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Review Article

Prognostic and clinicopathological implication of long non-coding RNA CCAT2 in various malignancies: a meta-analysis

Yue Ma[1,2*], Shan Zhu[3*], Shuai Wu[4], Chunquan Zheng[1,2]

[1]Department of Otolaryngology-Head and Neck Surgery, Eye Ear Nose and Throat Hospital, Fudan University, Shanghai, China; [2]Shanghai Key Clinical Disciplines of Otorhinolaryngology, Shanghai, China; [3]School of Medicine, Shandong University, Jinan, China; [4]Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai, China. [*]Equal contributors.

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Abstract: Purpose: Colon cancer-associated transcript 2 (CCAT2) is a recently discovered, long, non-coding RNA (lncRNA) that has been reported to be aberrantly expressed in various tumor tissues. To clarify the clinical value of CCAT2 in human cancers, a meta-analysis was performed. Methods: We searched the PubMed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Wanfang that had been published prior to January 14, 2017. According to rigorous inclusion and exclusion criteria, 13 relevant articles with a patient population of 1389 were selected. Then, we extracted original data reflecting the clinicopathological characteristics and prognosis of cancer patients, and we calculated a pooled hazard ratio (HR) or odds ratio (OR) with a 95% confidence interval (CI). Results: The aggregated results of this meta-analysis demonstrated that upregulated CCAT2 indicated poor prognosis for cancers regarding both the overall survival (OS) (HR=2.36, 95% CI=1.92-2.91, P=0.000, high to low) and other combined prognostic indicators (HR=2.19, 95% CI=1.79-2.69, P=0.000, high to low), including progression-free survival/relapse-free survival/disease-free survival/metastasis-free survival (PFS/RFS/DFS/MFS). Moreover, it also indicated that elevated expression of CCAT2 was positively associated with advanced clinical stage (III+IV: OR=3.89, 95% CI=1.80-8.43; P=0.001), deep local invasion (T3+T4: OR=1.85, 95% CI=1.20-2.85; P=0.005), positive lymphatic metastasis (OR=2.75, 95% CI=1.60-4.70; P=0.000) and positive distal metastasis (OR=4.38, 95% CI=1.58-12.15; P=0.005). Conclusions: CCAT2 could be a promising diagnostic biomarker for the prognosis and related clinicopathology of malignancies.

Keywords: CCAT2, cancers, prognosis, clinicopathology, meta-analysis

Introduction

Cancer has long been a challenge in the field of public health for its high morbidity and mortality [1]. In recent years, increasing interests have focused on novel biomarkers for the clinicopathology and prognosis of human cancers with an aim toward more efficacious treatments.

With revolutions in technologies, an increasing number of studies have confirmed that non-coding RNAs, which used to be considered merely as transcriptional noise or cloning artifacts, are indispensable in various biological processes [2]. Long non-coding RNAs (lncRNAs) (RNAs with more than 200 nucleotides and almost no protein-coding capacity) have aroused mounting interests for their critical role in tumorigenesis and progression [2, 3]. Investigations have proposed that lncRNA may be novel biomarkers and therapeutic targets of tumors.

Overexpression of CCAT2 has recently been reported in microsatellite-stable colorectal cancer (MSS CRC) as a transcript of chromosome 8q24, which is a highly conserved region harboring a single nucleotide polymorphism rs6983267. This single nucleotide polymorphism is closely associated to increased risk for malignancies [4]. It has been uncovered that CCAT2 could induce tumorigenesis, invasion, metastasis, and the reprogramming of cancer metabolism by upregulating the wnt signaling pathway

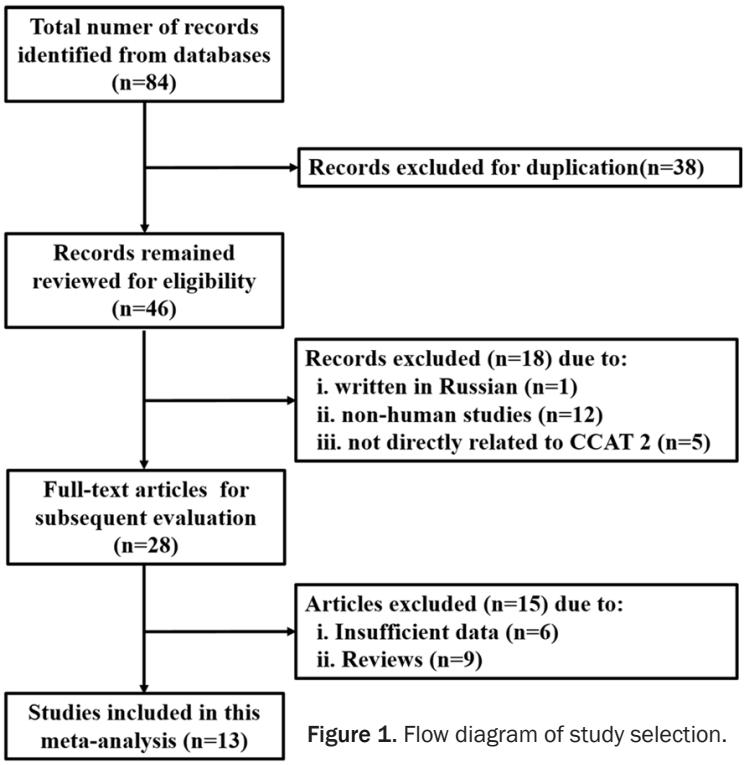


Figure 1. Flow diagram of study selection.

and increasing the expression levels of corresponding genes, including MYC, which is known to coordinate multiple molecular pathways [4, 5]. Nonetheless, the detailed mechanism has not yet been fully defined.

