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Review Article

Association between runx2 expression and survival outcome of cancer patients: a meta-analysis of 12 cohorts

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Abstract: Runt-related transcription factor 2 (Runx2) was reported to play a pivotal role in the progression of cancer. However, the prognostic value of Runx2 expression in cancers still remains unclear. Thus, we performed a systematically meta-analysis to evaluate the predictive effects of Runx2. The databases including Pubmed, Embase, Web of Science and Cochrane library were comprehensively searched. A total of 12 studies with 1700 cases were enrolled in our meta-analysis. The results based on the random-effect model indicated that high Runx2 expression predicted a worse outcome in cancer patients (HR=2.56, 95% CI=2.34-2.78). Besides, the subgroup analysis stratified by ethnicity indicated that the high level of Runx2 was related with a worse survival condition in Asian (HR=2.71, 95% CI=2.46-2.95) compared to Caucasian (HR=1.95, 95% CI=1.45-2.44). In conclusion, overexpression of Runx2 is significantly associated with a poor prognosis in cancer. Our study suggested Runx2 might serve as a biomarker and could predict prognosis in cancers.

Keywords: Runx2, prognosis, survival, cancer, meta-analysis

Introduction

The global incidence of cancer is increasing, especially in the developing country with low and middle income [1]. Malignant tumors are still one of the most common causes of death due to the inefficient diagnosis and limited treatment in the early stage of cancers [2]. There is no doubt that early diagnosis and optimum treatment are indispensable for cancer patients to improve health outcomes. However, the accurate diagnostic tools still remain a key obstacle because of the complex mechanism of carcinoma [3]. Therefore, it is very urgent to find better prediction biomarkers to fulfill the accuracy and utility of diagnostic tools of cancer.

Runt-related transcription factor 2 (Runx2), also called core-binding factor subunit alpha-1 (CBF-alpha-1), is a member of the RUNX family of transcription factors with a Runt DNA-binding domain [4]. Most often, as part of the CBF complex, Runx2 is involved in many pathological processes, such as differentiation, proliferation and inflammation [5, 6]. Runx2 has been reported to play a pivotal role during the osteogenic differentiation [7, 8]. Up to date, accumulating studies have reported that overexpression of Runx2 plays an important role in cancers, including breast cancer [9], panpreatic cancer [10], thyroid cancer [11], prostate cancer [12] and colon carcinoma [13]. However, the results are conflicting and vaguely when assessing the relationship between high expression of Runx2 and the progression in cancers. Recently, some research studies have focused on the prognostic value of Runx2 in cancers [14-16], while the underlying mechanism of this association still remains unclear.

In this study, we sought to conduct a comprehensively research and performed a meta-analysis to assess the prognostic value of overexpression of Runx2 in cancers.

Materials and methods

Literature research

A systematically research was conducted by searching Pubmed, Embase, Web of Science

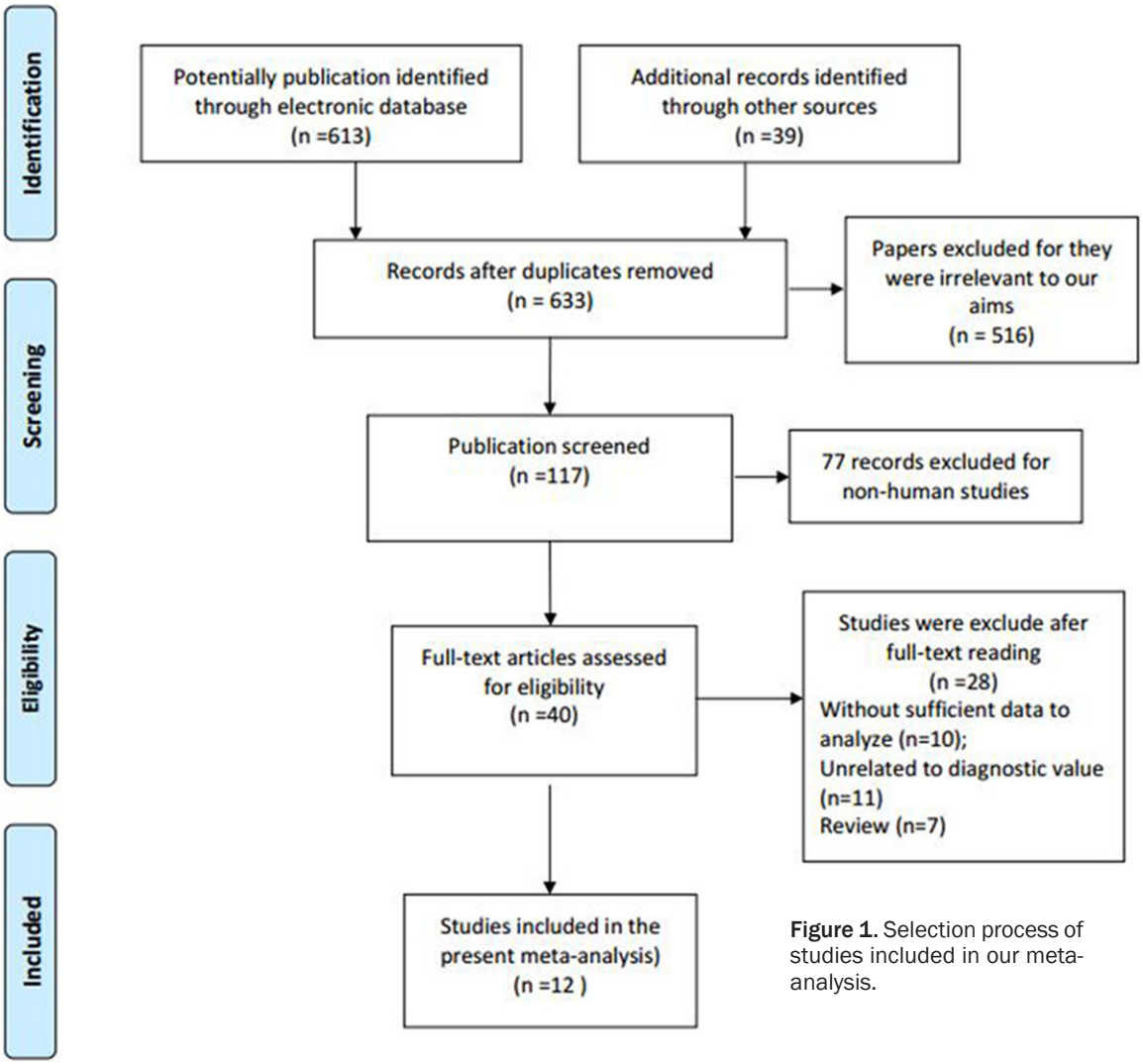

Figure 1. Selection process of studies included in our meta-analysis.

and Cochrane library for studies focused on Runx2 expression and its prognostic value in cancers up to March 8, 2017. The following combined items were used to retrieve eligible literature: "cancer", "carcinoma", "tumor" in combination with "Runt-related transcription factor 2", "Runx2", "CBF-alpha-1". The references of the included articles were also scanned for potential eligibility.

