Clinicopathological and prognostic value of long non-coding RNA CCAT1 expression in patients with digestive system cancer

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Abstract. Colon cancer associated transcript-1 (CCAT1) is known to play an important role in numerous types of human cancer, including bladder, prostate and ovarian cancer. However, a consistent perspective has not been established in digestive system cancer (DSC). To explore the prognostic value of CCAT1 in patients with DSC, a meta-analysis was performed. A systematic search of PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Chinese Biological Medical Literature database, Cochrane Library and WanFang database was applied to select eligible articles. Pooled odds ratios (ORs) or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated to estimate the effects of CCAT1 on pathological or clinical features. A total of 1,719 patients from 12 eligible articles were enrolled in the meta-analysis. The results revealed that elevated CCAT1 expression was significantly related to larger tumor size (OR, 1.81; 95% CI, 1.31-2.48), poorer differentiation (OR, 0.45; 95% CI, 0.31-0.64), earlier lymph node metastasis (OR, 3.14; 95% CI, 2.34-4.22) and advanced TNM stage (OR, 3.08; 95% CI, 2.07-4.59). In addition, high CCAT1 expression predicted a poorer outcome for overall survival rate (HR, 2.37; 95% CI, 2.11-2.67) and recurrence-free survival rate (HR, 2.16, 95% CI, 1.31-3.57). High expression levels of CCAT1 were therefore related to unfavorable clinical outcomes of patients with DSC. These results demonstrated that CCAT1 could serve as a prognostic predictor in human DSC.

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Introduction

Cancer has been a leading cause of disease-related deaths worldwide over the past decade (1). Digestive system cancer (DSC) is responsible for more deaths from cancer than cancer of any other system. Three out of five of the world's major sources of cancer-related death are from digestive system tumors (2). Although radiotherapy, chemotherapy, individualized precision therapy and immunotherapy have been developed for cancer diagnosis and treatment, the 5-year survival rate of patients with DSC remains poor (3,4). Recently, it has been established that numerous biomarkers, including des-γ-carboxyprothrombin, miR-12 and miR-15b, associated with tumor screening, diagnosis and prognosis, play significant roles in the development of DSC (5-7). However, only a small portion of these biomarkers is well accepted for clinical usage (8). This may be due to low specificity, sensitivity or consistency in tumor development. Therefore, it is clinically necessary and urgent to develop novel prognostic biomarkers for DSC.

Long non-coding RNAs (lncRNAs) are defined as non-protein coding RNAs that are >200 nucleotides and do not contain an open reading frame (9). Abnormal expression of lncRNAs is observed in various types of cancer, including breast, colorectal and lung cancer, and these lncRNAs are involved in tumorigenesis and progression through interactions with DNA, mRNA, microRNA (miR/miRNA) and proteins (10-12). In previous years, increasing evidence has suggested that lncRNAs, such as LINC00645 (13), LINC01133 (14), long non-coding RNA regulating IL-6 transcription (15) and growth arrest-specific 5 transcript (16), may serve as novel prognostic biomarkers and potential therapeutic targets for human cancer.

Colon cancer associated transcript-1 (CCAT1), a nuclear-restricted lncRNA located on chromosome 8q24.21, was first identified as an oncogene in colorectal cancer by Nissan (17). Overexpression of CCAT1 was found in various types of cancer and attracted the attention of a number of researchers due to its prognostic value (18-20). You *et al* (21) found that CCAT1 was overexpressed in prostate cancer tissue

samples and cell lines, and promoted cell proliferation, which indicated that CCAT1 might suggest an unfavorable outcome for the patient. Similarly, an investigation by Shen *et al* (22) suggested that CCAT1 was a key oncogenic lncRNA correlated with cervical cancer and played an important role in promoting cervical cancer progression via regulation of the miR-181a-5p/MMP14 axis. Moreover, Han *et al* (23) discovered that CCAT1 was upregulated in triple-negative breast cancer tissues, and patients with high CCAT1 expression had shorter overall survival (OS) times compared with those patients with low expression. A review by Wang *et al* (24) summarized that CCAT1 was associated with clinicopathological features, recurrence-free survival (RFS) and OS rates in patients, and that CCAT1 could serve as a diagnostic and prognostic marker in various types of human cancer, including gallbladder cancer, cholangiocarcinoma and pancreatic cancer. However, due to the relatively small sample size, these studies on CCAT1 were moderately limited, and there was no research to systematically clarify the prognostic value of CCAT1 in DSC. Therefore, the meta-analysis in the present study aimed to systematically evaluate the clinicopathological and prognostic role of CCAT1 in patients with DSC.

Materials and methods

Search strategy and literature selection. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were strictly followed during the meta-analysis (25).

