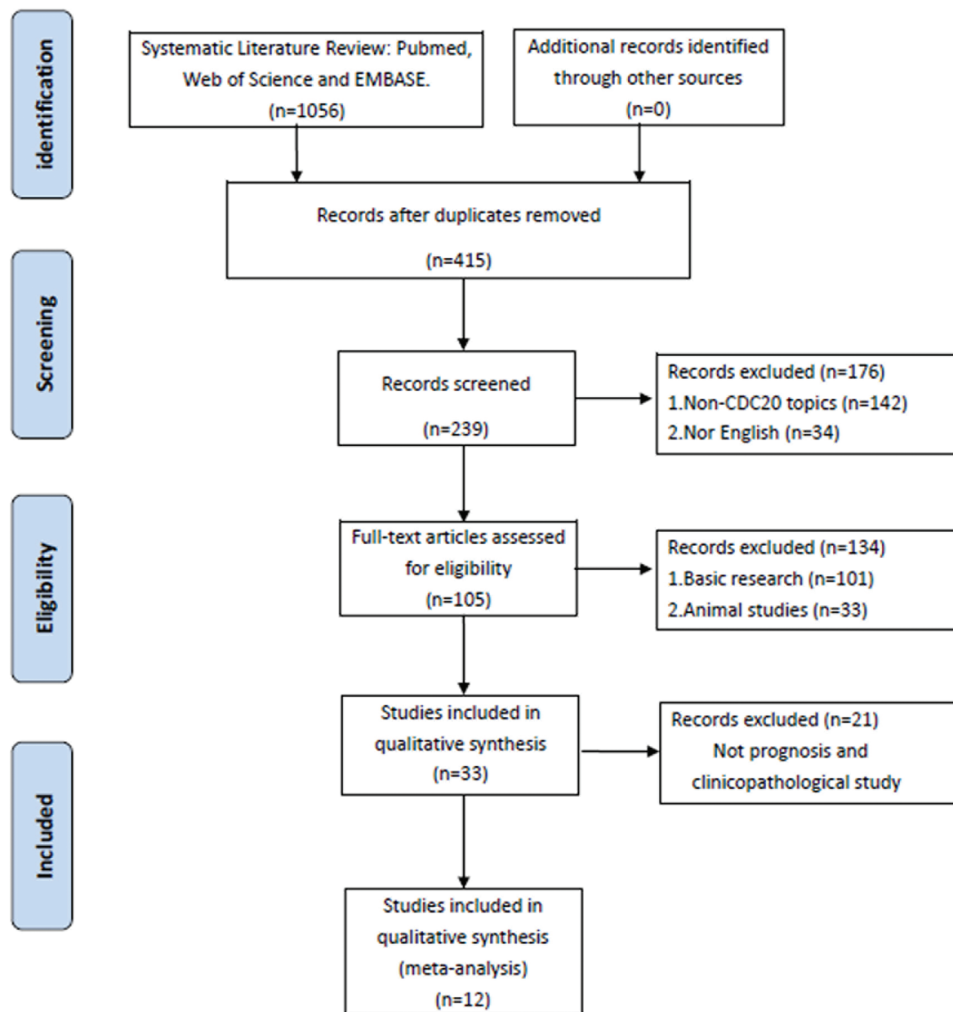
Figure 1. Flow diagram of the meta-analysis process.

4. Discussion

Identifying new biomarkers for better clinical decisions and treatments is under rigorous demand. As a common gene who have been investigated extensively among almost all cancers, SOX2 still plays an uncertain role. So correlation studies from published literatures are systematically evaluated between SOX2 and human solid tumors. This meta-analysis may be the first

Table 1

Characteristics of the included studies.