Inclusion/exclusion criteria

Studies were included if they met following criteria: 1) studies focused on the prognostic value of Runx2 in cancers; 2) efficient data can be extracted for calculating Hazard ratio (HR) and 95% confidence interval (CI); 3) the number of the specimen enrolled in studies is no less than 30; 4) the research subjects are human.

Studies were also excluded if they met following conditions: 1) lack of efficient information to calculate HR and 95% CI; 2) duplicated publications; 3) reviews, letters, editorials, expert opinions and case reports.

Data extraction

Detailed information and data were collected for every eligible study by two independent authors. The disagreement was solved by consensus. The following information was collected from each included study: first author, publication year, country, ethnicity, cancer types, sample size, testing methods, cut-off value, analysis type, mean age, follow-up time, survival condition, Hazard ratio (HR) and corresponding 95% confidence interval (CI). The soft-

Table 1. Basic Characteristics of the studies enrolled

No.	First Author	Year	Country	Ethnicity	Cancer type	Sample size	Mean Age (Year)	Duration of Follow-up (month)	Analysis Model	Testing methods	Cut-off value	Survival condition	RR (95% CI)
1	Laura McDonald	2014	UK	Caucasian	Breast cancer	384	54.5	180	M	IHC	Histoscore≥25	OS	2.40 (1.31-4.41)
2	Zhengjun Guo	2015	China	Asian	Gastric cancer	305	53.0	NM	NM	IHC	Score 3	OS	3.06 (2.12-4.43)
3	Chih-Hao Chang	2014	China	Asian	Breast cancer	108	59.2 (35-102)	80	M	IHC	Score 3	RFS	3.02 (1.50-6.07)
4	Tomohiko Sase	2012	Japan	Asian	Colon cancer	157	67.0 (35-85)	100 (1-149)	M	IHC	Score 3	OS	1.23 (0.44-3.40)
5	Eman Abdelzaher	2016	Egypt	Caucasian	Urothelial cancer	87	58.1 (40-72)	25	M	IHC	Score 3	PFS	1.13 (0.41-3.11)
6	Qian Wang	2016	China	Asian	Hepatocellular carcinoma	96	NM	35 (1-60)	NM	IHC	NM	OS	2.18 (1.11-4.66)
												DFS	3.648 (1.084-5.103)
7	Saba Mohamed El-Gendi	2016	Egypt	Caucasian	Breast cancer	84	50.2 (27-76)	36.0	M	IHC	Score 3	OS	1.008 (0.497-2.85)
												DFS	1.024 (0.601-1.744)
8	Wein-min Chang	2016	Chian	Asian	Head and neck squamous cell carcinoma	87	NM	100	M	IHC	NM	OS	2.30 (1.28-4.14)
9	Chak-kaphanKhenjanta	2014	Thailand	Asian	Cholangiocarcinoma	30	56.5 (37-73)	32.4	M	IHC	NM	OS	0.23 (0.07-0.73)
10	Hong Li	2013	China	Asian	Nonsmall cell lung cancer	121	58.3 (45-81)	60.0	M/U	IHC	SI=4	OS	1.48 (0.68-2.14)
11	Zhengjun Yang	2015	China	Asian	Breast cancer	125	61.3 (50-73)	89 (30-123)	M/U	IHC	Score 4	OS	5.49 (1.844-16.342)
												DFS	3.436 (1.588-7.433)
12	Weiping Li	2012	China	Asian	Epithelial Ovarian Cancer	116	53.4	66.8 (2.2-118.9)	M/U	IHC	LI=55.1%	OS	12.49 (1.74-33.03)
												PFS	9.02 (1.83-26.10)

Abbreviations: NM: not mentioned; IHC: immunohistochemistry; M: Multivariate analysis; M/U: Multivariate/Univariate; SI: Staining Index; LI: Labeling index; OS: overall survival; PFS: progress-free survival.

Table 2. Quality assessment of studies enrolled using the Newcastle-Ottawa Quality Assessment Scale

Study (author, year)	Selection				Comparability	Outcome			Scores
	1	2	3	4		1	2	3	
Laura McDonald	★	-	★	★	★★	★	★	★	8
Zhengjun Guo	★	★	★	-	★	-	★	★	6
Chih-Hao Chang	★	★	★	★	★★	★	-	★	8
Tomohiko Sase	★	-	★	-	★★	-	★	★	6
Eman Abdelzaher	★	★	★	★	★	★	★	★	8
Qian Wang	★	–	-	★	★★	-	★	★	6
Saba Mohamed El-Gendi	★	★	★	★	★	★	★	-	7
Wein-min Chang	★	-	★	★	★★	★	★	★	8
ChakkaphanKhenjanta	★	★	★	★	★★	★	★	★	9
Hong Li	-	★	★	★	★	-	★	★	6
Zhengjun Yang	★	★	-	★	★★	★	-	★	7
Weiping Li	★	★	-	-	★★	★	★	★	7

ware Engauge Digitizer 4.1 was used to calculate HR and 95% CI if a Kaplan-Meier curve was only provided.

Statistical analysis

All the statistical analysis was conducted by STATA 12.0 software. In the present study, the hazard ratio (HR) and corresponding 95% confidence interval were used to assess the prognostic value of Runx2 in cancer. While odds ratio (OR) and corresponding 95% confidence interval were used to evaluate the association between Runx2 expression and the clinicopathological features. A fixed effect model was used for the analysis if no significantly statistical heterogeneity existed ($P \geq 0.05$, $I^2 < 50\%$), otherwise a random effect model was used. Q test and I^2 test was performed to evaluate the statistical heterogeneity and Begg's and Egger's test were used to measure the potential publication bias. To further investigate the exact role of Runx2 in cancers, subgroup analysis was also conducted based on cancer types, ethnicity, follow-up time, sample size and survival conditions.