A growing number of studies have also revealed that the expression of CCAT2 was upregulated in a variety of human cancers and was associated with prognosis and clinicopathology [4, 6-17]. Based on those facts, we performed this meta-analysis to evaluate its potential as a novel biomarker.

Methods and materials

As a first step, on-line databases such as PubMed, Embase, Cochrane library, Chinese National Knowledge Infrastructure (CNKI), and Wanfang were searched for all potential articles updated to January 14, 2017. We used both MeSH terms and free-text words to increase searching sensitivity. The following were used as searching terms: "CCAT2", "CCAT 2", "CCAT-2", as well as "colon cancer-associated transcript 2". All references in these articles were also screened for any relevant studies.

Study identification

Two investigators independently assessed all relevant articles according to the following inclusion criterias: (1) the expression levels of CCAT2 detected in primary tumor tissues by quantitative real-time PCR (q-RT-PCR); (2) the prognostic or clinicopathological features reported; (3) whether there was adequate information for a hazard ratio (HR) and associated 95% confidence interval (CI); (4) high and low expression groups of patients divided according to a reasonable cut-off of CCAT2 level. The exclusion criterias were: (1) reviews, letters, commentaries, case reports, or experiments with animal models or cell lines; (2) insufficient data for pooled results; (3) if articles were written in another language except for English and Chinese. Disagreements were discussed with a third investigator until a consensus was reached. For duplicated articles, only the one with the most comprehensive population and data was included.

Data extraction

Data from all selected articles were collected by two investigators independently. The two investigators collected the authors' names, publication years, population of each study, patients' detailed information (age, gender, tumor size, histological and clinical stages, and lymphatic and distant metastasis), cut-off value, duration of follow-up, HRs with their 95% CIs for OS or other prognostic indicators such as PFS, RFS, DFS or MFS.

Quality control

Since all included studies were non-randomized studies, quality control was conducted according to the Newcastle-Ottawa assessment scale (NOS) [18]. Articles were excluded when the NOS score was lower than six. Any discrepancies were solved by discussion until a consensus was reached.

Table 1. Characteristics of the included studies

First Author	Country	Cancer type	Studied population	Tumor stage	Follow-up (months)	Cut-off of CCAT2 expression	Detection method	Outcome measures	Multivariate analysis	NOS
Yong-Jun Wang (2016)	China	GC	108	54/54 (I-II/III-IV)	Over 60	Median level	qRT-PCR	OS & DFS	Yes	9
Yuta Kasagi (2016)	Japan	CRC	149	NA	Over 60	95% CI	qRT-PCR	OS & RFS	No	8
Shi-Feng Chen (2016)	China	SCLC	112	Limited/extensive (32/80)	60	Median level	qRT-PCR	OS	Yes	9
Jin-Feng Zheng (2016)	China	PC	96	NA	60	Mean level	qRT-PCR	OS & PFS	Yes	9
Shu-Ying Huang (2016)	China	OC	109	33/76 (I-II/III-IV)	60	Mean level	qRT-PCR	OS & DFS	Yes	9
Jian-Fa Li (2016)	China	BlaC	48	12/36 (0-I/II-III-IV)	/	NA	qRT-PCR	/	/	/
Zhen-Hai Lu (2016)	China	CC	102	47/55 (A-B/C-D)	/	Level of non-tumorous tissue	qRT-PCR	/	/	/
Yi Cai (2015)	China	BC	67	NA	60	Eight-fold change	qRT-PCR	OS	No	8
Xin Chen (2015)	China	CSCC	123	62/61 (Ib-IIa/IIb-IIIa)	60	Median level	qRT-PCR	OS & PFS	Yes	8
Yi-Min Hu (2015)	China	RCC	32	20/12 (I-II/III-IV)	/	Mean level	qRT-PCR	/	/	/
Xue-Ling Zhang (2014)	China	ESCC	229	125/100 (I-II/III-IV)	66	Median level	qRT-PCR	OS	Yes	8
Chen-Yu Wang (2014)	China	GC	85	43/42 (I-II/III-IV)	60			OS & PFS	Yes	9
Hui Ling (2013)	Netherlands	BC	129	NA	120	Median level	qRT-PCR	MFS	Yes	7

Abbreviations: GC, gastric cancer; CRC, colorectal cancer; SCLC,small cell lung cancer; PC, prostate cancer; OC, ovarian cancer; BlaC, bladder cancer; CC, colon cancer; BC, breast cancer; CSCC, cervical squamous cell cancer; RCC, renal carcinoma; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; OS, overall survival; DFS, disease-free survival; MFS, metastasis-free survival; qRT-PCR, quantitative real-time-polymerase chain reaction; NA, not available.