References	Country	Cancer type	Case No.	Male/ female	Age (years)	Detect method (cut-off)	Increased SOX2 (%)	Fellow-up (months)	Survival analysis	HR (95%CI)	NOS (scores)
Bin Wang et al (2015)[16]	China	Glioma	123	68/55	57/66 (<41y/≥41y)	IHC (score≥1)	54 (43.9%)	80	OS(U)	1.91 (1.39–2.63)	9
ten Kate et al (2017)[10]	UK	Esophagus cancer	756	602/132	Mean 65.4	IHC (NE ≥ 50%)	224 (33.9%)	60	OS(M) OS(U)	1.42 (1.14–1.77) 1.55 (1.25–1.93)	8
Fan Yang et al (2018)[13]	China	Breast cancer	134	0/134	Mean 53.8	IHC (score ≥ 3)	28 (20.9%)	130	OS(U)	1.96 (0.96–3.99)	6
Fang Yang et al (2013)[18]	China	Lung cancer	222	140/82	162/60 (<60y/≥60y)	IHC (score ≥ 4)	124 (55.8%)	115	OS(M)	1.36 (1.02–1.82)	8
Ida V. Lundberg et al (2014)[15]	Sweden	Colorectal cancer	441	243/198	188/253 (<70y/≥70y)	IHC (score ≥ 2)	47 (10.7%)	210	OS(M)	1.64 (1.04–2.58)	8
Ji Hyun Chung et al (2018)[19]	Korea	Head and neck carcinoma	772	593/179	Mean 60.5	IHC (score ≥ 3)	373 (48.3%)	60	OS(M) OS(U)	1.45 (1. 09–1.92) 1.59 (1.23–2.06)	9
Jiaming Zhang et al (2018)[12]	China	Breast cancer	127	0/127	Mean 54.5	IHC (score ≥ 2)	21 (16.5%)	150	OS(U)	1.60 (0.87–2.96)	8
Judith Honing et al (2014)[11]	Netherland	Esophagus cancer	94	83/11	41/53 (<65y/≥65y)	IHC (score ≥ 6)	76 (80.9%)	78	OS(M) OS(U)	1.59 (0. 87–2.93) 2.38 (1.36–4.15)	9
Liangfang Shen et al(2014)[20]	China	Cervical cancer	132	0/132	49/83 (<50y/≥50y)	IHC (score ≥ 3)	83 (62.9%)	85	OS(M)	2.29 (1.01–5.20)	8
Liuping You et al (2018)[14]	China	Rectal cancer	153	83/70	Mean 66.0	IHC (score ≥ 2)	72 (47.1%)	80	OS(U)	1.44 (0.90–2.30)	8
Imeng Wang et al (2015)[17]	China	Gastric cancer	203	132/71	124/79 (<60y/≥60y)	IHC (score ≥ 2)	48 (23.6%)	120	OS(M)	2.17 (1.21–3.89)	8
Xiabing Tang et al (2013)[21]	China	Laryngeal carcinoma	161	152/9	63/98 (<60y/≥60y)	IHC (score ≥ 6)	66 (41.0%)	60	OS(M)	1.91 (1.04–3.52)	8

HR = hazard ratios, IHC = immunohistochemistry, M = multivariate analysis, NE = nuclear expression, No. = number, NOS = Newcastle-Ottawa Scale, OS = overall survival, U = univariate analysis.
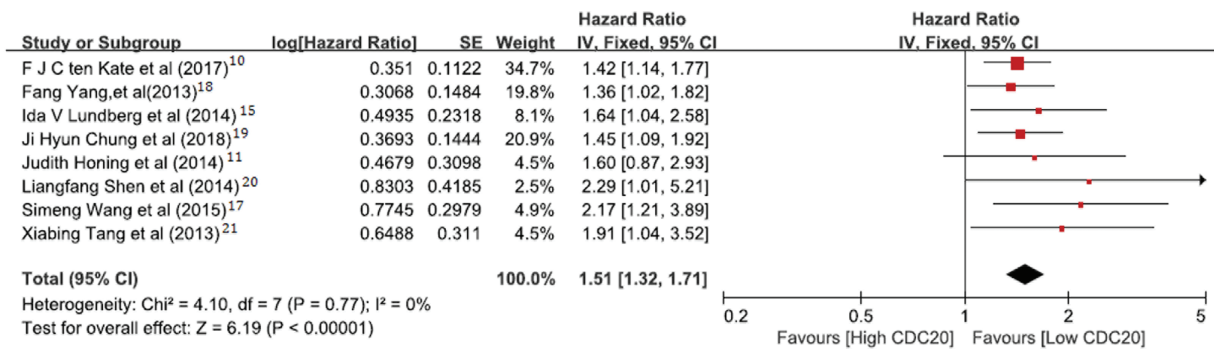
Figure 2. Meta-analysis of the association between SOX2 and OS (multivariate analysis) in patients with solid tumors.
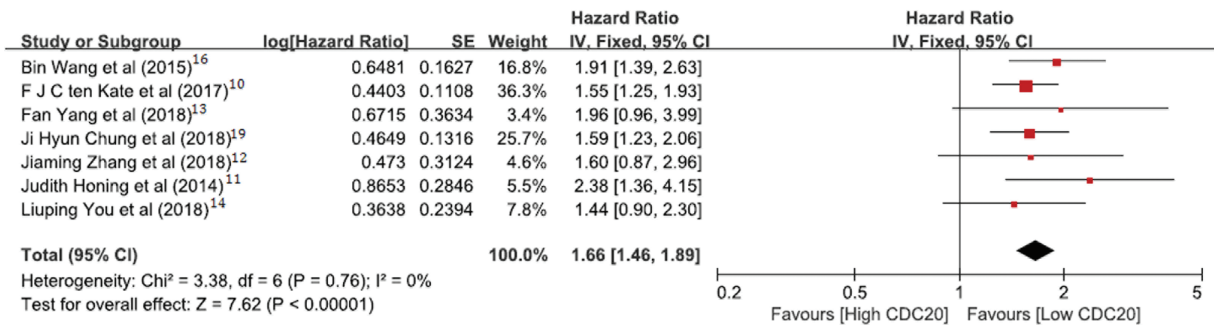