Quality assessment

We used Newcastle-Ottawa Assessment Scale (NOS) to assess the quality of each study included in our meta-analysis. The NOS evaluate the quality of study through 3 domains: selection, comparability and exposure. Each item could be rewarded with a score if they met the criteria. The total score ranged from 0 to 9, and studies with 6 or more scores were considered high quality.

Results

Literature research

A total of 633 studies were initially identified as potential reports due to the comprehensively searching. After scanning the title and abstracts, 516 studies were excluded for they were irrelevant to our aims. Subsequently, an additional 164 researches were eliminated because they were non-human studies. Therefore, a remaining 40 reports were systematically assessed by reading the full test. Among them, 10 studies were excluded because of the inefficient data to analysis; 11 studies were excluded because they were unrelated to the diagnostic value of Runx2; 7 studies were excluded for they were reviews. Eventually, 12 studies [13, 17-27] were enrolled in our meta-analysis (**Figure 1**).

Study characteristics

The characteristics of studies enrolled in our meta-analysis were presented in **Table 1**. The publication years of included studies were from 2012 to 2016. Among them, 7 studies were performed in China, 2 were in Egypt and 3 were in UK, Japan and Thailand, respectively. A total of 1700 cases enrolled, with a range from 30 to 384. All of the studies used immunohistochemistry (IHC) to evaluate the expression level of Runx2. Seven studies used Multivariate analy-

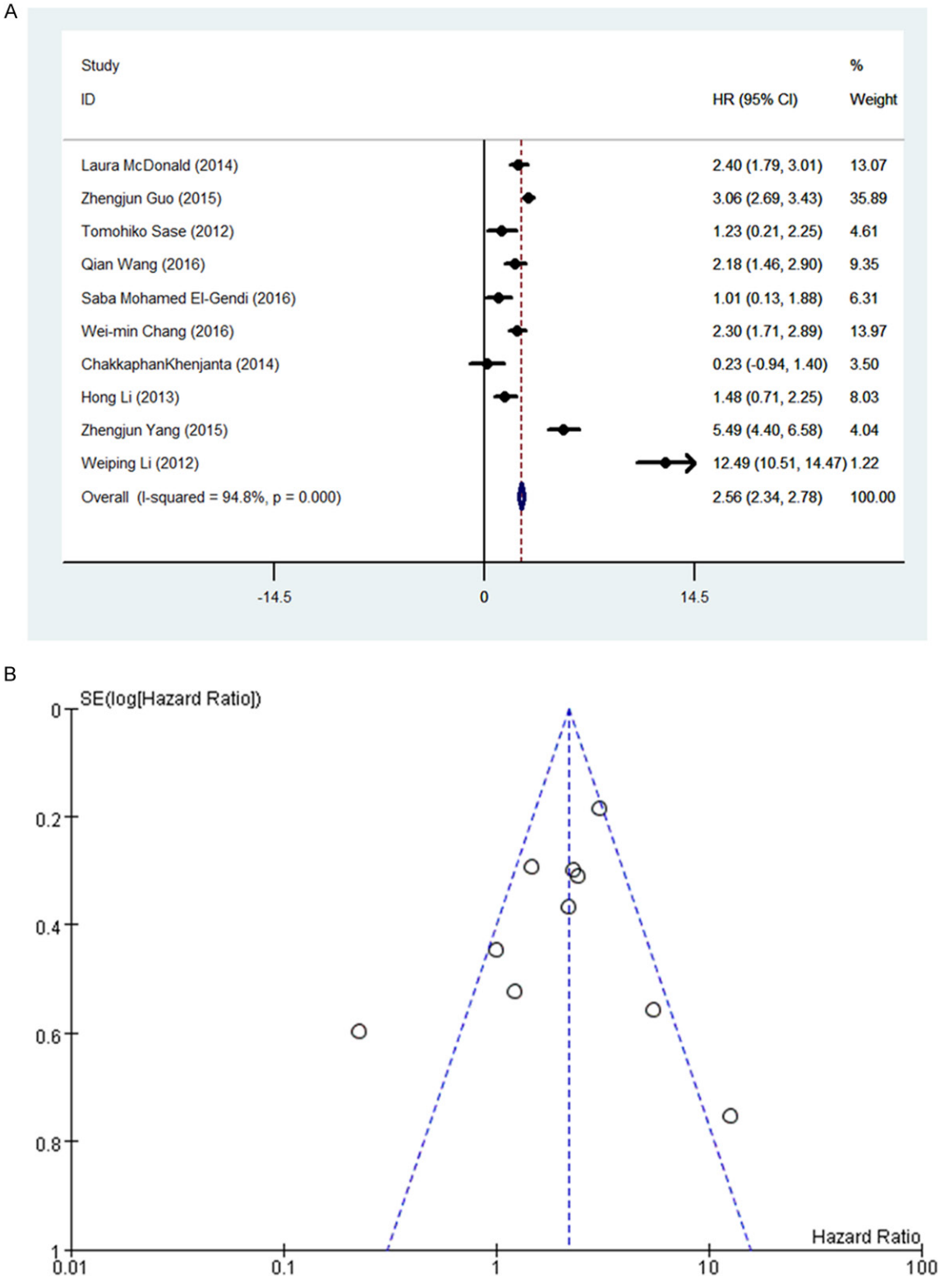

Figure 2. Main analytical results of assessing the relationship between Runx2 expression and overall survival of patients with cancers. A. The forest plot exhibiting the pooled HR and the corresponding 95% CI. B. Funnel plot analysis investigating the publication bias.