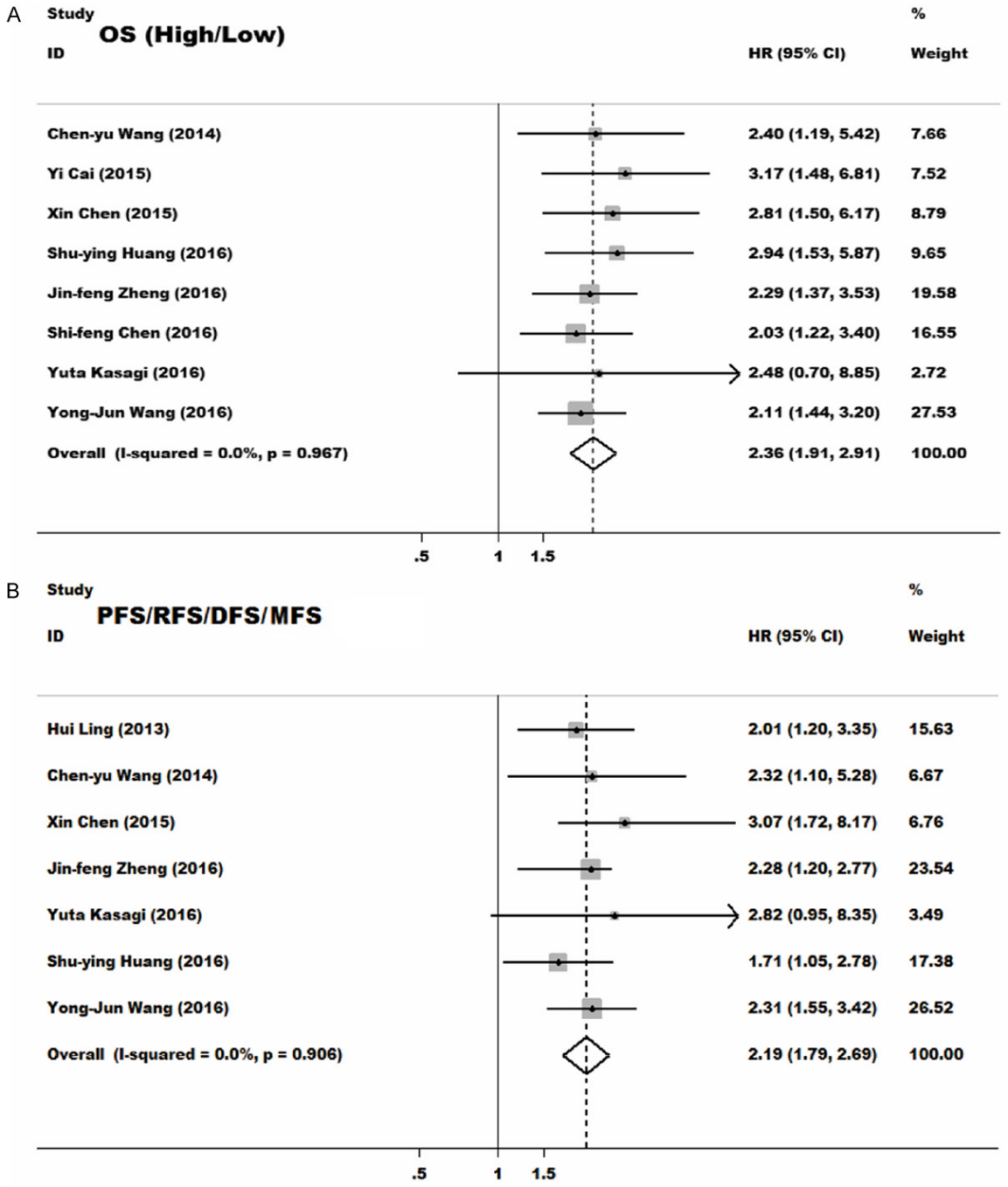


Figure 2. Meta-analysis for the association between CCAT2 and OS (A) and PFS/RFS/DFS/MFS (B) of cancer.

Statistical analysis

The role of CCAT2 as a novel biomarker for malignancies under study was evaluated by pooled HRs with their corresponding 95% CIs of OS, PFS, RFS, DFS or MFS from the primary studies. The impact of CCAT2 on clinicopathological features was evaluated by odds ratios (ORs). Reported HRs and their 95% CIs were extracted directly from the articles. When direct HRs and their 95% CIs values were not available, estimating methods reported by Tierney et al. [19] and Parmar et al. [20] were used. In regard to between-study heterogeneity, we applied the I^2 metric and Q test. A random-effects model was chosen to deal with significant heterogeneity (I^2>50% or P<0.1); otherwise, a fixed-effects model was applied. Sen-

Table 2. Pooled results of the association between over-expressed CCAT2 and clinicopathological parameters

Clinicopathological parameter	Studies (n)	Number of Patients	OR (95% CI)	*P*-value	Heterogeneity		
					I^2 (%)	P_h	Model
Age (Old vs. Young)	10	1044	1.01 (0.79-1.30)	0.919	0.0	0.719	Fixed effects
Gender (Female vs. Male)	8	865	0.96 (0.72-1.29)	0.791	0.0	0.968	Fixed effects
Tumor size (Large vs. Small)	9	1012	1.07 (0.70-1.62)	0.765	61.9	0.007	Random effects
Local invasion (T3/T4 vs. T1/T2)	5	593	1.85 (1.20-2.85)	0.005	17.8	0.301	Fixed effects
Lymph node metastasis (Present vs. absent)	9	1052	2.75 (1.60-4.70)	0.000	69.6	0.001	Random effects
Distal metastasis (Present vs. absent)	6	653	4.38 (1.58-12.15)	0.005	77.7	0.000	Random effects
Differentiation (Poor vs. Well/moderate)	9	1049	1.76 (0.98-3.16)	0.04	73.3	0.000	Random effects
Clinical stage (III/IV vs. I/II)	5	553	3.89 (1.80-8.43)	0.001	73.3	0.005	Random effects

sitivity analysis was also performed to assess the validity and reliability of the pooled results, and $P<0.05$ was considered statistically significant. Funnel plots as well as Begg's and Egger's test were introduced to avoid potential publication bias. Statistical analyses were all carried out using the STATA 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Search results and study characteristics