Figure 3. Meta-analysis of the association between CDC20 and OS (univariate analysis) in patients with solid tumors.

systematic review to investigate the relevant OS when SOX2 overexpressed in solid tumors. Survival data for 3318 solid tumor patients in 12 different studies were analyzed. In this meta-analysis, the overexpression of SOX2 was a biomarker leading to poor prognosis in human solid tumors, with similar OS results with multivariate analysis and univariate analysis. Concerning solid tumor sites, high SOX2 expression

was associated with poor OS in digestive system neoplasms and other system neoplasms. In summary, these findings showed that high SOX2 expression is correlated with poor survival in solid tumors. Further studies are required to verify the potential mechanism and impact of SOX2 in the pathogenesis of human solid tumors in addition to its value in prognosis.

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	7	2159	1.66 (1.46–1.89)	<.001	0	.76
Multivariate	8	2781	1.51 (1.32–1.71)	<.001	0	.77
Tumor type (univariate)						
Digestive system neoplasm	3	1003	1.61 (1.34–1.94)	<.001	9	.33
Others	4	1156	1.72 (1.43–2.06)	<.001	0	.81
Tumor type (multivariate)						
Digestive system neoplasm	4	1494	1.53 (1.28–1.83)	<.001	0	.59
Others	4	1287	1.48 (1.23–1.79)	<.001	0	.55
Country (univariate)						
China	4	537	1.75 (1.39–2.20)	<.001	0	.77
Others	3	1622	1.62 (1.38–1.90)	<.001	0	.37
Country (multivariate)						
China	4	718	1.60 (1.27–2.01)	<.001	10	.34
Others	4	2063	1.46 (1.25–1.71)	<.001	0	.94
Ethnicity (multivariate)						
Asian	5	1490	1.54 (1.29–1.84)	<.001	0	.46
Others	3	1291	1.47 (1.22–1.78)	<.001	0	.83

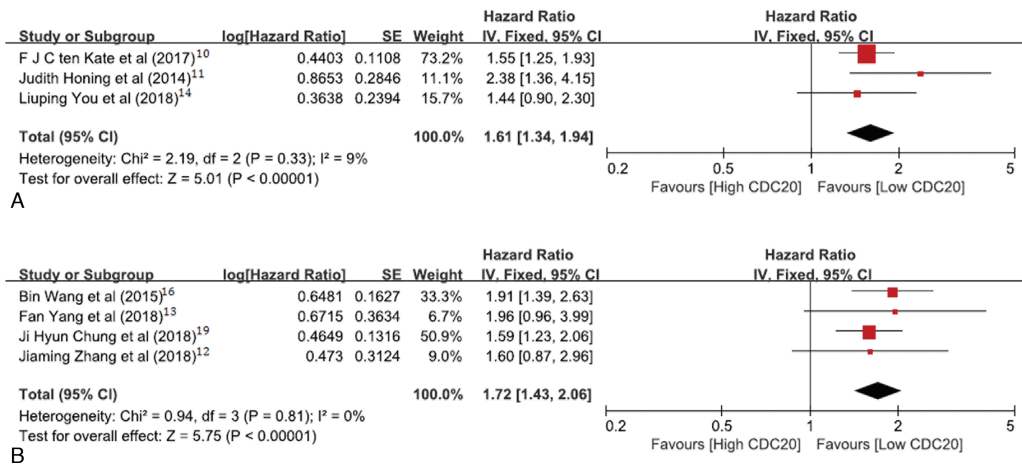CI = confidence interval, HR = hazard ratios, No. = number.