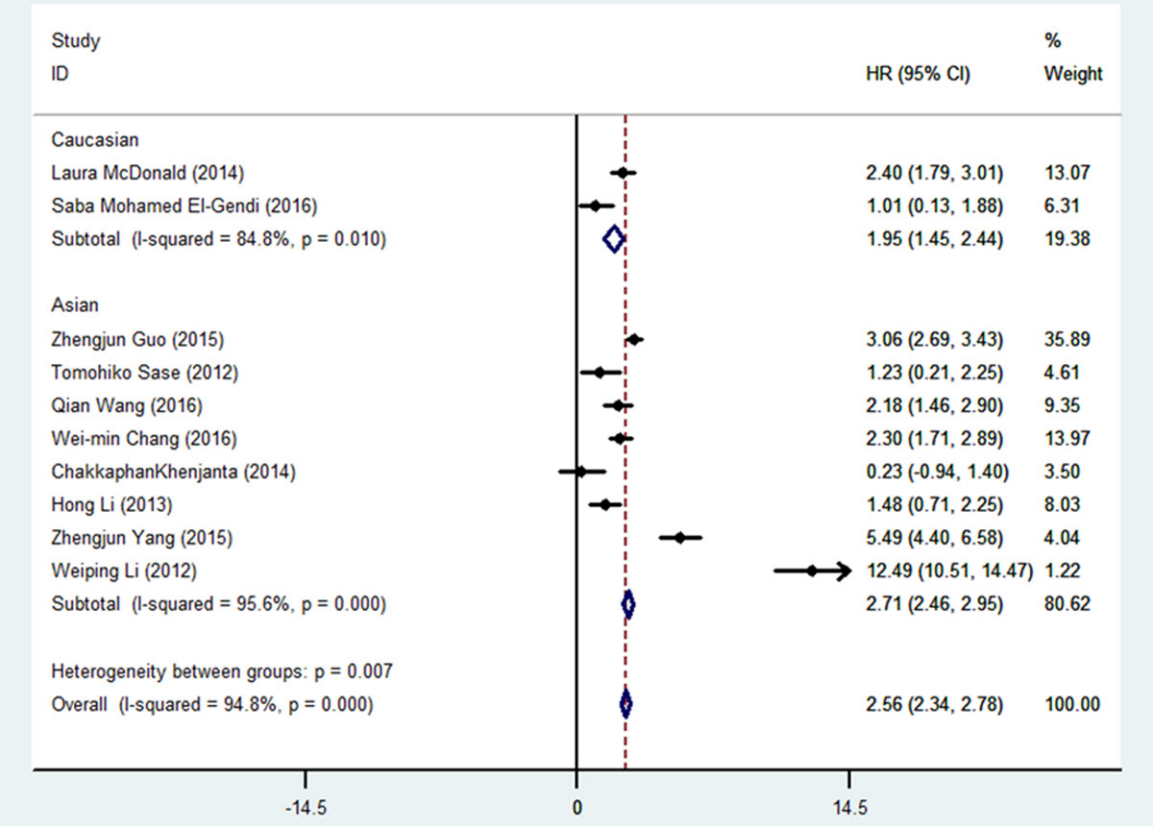

Figure 3. Subgroup analysis results based on ethnicity.

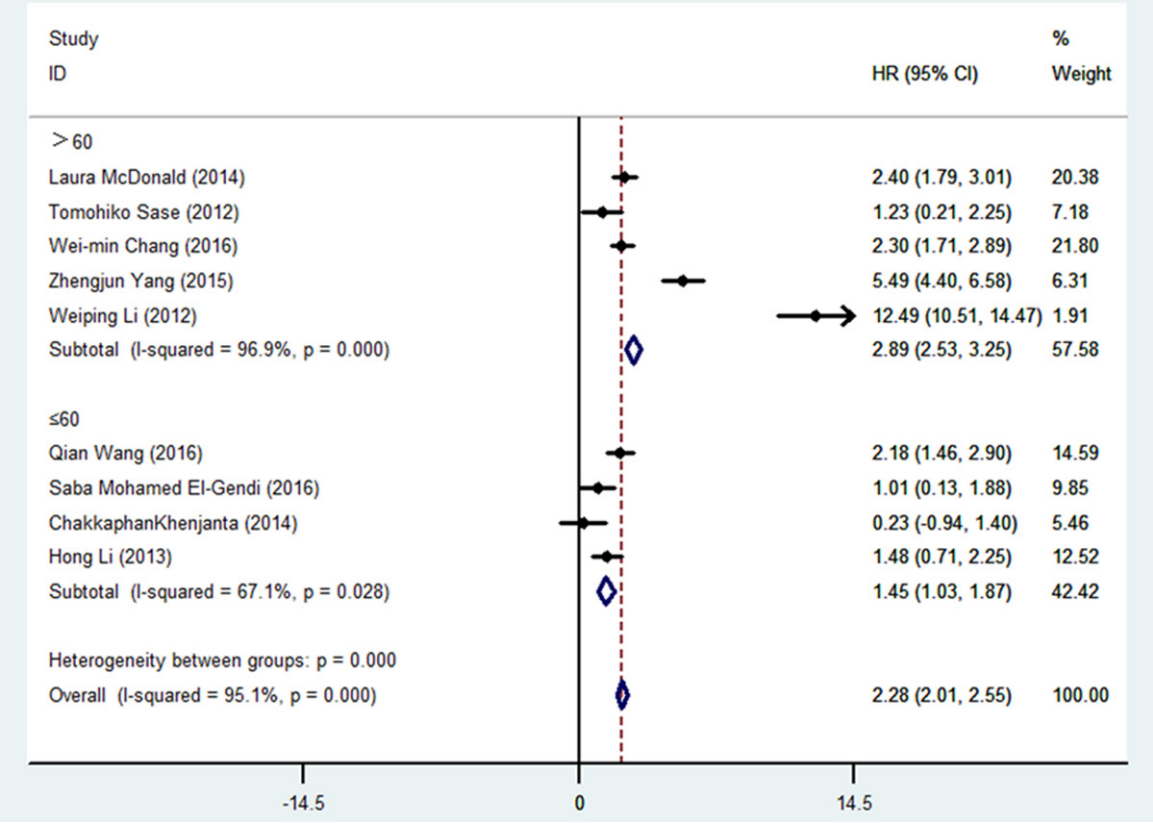

Figure 4. Subgroup analysis results based on duration of follow-up.