Details in our searching process for this meta-analysis are shown in **Figure 1**. A total of 84 articles were identified from selected databases. After excluding 38 duplicated articles, 46 articles remained for further reading. After detailed evaluation, 13 articles with 1389 patients in total were included in the current meta-analysis according to the inclusion and exclusion criteria described above. Among 13 eligible studies published from 2013 to 2016, 1 came from Japan, 1 from Netherlands, and the remaining 11 were conducted in China. Eleven different types of malignancies were covered in our selected studies, including two breast cancer (BC) studies, one colorectal cancer (CRC), one small cell lung cancer (SCLC), one prostate cancer (PC), one ovarian cancer (OC), one bladder cancer (BlaC), one colon cancer (CC), one cervical squamous cell cancer (CSCC), one renal cell carcinoma (RCC), one esophageal squamous cell cancer (ESCC), and two gastric cancer (GC). Ten studies reported the OS of cancer patients, while seven were concerned with the PFS/RFS/DFS.

Further information on the characteristics of the included 13 studies has been summarized in **Table 1**, and all studies have been assessed to be of high quality using the NOS (Table S1).

Expression of CCAT2 and prognosis of tumor patients

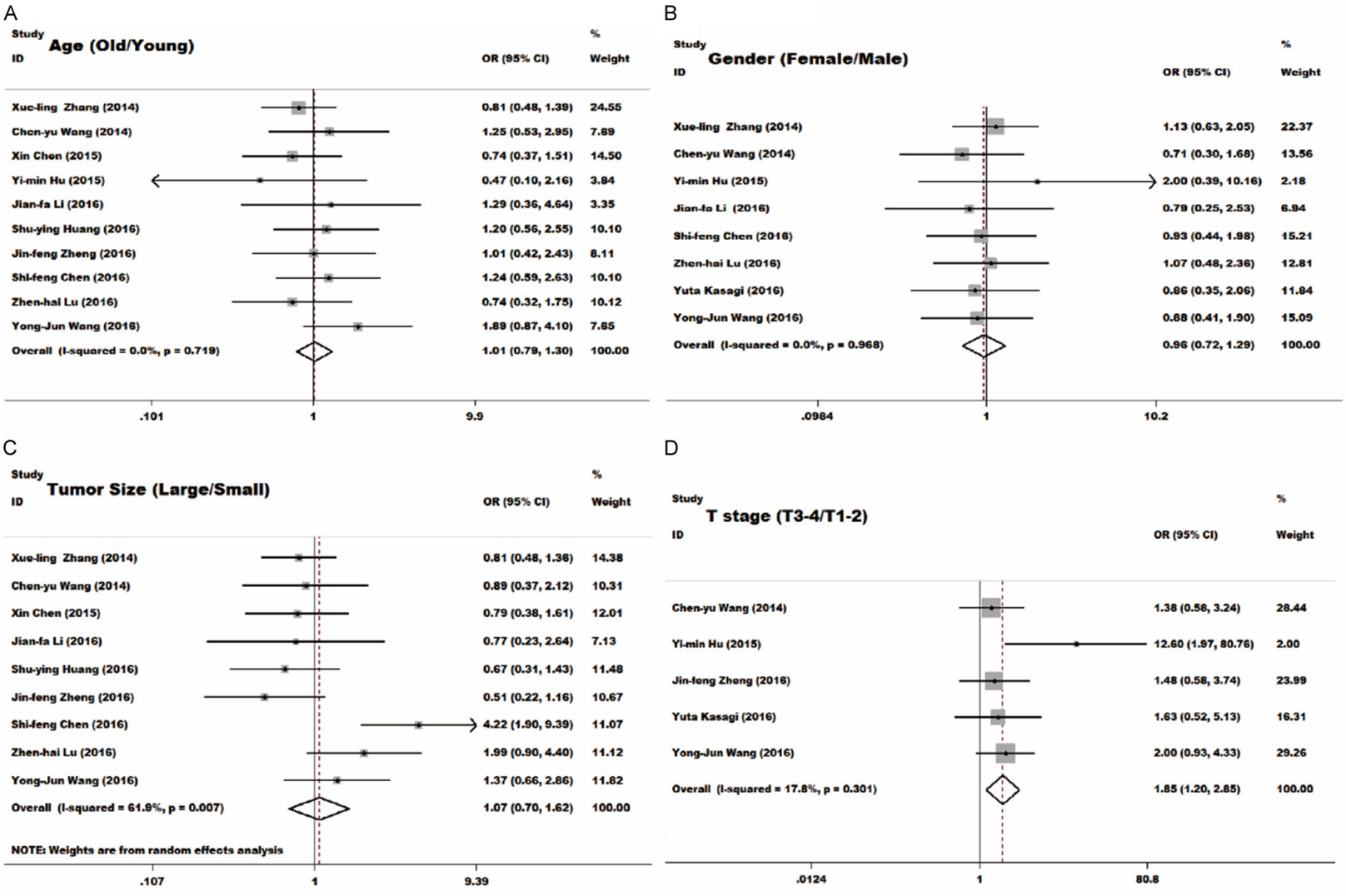
While the measures for tumor prognosis, so far, were dazzling, we divided them into two groups according to outcome events, one of which was OS with an event of death from any cause, and the other was combined prognostic indicators (PFS/RFS/DFS/MFS) with events of recurrence or metastasis rather than death.

The OS has been reported in nine studies. However due to the significance of publication bias and subsequent sensitivity analysis (further discussed below), data in eight out of nine studies were used (**Figure 2A**). Seven studies reported other combined prognostic indicators (PFS/RFS/DFS/MFS) (**Figure 2B**). In these, no significant heterogeneity and publication bias were observed. It was found that high level of CCAT2 expression might be associated with poor prognosis for cancer regarding both the OS (HR=2.36, 95% CI=1.92-2.91, P=0.000, high to low) and PFS/RFS/DFS/MFS (HR=2.19, 95% CI=1.79-2.69, P=0.000, high to low) of patients.