A systematic search was performed using PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), Web of Science (https://www.webofscience.com), China National Knowledge Infrastructure (https://en.cnki.com.cn), Cochrane Library (https://www.cochranelibrary.com/), Chinese Biological Medical Literature database (http://www.sinomed.ac.cn/zh/) and WanFang database (https://www.wanfangdata.com.cn). The search terms used for literature retrieval were as follows: 'colon cancer associated transcript-1' or 'colon cancer associated transcript 1' or 'CCAT1' or 'lncRNA CCAT1' and 'digestive system' and 'cancer' or 'tumor' or 'neoplasm' or 'carcinoma' or 'malignancy'. Articles were searched from the creation of each database to March 31, 2022. Articles eligible for this study were updated on April 10, 2022.

The initial database search yielded 355 articles according to the search strategy. After screening the titles and abstracts, 256 literature studies were eliminated due to article duplication. The remaining 99 articles were quickly browsed, and 47 articles were excluded, as they were reviews, conference summaries or comments. Following a further assessment of the remaining 52 articles, 40 articles were excluded, as they did not analyze enough samples or extract data. Finally, 12 articles with a total of 1,719 patients qualified for the present study. Among the 12 included, 1 article was published in 2014, 4 in 2015, 1 in 2016, 5 in 2017 and 1 in 2020. The time range of the studies used for the meta-analysis was therefore 2014-2020. The details of the screening process are shown in Fig. 1.

Inclusion and exclusion criteria. Inclusion criteria were as follows: i) Expression levels of CCAT1 were detected in human DSC; ii) the method of detecting CCAT1 expression

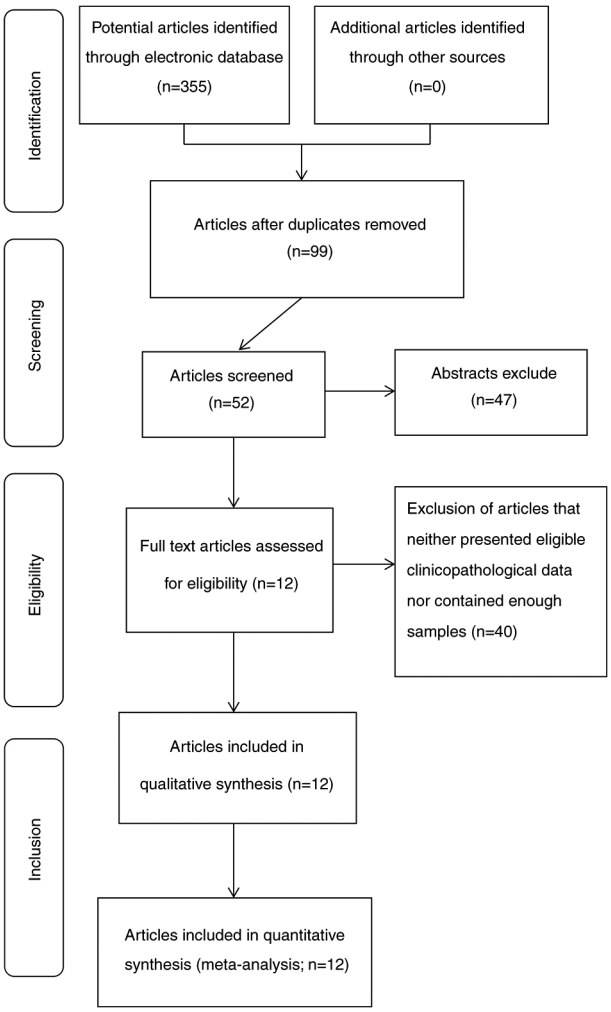

Figure 1. Flow chart representing the literature search and selection process.

was reverse transcription-quantitative PCR (RT-qPCR); iii) the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were reported directly or could be calculated from Kaplan-Meier survival curves; iv) evaluation of a relationship between high/low CCAT1 expression and clinical outcomes; v) results included clinicopathological features or survival rate (OS or RFS); vi) available full-text articles; and vii) articles were published in English.

Exclusion criteria were as follows: i) Duplicate publications; ii) studies missing a control group; iii) no data could be extracted and/or the studies were published as reviews, abstracts, comments, case reports, expert opinions letters or editorials; iv) non-human studies; v) articles missing OS or RFS data; vi) small sample size (total patients <20); vii) articles not published in English; and viii) HRs could not be calculated from the published data.

Data extraction and quality assessment. All data and usable information were screened and extracted by 2 independent investigators. For all included studies, the following information was collected: First author, country of research, publication date, type of cancer, number of patients, CCAT1 detection method, clinicopathological parameters, survival analysis and outcome measure. Newcastle-Ottawa Scale (NOS)

Table I. Basic information of the studies included in the meta-analysis.