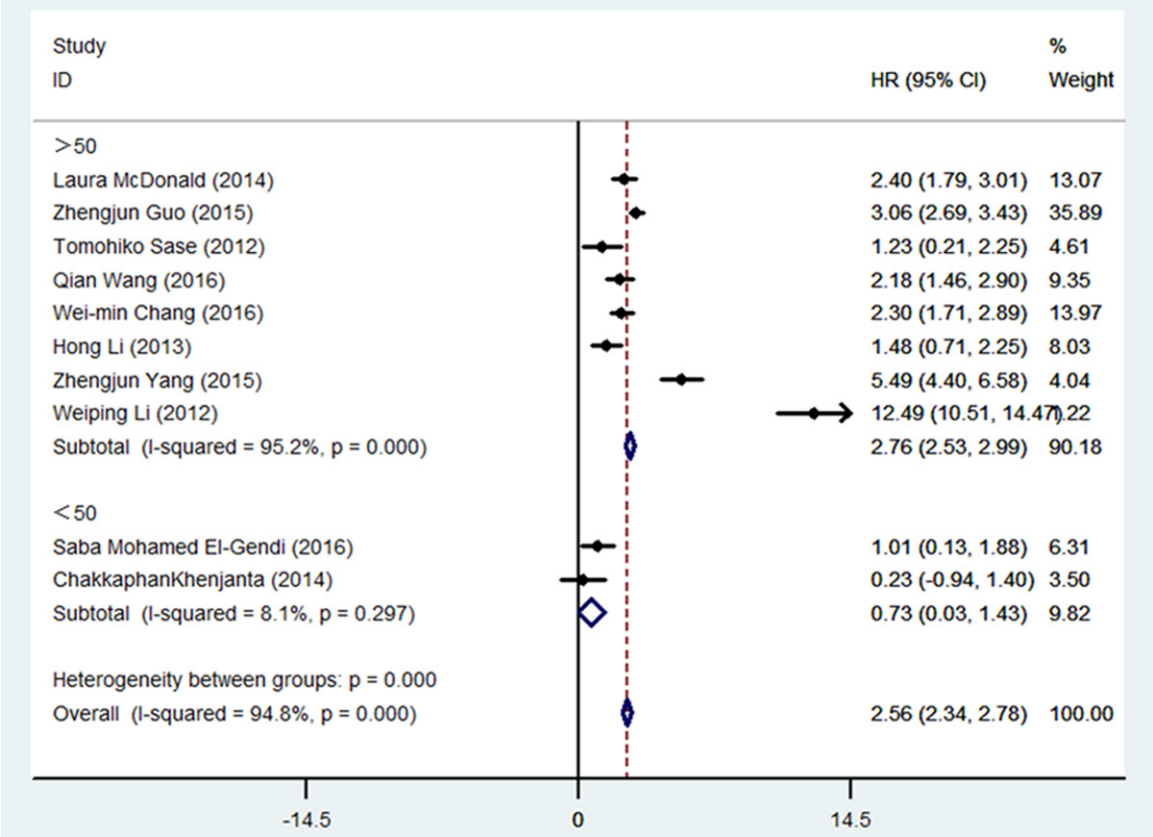

Figure 5. Subgroup analysis results based on sample size.

sis model to estimate the prognostic value of Runx2 and 3 studies used Multivariate and Univariate analysis model.

Quality assessment

We used the Newcastle-Ottawa Scale (NOS) to conduct the quality evaluation of each study enrolled in our meta-analysis. We evaluate the studies through 3 domains: selection, comparability and exposure. Studies scored from 6 to 9 after all the stars added up, and were considered as high quality based on our evaluation system. The results were presented in **Table 2**.

Polled diagnostic values

A random-effects model was used to conduct the overall analysis due to the high heterogeneity (I^2=94.8%, P<0.00001). The results indicated that Runx2 overexpression was significantly associated with poor overall survivor of cancer patients (HR=2.56, 95% CI=2.34-2.78, **Figure 2**). To explore the potential sources of the OS heterogeneity, subgroup analysis were also conducted based on ethnicity (**Figure 3**), median follow-up time (**Figure 4**), sample size (**Figure 5**), country (**Figure 6**) and analysis model (**Figure 7**). In subgroup analysis based on ethnicity, the results suggested that the high level of Runx2 was associated with a worse outcome in Asian (HR=2.71, 95% CI=2.46-2.95) compared to Caucasian (HR=1.95, 95% CI=1.45-2.44). When stratified by follow-up time, the results indicated that the overexpression predicted a poor outcome of cancer patients in the group >60 (HR=2.89, 95% CI=2.53-3.25) and group <60 (HR=2.28, 95% CI=2.01-2.55). In subgroup analysis stratified by sample size, the high expression was associated with much worse outcome of cancer patients in the group with more than 50 cases (HR=2.76, 95% CI=2.53-2.99) compared to the group with less

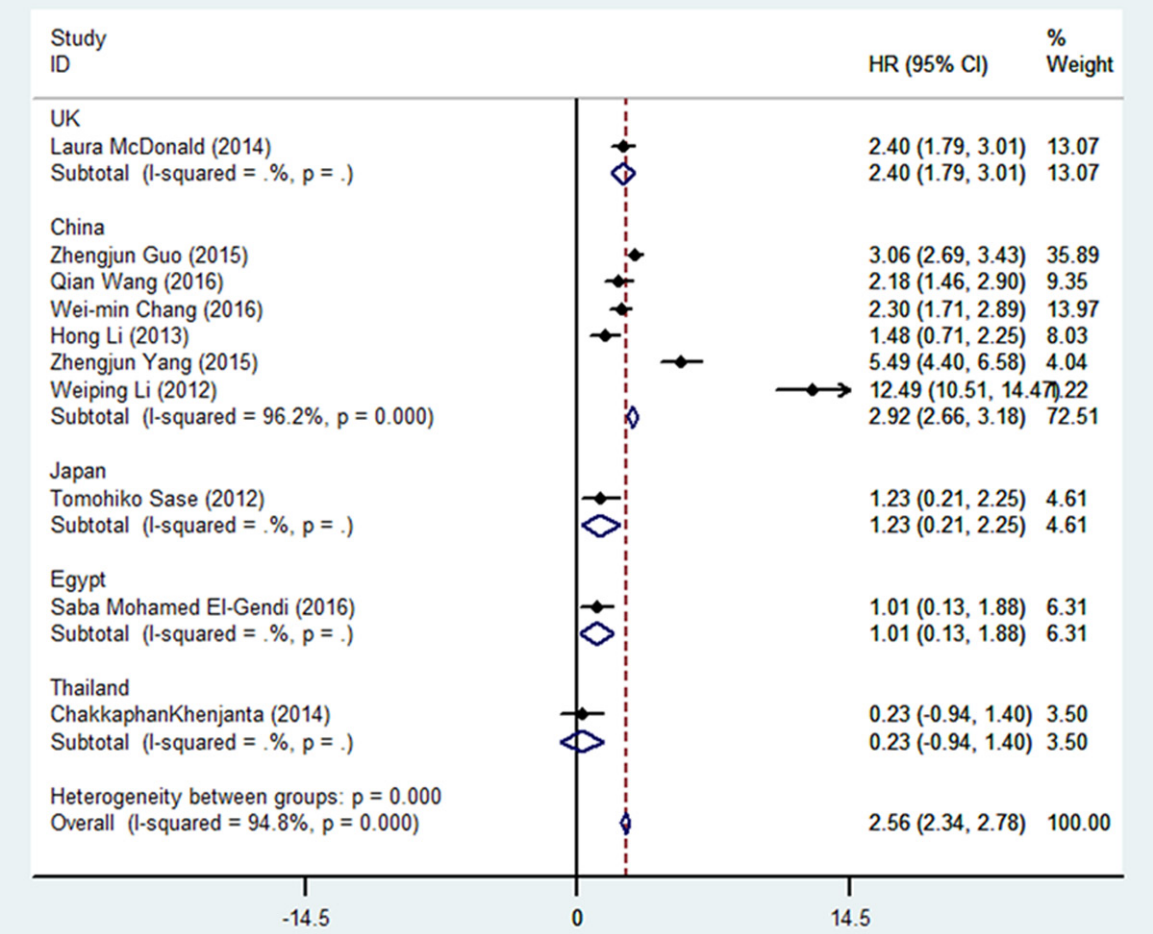

Figure 6. Subgroup analysis results based on country.