Expression of CCAT2 and clinicopathological features

The data on key clinicopathological features (age, gender, tumor size, local invasion, lymphatic and distal metastasis, histological differentiation, and clinical stage) of the involved cancer patients has been collected, calculated, and presented in **Table 2**.

The pooled ORs (**Figure 3A-H**) have shown that upregulation of CCAT2 is significantly associat-


A
Study ID
Age (Old/Young)
OR (95% CI)
% Weight
Xue-ling Zhang (2014) 0.81 (0.48, 1.39) 24.55
Chen-yu Wang (2014) 1.25 (0.53, 2.95) 7.69
Xin Chen (2015) 0.74 (0.37, 1.51) 14.50
Yi-min Hu (2015) 0.47 (0.10, 2.16) 3.84
Jian-fa Li (2016) 1.29 (0.36, 4.64) 3.35
Shu-ying Huang (2016) 1.20 (0.56, 2.55) 10.10
Jin-feng Zheng (2016) 1.01 (0.42, 2.43) 8.11
Shi-feng Chen (2016) 1.24 (0.59, 2.63) 10.10
Zhen-hai Lu (2016) 0.74 (0.32, 1.75) 10.12
Yong-Jun Wang (2016) 1.89 (0.87, 4.10) 7.65
Overall (I-squared = 0.0%, p = 0.719) 1.01 (0.79, 1.30) 100.00
.101
1
9.9
B
Study ID
Gender (Female/Male)
OR (95% CI)
% Weight
Xue-ling Zhang (2014) 1.13 (0.63, 2.05) 22.37
Chen-yu Wang (2014) 0.71 (0.30, 1.68) 13.56
Yi-min Hu (2015) 2.00 (0.39, 10.16) 2.18
Jian-fa Li (2016) 0.79 (0.25, 2.53) 6.94
Shi-feng Chen (2016) 0.93 (0.44, 1.98) 15.21
Zhen-hai Lu (2016) 1.07 (0.48, 2.36) 12.81
Yuta Kasagi (2016) 0.86 (0.35, 2.06) 11.84
Yong-Jun Wang (2016) 0.88 (0.41, 1.90) 15.09
Overall (I-squared = 0.0%, p = 0.968) 0.96 (0.72, 1.29) 100.00
.0984
1
10.2
C
Study ID
Tumor Size (Large/Small)
OR (95% CI)
% Weight
Xue-ling Zhang (2014) 0.81 (0.48, 1.36) 14.38
Chen-yu Wang (2014) 0.89 (0.37, 2.12) 10.31
Xin Chen (2015) 0.79 (0.38, 1.61) 12.01
Jian-fa Li (2016) 0.77 (0.23, 2.64) 7.13
Shu-ying Huang (2016) 0.67 (0.31, 1.43) 11.48
Jin-feng Zheng (2016) 0.51 (0.22, 1.16) 10.67
Shi-feng Chen (2016) 4.22 (1.90, 9.39) 11.07
Zhen-hai Lu (2016) 1.99 (0.90, 4.40) 11.12
Yong-Jun Wang (2016) 1.37 (0.66, 2.86) 11.82
Overall (I-squared = 61.9%, p = 0.007) 1.07 (0.70, 1.62) 100.00
NOTE: Weights are from random effects analysis
.107
1
9.39
D
Study ID
T stage (T3-4/T1-2)
OR (95% CI)
% Weight
Chen-yu Wang (2014) 1.38 (0.58, 3.24) 28.44
Yi-min Hu (2015) 12.60 (1.97, 80.76) 2.00
Jin-feng Zheng (2016) 1.48 (0.58, 3.74) 23.99
Yuta Kasagi (2016) 1.63 (0.52, 5.13) 16.31
Yong-Jun Wang (2016) 2.00 (0.93, 4.33) 29.26
Overall (I-squared = 17.8%, p = 0.301) 1.85 (1.20, 2.85) 100.00
.0124
1
80.8