Figure 4. Subgroup analysis of OS (univariate analysis) by CDC20 expression in various tumor types. (A) Digestive system neoplasm; (B) others.
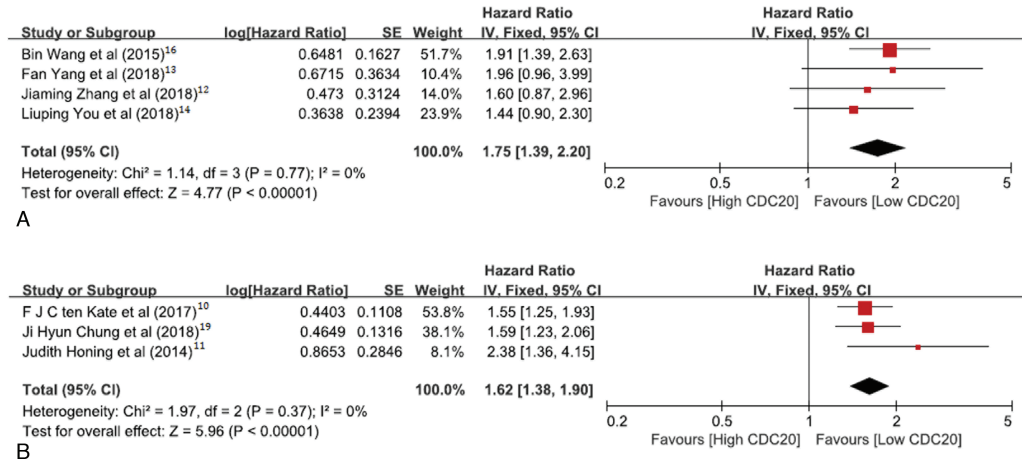

Figure 5. Subgroup analysis of OS (univariate analysis) by CDC20 expression in country. (A) China; (B) others.
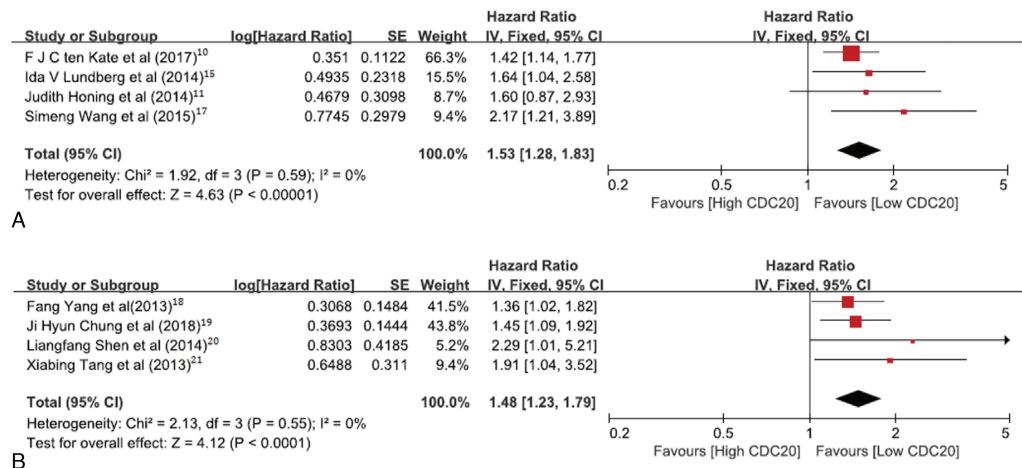