than 50 cases (HR=0.73, 95% CI=0.03-1.42). 10 studies used Multivariate analysis model to poll the prognostic value of Runx2 and the results indicated that overexpression of Runx2 was significantly related with poor survival of cancer patients (HR=2.38, 95% CI=2.13-2.63). The similar results were presented in the analysis using Univariate analysis model (HR=3.43, 95% CI=2.95-3.90). When stratified by country, the overexpression of Runx2 predicted a worse overall survivor in Chinese cancer patients (HR=2.92, 95% CI=2.66-3.18), especially. We also conducted a polled analysis to estimate the high expression of Runx2 with the PFS/DFS/RFS, the results showed that high level of Runx2 predicted a poor outcome of cancers (HR=2.66, 95% CI=2.35-2.97, **Figure 8**). The summary of overall and subgroup analysis evaluating the relationship between Runx2 expression and the outcome of cancers presented in **Table 3**.

Publication bias and sensitivity analysis

To investigate the publication bias in our meta-analysis, Begg's and Egger's test were conducted and the results indicated that no publication bias was observed in our meta-analysis (**Figure 9**). We also performed a Trim-and-fill analysis to illustrate the paradox between Begg's and Egger's test, and the data showed the same results after correction (**Figure 9**). By omitting a study each time, we conducted a sensitivity analysis to assess the stability of our results. The pooled HR was ranging from 1.43 to 3.42, indicating that our results were quite steady (**Figure 10**).

Discussion

As a transcription factor Runx2 has been regarded as a critical regulator during a variety of pathological and biological processes, such as proliferation, metastasis, invasion and

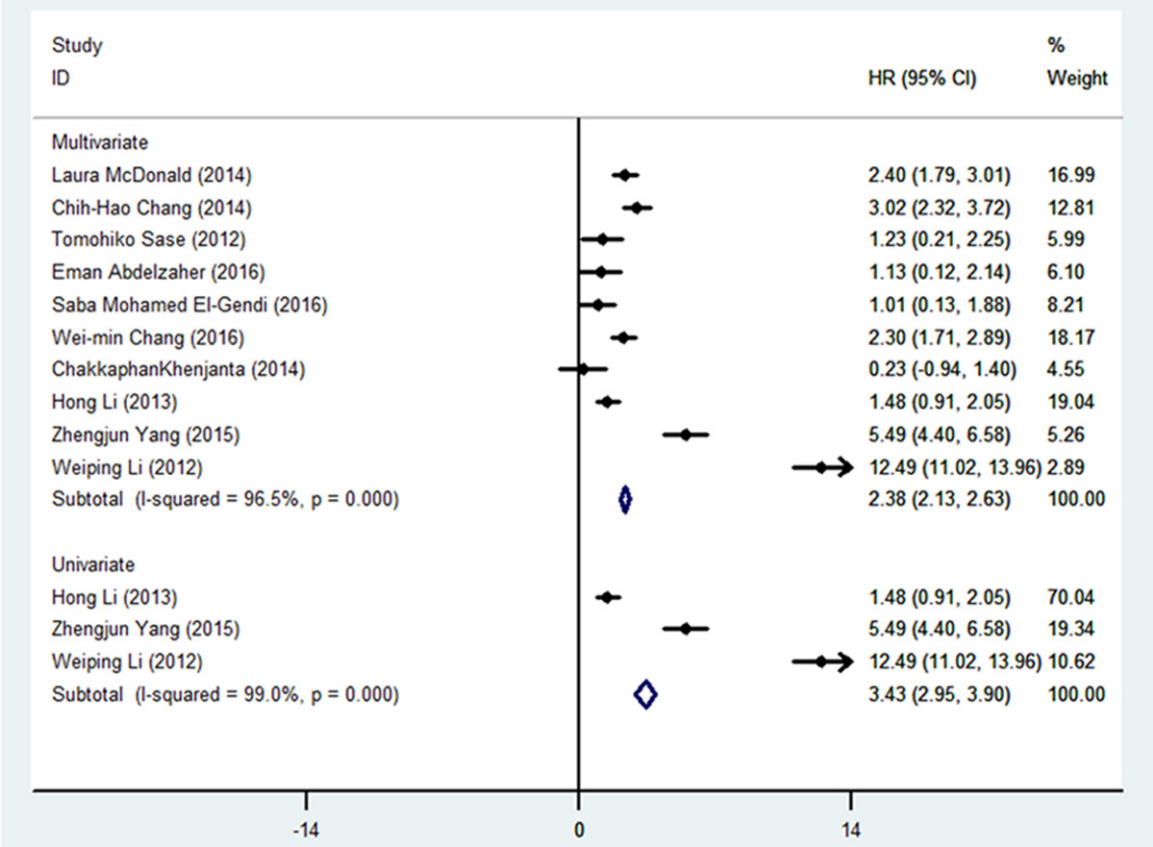

Figure 7. Subgroup analysis results based on analysis model.