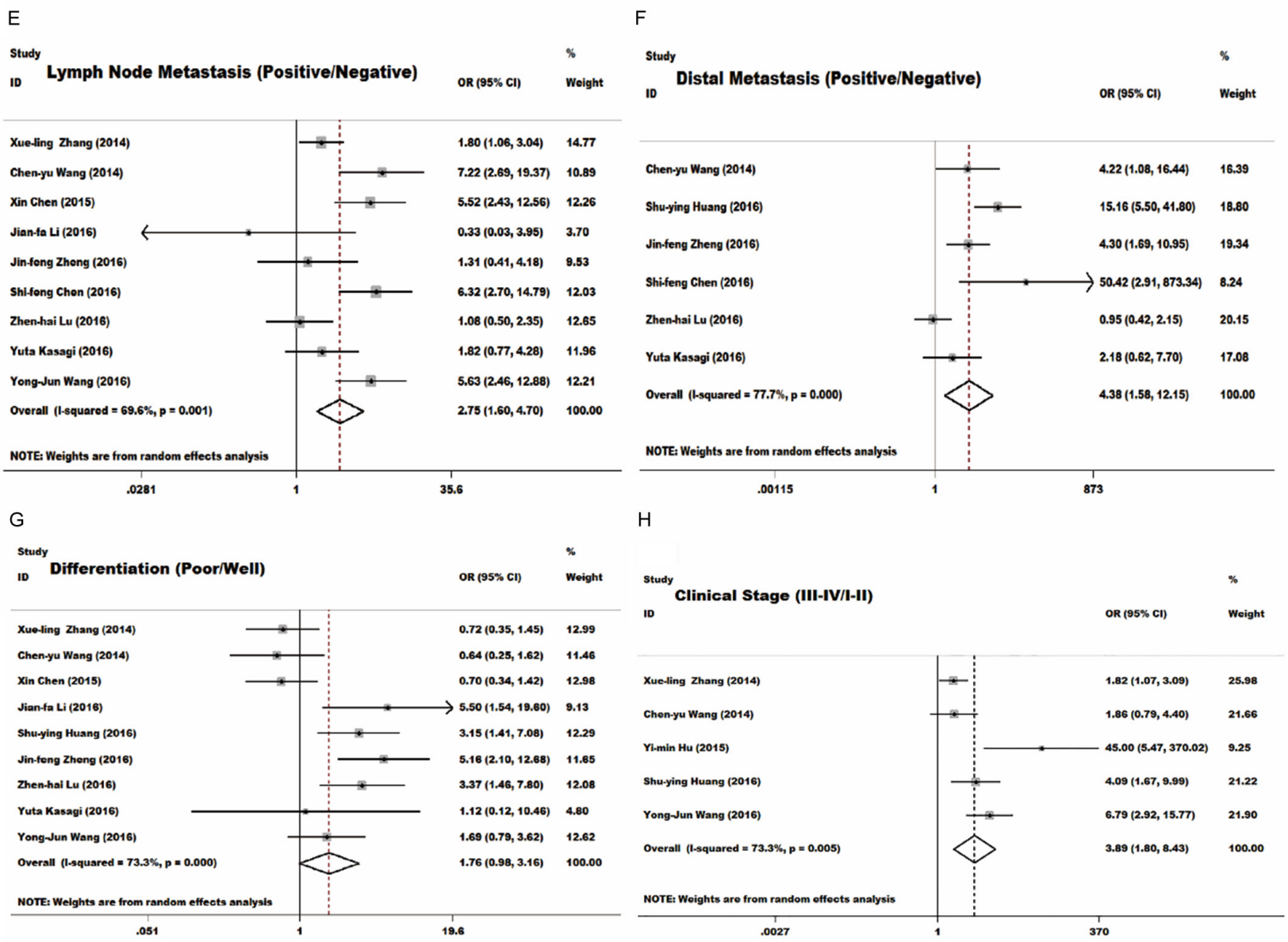


Figure 3. Meta-analysis for the association between upregulation of CCAT2 and related clinicopathological features. (A-H: The association between high level of CCAT2 and age, gender, tumor size, T stage, lymphatic metastasis, distal metastasis, differentiation and clinical stage).

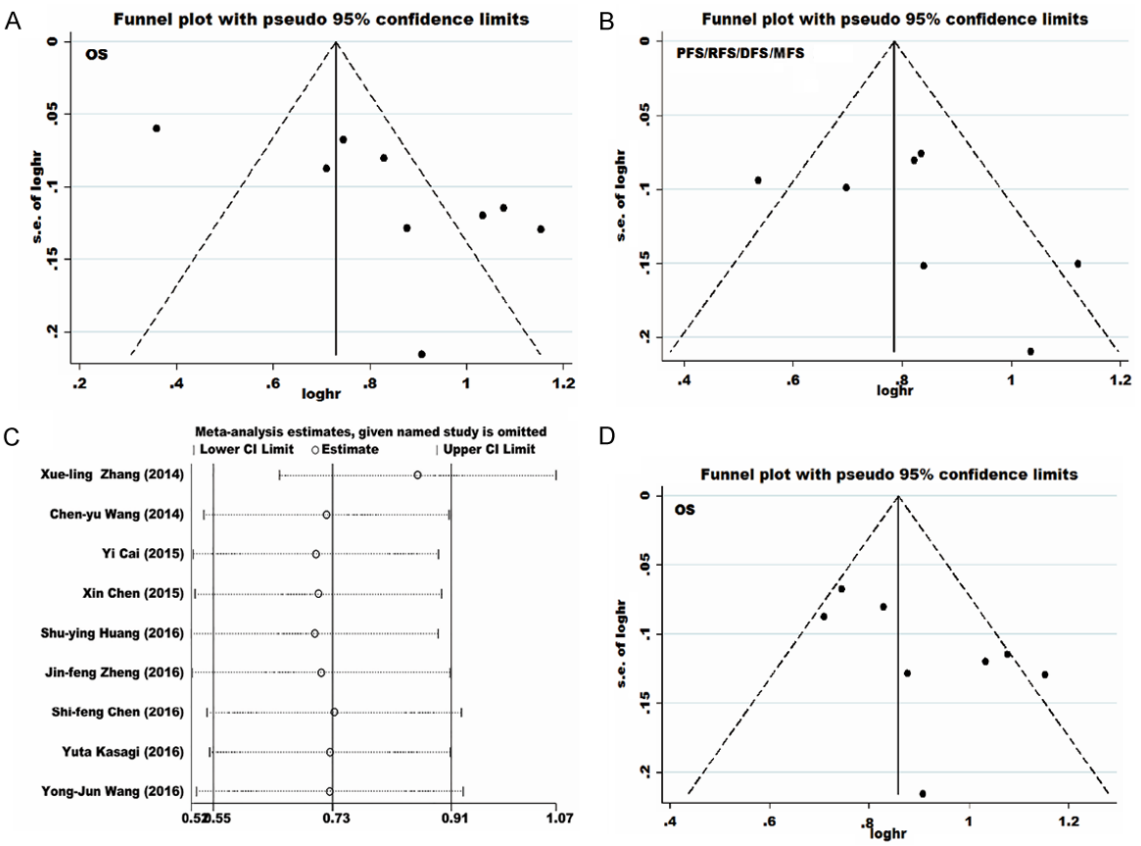


Figure 4. Funnel plots for publication bias of OS (A and D) and PFS/RFS/DFS/MFS (B), sensitivity analysis of OS (C).