Figure 6. Subgroup analysis of OS (multivariate analysis) by CDC20 expression in various tumor types. (A) Digestive system neoplasm; (B) others.
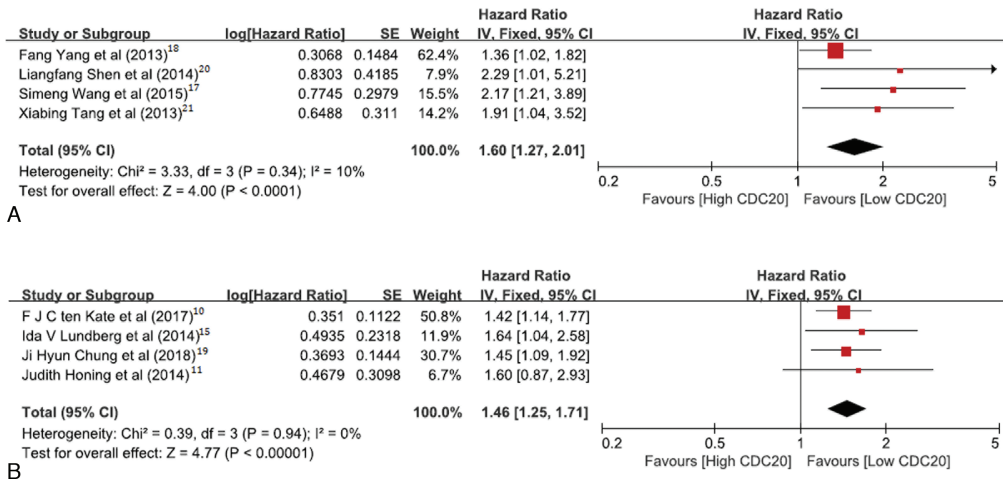
Figure 7. Subgroup analysis of OS (multivariate analysis) by CDC20 expression in country. (A) China; (B) others.
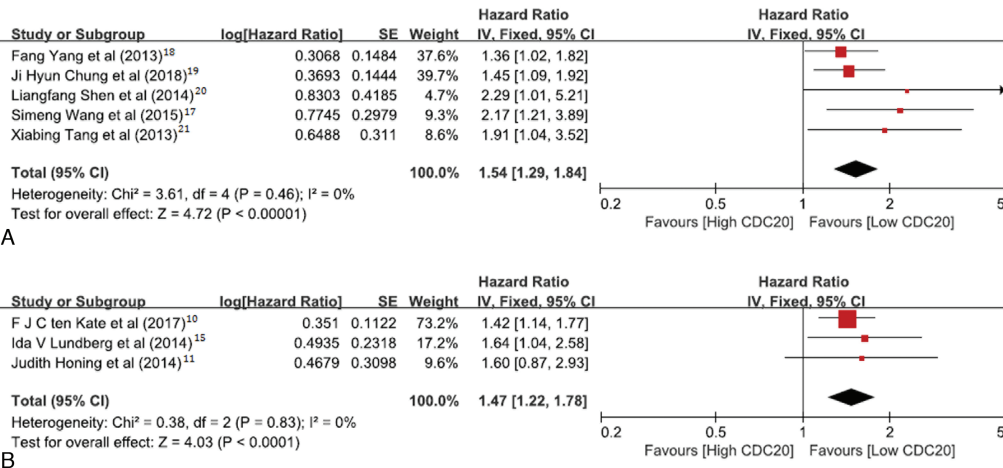

Figure 8. Subgroup analysis of OS (multivariate analysis) by CDC20 expression in ethnicity. (A) Asian; (B) others.

SOX2 expression is associated with adverse outcomes in various human solid tumors including esophagus cancer, breast cancer, lung cancer, gastric cancer, colorectal carcinoma, glioma, head and neck carcinoma, cervical cancer, and laryngeal carcinoma, which indicating that SOX2 may be used as a new tumor biomarker in potential clinical application.

However, there are some limitations in this meta-analysis. First, although the results show no significant publication bias,
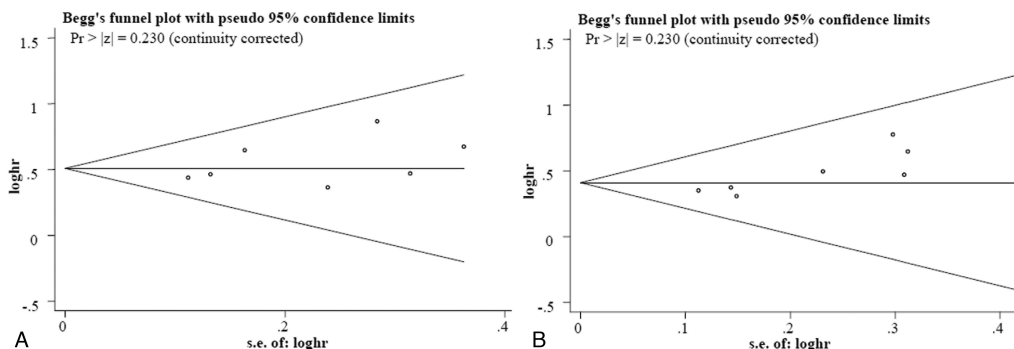

Figure 9. Begg's funnel plot estimated the publication bias of the included literature for OS with univariate analysis (A) and multivariate analysis (B).

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 analytical methods for evaluating SOX2 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, towards the case of most human solid tumors, this meta-analysis makes it clear that SOX2 overexpression is related to poor OS. It also suggests that SOX2 is both a new prognostic indicator and a therapeutic target for human solid tumors.

Author contributions

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Project administration: Lin Xu.
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Supervision: Lin Xu and Guangwen Sun.
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Visualization: Xiaozhen Zhan and Tujin Wu.
Writing – original draft: Ying Chen and Bing Chen.
Writing – review & editing: Shengjie Wang and Lin Xu.

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