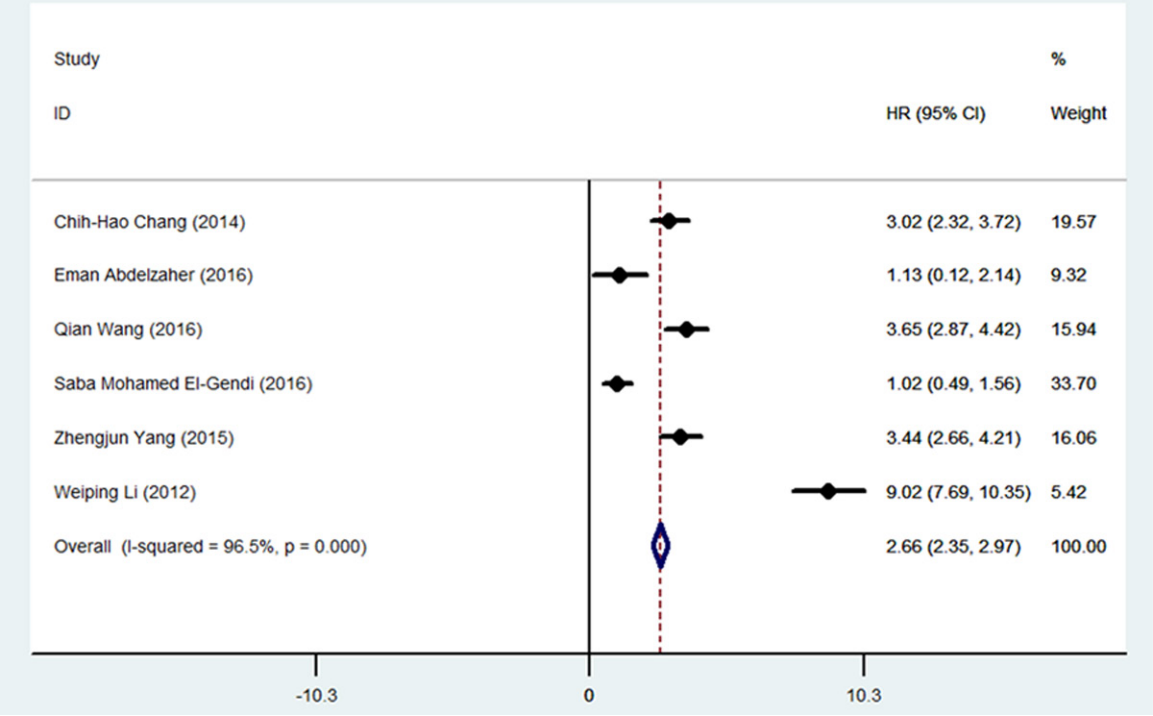

Figure 8. The forest plot exhibiting the relationship between Runx2 expression and PFS/DFS/RFS of patients with cancers.

Table 3. A summary of overall and subgroup analysis evaluating the relationship between Runx2 expression and the outcome of cancers

Categories	Cohorts (n)	HR (95% CI)	*P* Value	I^2 (%)	Model types
OS	10 (1465)	2.56 (2.34-2.78)	<0.00001	94.8	Random-effects
PFS/DFS/RFS	6 (616)	2.66 (2.35-2.97)	<0.00001	96.5	Random-effects
Ethnicity					
Asian	8 (1037)	2.71 (2.46-2.95)	<0.00001	95.6	Random-effects
Caucasian	2 (428)	1.95 (1.45-2.44)	<0.00001	84.8	Random-effects
Median follow-up time (m)					
>60	4 (869)	2.89 (2.53-3.25)	<0.00001	96.9	Random-effects
<60	4 (291)	2.28 (2.01-2.55)	<0.00001	67.1	Random-effects
Sample size					
>50	5 (1391)	2.76 (2.53-2.99)	<0.00001	95.2	Random-effects
<50	2 (74)	0.73 (0.03-1.42)	0.297	8.1	Fixed-effects
Analysis type					
Multivariate	10 (1299)	2.38 (2.13-2.63)	<0.00001	96.5	Random-effects
Univariate	3 (362)	3.43 (2.95-3.90)	<0.00001	99.0	Random-effects
Country					
UK	1 (384)	2.40 (1.79-3.01)	-	-	-
China	6 (850)	2.92 (2.66-3.18)	<0.00001	96.2	Random-effects
Japan	1 (157)	1.23 (0.21-2.25)	-	-	-
Egypt	1 (44)	1.01 (0.13-1.88)	-	-	-
Thailand	1 (30)	0.23 (0.94-1.40)	-	-	-

tumor progression [28]. Passaniti A *et al.* demonstrated that Runx2 inhibited the YAP-TEAD complex to promote the epithelial to mesenchymal transition in human cancer [29]. Bendre A *et al.* reported that Runx2 could be regulated by deregulation of Fam3c during the osteoblast differentiation, which might provide a new therapeutic strategy [30]. Recently, a number of researchers have focused on the potential effects of Runx2 in various cancers [31, 32]. However, the underlying effects were uncertain when assessing the association between effect of Runx2 and the survival of cancer patients. Thus, we performed a systematically analysis to illustrate the effects of Runx2 expression in cancers.

This might be the first meta-analysis to investigate the prognostic value of Runx2 in cancers. In the present study, 12 studies enrolled 1700 cancer patients were pooled. The results suggest that cancer patients with high expression of Runx2 have a worse outcome than those with low expression of Runx2 (HR=2.56, 95% CI=2.34-2.78). We further investigated the predict value of Runx2 among ethnicity, and the results indicated that the high level of Runx2 was related with a worse survival condition in Asian (HR= 2.71, 95% CI=2.462.95) compared to Caucasian (HR=1.95, 95% CI=1.45-2.44). This slight difference may be generated by the genetic inheritance. A study [33] from Japan indicated that abnormal expression of Runx2 was associated with clediocranial dysplasia, which is consistent with our results. Meanwhile, the subgroup analysis based on the duration of follow-up time demonstrated that studies with large size of sample tented to have a much worse outcome (HR=2.76, 95% CI=2.53-2.99) compare to the studies with small sample size (HR=0.73, 95% CI=0.03-1.42). The underlying mechanisms are unclear due to the limitation of Runx2 research. It is well accepted that the function of the Runx2 largely depends on the location and the normal expression. High level of Runx2 expression is inevitably translocated into the nuclear, thus leading to the increased transcription of downstream proteins.