ed with advanced clinical stage (OR=3.89, 95% CI=1.80-8.43; P=0.001), deep local invasion (OR=1.85, 95% CI=1.20-2.85; P=0.005), positive lymphatic metastasis (OR=2.75, 95% CI=1.60-4.70; P=0.000), and positive distal metastasis (OR=4.38, 95% CI=1.58-12.15; P=0.005). However, no significant correlation was observed between in the age, gender, tumor differentiation, and tumor size.

Because considerable heterogeneity was reported among tumor size, lymphatic metastasis, distant metastasis, and clinical stage (**Table 2** and **Figure 3C**, **3E**, **3F**, **3H**), the random-effect model was applied.

Publication bias and sensitivity analysis

Publication bias was not obvious for PFS/RFS/DFS/MFS through Begg's and Egger's test and a funnel plot in this meta-analysis (P=0.76 in Begg's test and 0.33 in Egger's test, **Figure 4B**). However, there was significant publication bias for OS with *P*=0.02 in Egger's test and an asymmetrical funnel plot (**Figure 4A**). Following these tests. Then, we conducted a sensitivity analysis to exclude the study responsible for the publication bias. Consequently, we believe that the result of Xue-lin Zhang et al. [16] was the leading cause for publication bias (**Figure 4C**).

After removing this results, any obvious publication bias disappeared (*P*=0.11 in Begg's test and 0.08 in Egger's test) without changing the association between the expression of CCAT2 and OS (**Figure 4D**).

In addition, funnel plots of studies with clinicopathologicalfeatures did not reveal obvious asymmetry (**Figure 5A-H**), suggesting that publication bias was also not observed among these studies.

Discussion

In the field of cancer research, accumulated evidence has pointed to the fact that lncRNAs are crucial in gene regulation and influence different biological progresses through regulating

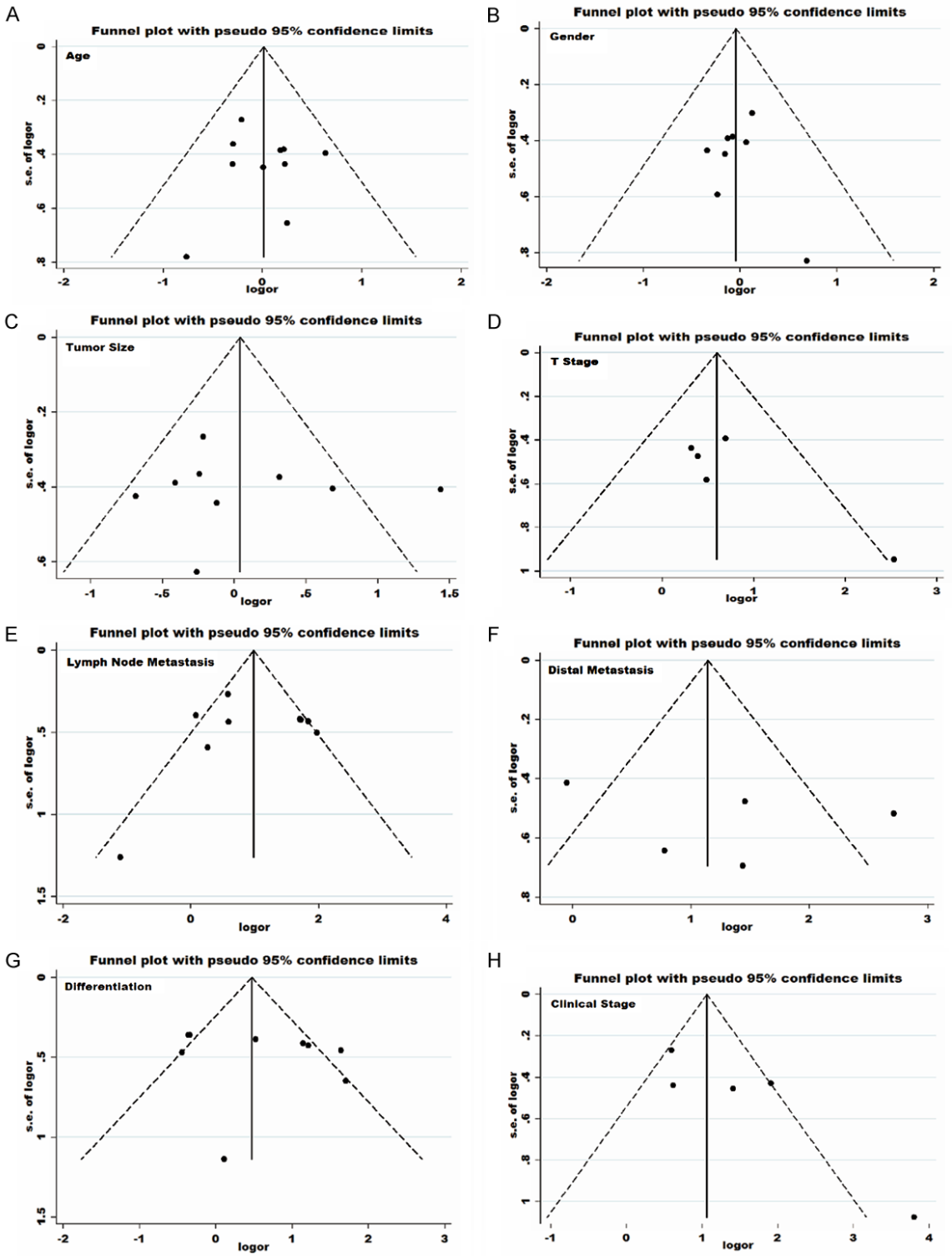


Figure 5. Funnel plots for potential publication bias of clinicopathological features. (A-H: The association between high expression of CCAT2 and age, gender, tumor size, T stage, lymphatic metastasis, distal metastasis, differentiation and clinical stage).