However, there are still some limitations existed in our meta-analysis. Firstly, 12 studies including 1700 cases enrolled in our analysis were relatively small. More studies focused on the prognostic value of Runx2 in cancers are encouraged to confirm our conclusion. Secondly, software Engauge Digitizer 4.1 was

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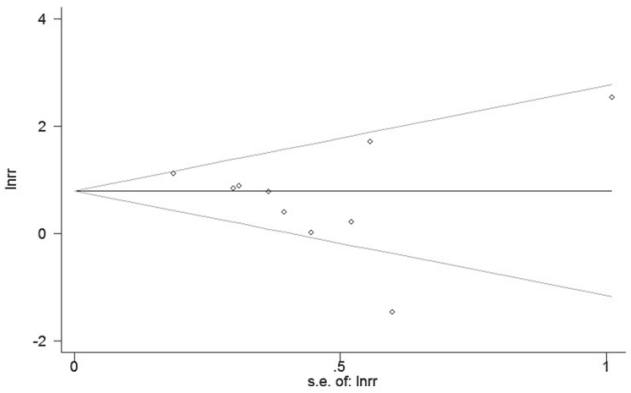

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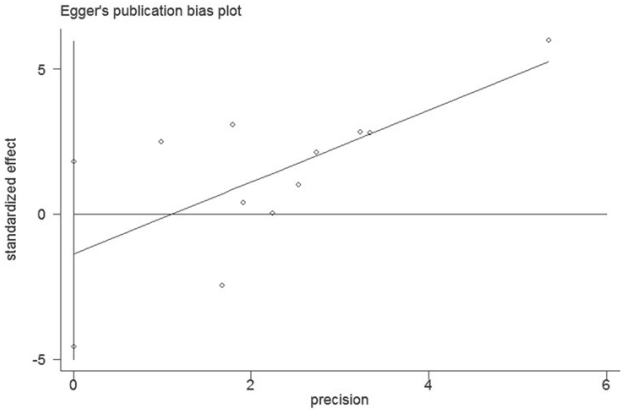

C

Begg's Test

adj. Kendall's Score (P-Q)	-13
Std. Dev. of Score	11.18
Number of Studies	10
z	-1.16
Pr > |z|	0.245
z	1.07 (continuity corrected)
Pr > |z|	0.283 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.239864	.4888956	2.54	0.035	.1124693	2.36726
bias	-1.376271	1.381155	-1.00	0.348	-4.56122	1.808679

D

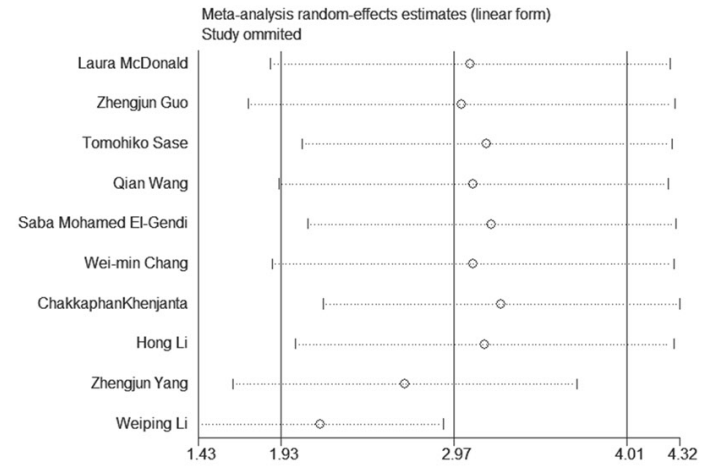

Figure 9. Measurement of publication bias with Begg's and Egger's test. A. Begg's funnel plot with pseudo 95% confidence limits. B. Egger's publication bias plot. C. Test for publication bias. D. The results of Trim and Filling method.

used to estimate the data in some studies, thereby, the calculation error was inevitable. Thirdly, the studies included in our analysis involved 8 types of cancers; each type of them has less than two studies to estimate the pooled effects. Finally, during the determination of high expression of Runx2, the cut-off value was quite different among studies based on the IHC detection. Therefore, more studies are needed to confirm our results for further evaluation the prognostic value of Runx2 high expression in cancer patients.

The present meta-analysis demonstrated that overexpression of Runx2 is significantly associated with the survival of cancer patients and predict a poor prognosis in cancer. Our study suggested Runx2 might serve as a biomarker and could predict prognosis in cancers.

Acknowledgements

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Disclosure of conflict of interest

None.

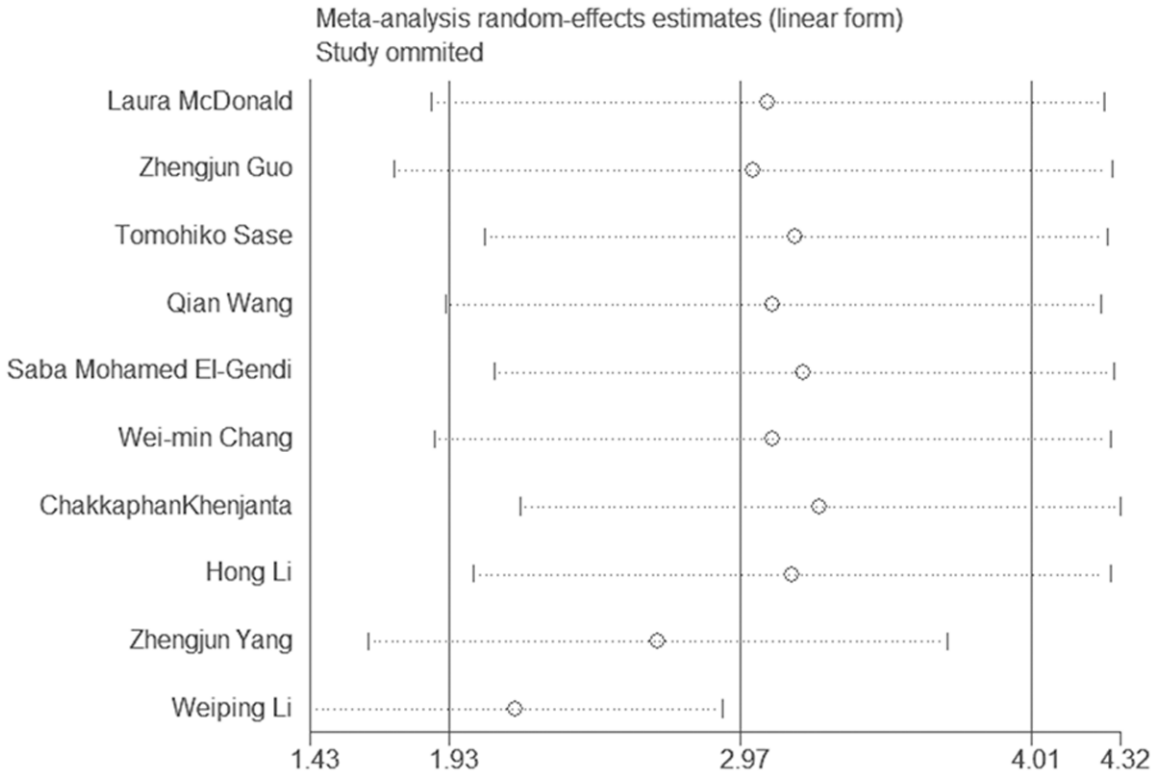

Figure 10. Sensitivity test among studies included.

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