gene transcription [21] and translation [22], sponging miRNAs [23, 24], alternative splicing [25], and functioning in epigenetics [26]. Aberrant lncRNA expression has been detected in

multiple human cancers with distinct models of action [27], indicating a series of promising diagnostic and prognostic biomarkers as well as therapeutic targets.

CCAT2 was first detected in colorectal cancer and subsequently found in other cancers. In these studies, it has been discovered that CCAT2 is associated with the tumorigenesis and progression of cancers. Additionally, upregulated CCAT2 in cancers is closely related to high risk of poor outcomes. Efforts have been made to understand the underlying mechanisms of CCAT2 in oncogenesis and cancer progression. Hui et al. first demonstrated in colon cancer that CCAT2 upregulated MYC, miR-20a, and miR-17-5p through binding to the protein transcription factor 7-like 2 (TCF7L2), activating the Wnt signaling pathway and, consequently, leading to the generation of colon cancer [4]. Recently, Roxana S uncovered that by binding with cleavage factor I (CFI) complex, CCAT2 regulated several metabolic enzymes and/or metabolites, such as glutaminase and glutamate, which leads to the reprogramming of cellular metabolism in colon tumors [5].

To evaluate the diagnostic role of CCAT2 in the clinicopathological characteristics and prognosis of cancer, Xue et al. [28] reported the first meta-analysis of CCAT2 as an independent prognostic marker in December, 2015, involving only 4 studies with a patient population of 576. There have been another 52 articles available online after the publication of the previous meta-analysis. Therefore, a meta-analysis with the most comprehensive publications up to now was still necessary.

In the present meta-analysis, our results provided convincing evidence that a high expression level of CCAT2 had an unfavorable impact on the prognosis of tumor patients, which was consistent with the previous meta-analysis. Moreover, pooled results of clinicopathological features indicated that an elevated CCAT2 expression level was positively associated with advanced clinical stage, deep, local invasion as well as the presence of lymphatic and distal metastasis, which may serve as an explanation for why a high level of CCAT2 expression was related to poor prognosis for the cancer patients involved in these studies.

Before drawing conclusions, several limitations of this meta-analysis will need further discussion. First, the number of studies included was still relatively small. Second, not all studies reported the CCAT2 expression cut-off values, and those with cut-off values were also unified. Third, the definition of the same endpoint may vary with studies. Hence, more comprehensive data from future studies focused on this field are urgently needed.

To conclude, this meta-analysis revealed that a high expression level of CCAT2 was a predictor of poor prognosis and closely associated with advance clinical stage, deep, local invasion as well as the presence of lymphatic and distal metastasis of tumors. Therefore, CCAT2 may serve as a diagnostic biomarker for the prognosis and related clinicopathology of malignancies, based on which patients could be divided into subgroups for individualized treatment. Moreover, inspired by the findings of two case-controlled studies indicating the predictive value of variants of the highly-upregulated-in-liver-cancer (HULC) gene [29, 30], SNP of CCAT2 is a potential cancer susceptibility marker. With further understanding of its regulatory mechanisms, CCAT2 will be a promising new therapeutic target in novel cancer management.

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Disclosure of conflict of interest

None.

Authors' contribution

Yue Ma and Shan Zhu contributed to publication search, quality assessment, data collection, manuscript writing; Shuai Wu contributed to statistics and editing; Chunquan Zheng contributed to conception and design.

Address correspondence to: Chunquan Zheng, Department of Otolaryngology-Head and Neck Surgery, Eye Ear Nose and Throat Hospital, Fudan University, Shanghai 200030, China. Tel: 153178-28193; E-mail: zheng_ent96@163.com

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Table S1. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa scale for assessing the quality of cohort studies

Author	Year	Selection (score)			Comparability (score)	Exposure (score)				Total score
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Based on the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Hui Ling	2013	1	0	1	1	1	1	1	1	7
Chen-Yu Wang	2014	1	1	1	1	2	1	1	1	9
Xue-ling Zhang	2014	1	1	0	1	1	1	1	1	8
Yi-min Hu	2015	—	—	—	—	—	—	—	—	—
Xin Chen	2015	1	1	1	1	1	1	1	1	8
Yi Cai	2015	1	1	1	1	1	1	1	1	8
Zhen-hai Lu	2016	—	—	—	—	—	—	—	—	—
Jian-fa Li	2016	—	—	—	—	—	—	—	—	—
Shu-ying Huang	2016	1	1	1	1	2	1	1	1	9
Jin-feng Zheng	2016	1	1	1	1	2	1	1	1	9
Shi-feng Chen	2016	1	1	1	1	2	1	1	1	9
Yuta Kasagi	2016	1	1	1	1	1	1	1	1	8
Yong-Jun Wang	2016	1	1	1	1	2	1	1	1	9