First author, year	Country	Cancer type	CCAT1 detection method	Survival information	Newcastle-Ottawa Scale score	(Refs.)
He *et al*, 2014	China	CC	RT-qPCR	OS	6	(30)
Zhu *et al*, 2015	China	HCC	RT-qPCR	OS, RFS	7	(31)
Deng *et al*, 2015	China	HCC	RT-qPCR	OS, RFS	7	(33)
McCleland *et al*, 2016	USA	CRC	RT-qPCR	OS	8	(37)
Wang *et al*, 2017	China	HCC	RT-qPCR	OS, DFS	8	(36)
Zhang E *et al*, 2017	China	ESCC	RT-qPCR	OS	8	(38)
Jiang *et al*, 2017	China	CCA	RT-qPCR	OS	6	(34)
Ozawa *et al*, 2017	USA	CRC	RT-qPCR	OS, RFS	8	(35)
Liu and Shangguan, 2017	China	GC	RT-qPCR	OS, RFS	8	(32)
Zhang *et al*, 2017	China	CCA	RT-qPCR	NA	7	(39)
Li *et al*, 2017	China	GC	RT-qPCR	NA	8	(40)
Shang *et al*, 2020	China	CRC	RT-qPCR	NA	7	(41)

CC, colon cancer; CCA, cholangiocarcinoma; CCAT1, colon cancer associated transcript-1; CRC, colorectal cancer; DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; RT-qPCR, reverse transcription-quantitative PCR; NA, (data) not available.

criteria were employed to evaluate the quality of each included study (26). Studies with an NOS score ≥6 were considered to be of high quality; otherwise, they were defined as low quality. All the studies included in the present meta-analysis were considered as high quality.

Statistical analysis. The statistical analyses were performed using STATA 14.0 software (StataCorp LP). Statistical analysis with a two-sided P-value of <0.05 was considered statistically significant. The original study aims were divided into two categories in the meta-analysis. The first aim was to assess the correlation of high CCAT1 expression with clinicopathological characteristics, including age, sex, depth of infiltration, tumor size, histological differentiation, lymph node metastasis and TNM stage. The characteristic standards were based on the latest guidelines by the publication date (27-29). Pooled odds ratios (ORs) with corresponding 95% CIs were used to evaluate the association between CCAT1 expression and clinicopathological parameters. Q test and I2 test were used to assess the statistical heterogeneity. Heterogeneity was considered present when I2>50% or P<0.05 for the Q test. A random effects model was used to analyze the data, as heterogeneity was expected for the intervention effects among multiple studies from different groups and geographical locations. The second aim was to evaluate the prognostic value of CCAT1 on OS and RFS with HRs and corresponding 95% CIs. HRs with corresponding 95% CIs were calculated by the survival data extracted from Kaplan-Meier curves with Engauge Digitizer version 4.1 (https://markummitchell.github.io/engauge-digitizer/) when not directly presented in articles. The standard error (SE) of the HR was computed using lnhr and the upper (lnul) and lower limit (lnll) of the CIs, taking the mean of the SE of the lnll and lnul, and selnhr=(lnul-lnll)/(1.96x2). Begg's test was performed to assess the potential publication bias, and P<0.05 was considered to indicate a statistically significant difference. The sensitivity analysis was performed to assess the reliability of the meta-analysis. STATA 14.0 software (Stata Corp LLC) was used for the sensitivity analysis, which was performed by excluding studies one by one and observing whether the heterogeneity changed.

Results

Characteristics of eligible studies. A total of 12 eligible studies (30-41) focusing on DSC (1 on colon cancer, 1 on esophageal squamous cell carcinoma, 2 on cholangiocarcinoma, 2 on gastric cancer, 3 on colorectal cancer and 3 on hepatocellular carcinoma) were enrolled in the present meta-analysis. The basic information and characteristics of each study are summarized in Tables I and II. Among the included studies, 2 came from the USA and the rest were from China. The expression levels of CCAT1 were examined by RT-qPCR in all studies. The median expression levels of CCAT1 in the studies conducted by He *et al* (30), Zhu *et al* (31) and Deng *et al* (33) were regarded as the cut-off values, while the mean expression levels were set as the cut-off values in the studies conducted by Zhang *et al* (38) and Li *et al* (40). The cut-off value in the study conducted by Liu and Shangguan (32) was 0.041 and the setting standard was not introduced. However, the other eligible articles did not report the cut-off value. Of the 12 studies, 9 provided OS information, 4 presented RFS information and 1 presented DFS information. Moreover, the included studies were published from 2014 to 2020 with a sample size ranging from 48 to 638.

Correlation of CCAT1 expression with clinicopathological characteristics. The association between CCAT1 expression and clinicopathological characteristics was assessed in 12 studies with six types of DSC. As shown in Figs. 2 and 3, and Table III, high CCAT1 expression levels were significantly

Table II. Characteristics of the studies included in the meta-analysis.

	Colon cancer associated transcript-1 expression level																
	High								Low								
First author, year	Total patients, n	LNM staging, n	Age ≥60 years, n	T1/2 stage, n	HTS, n	TS>5, n	LD, n	M, n	Total patients, n	LNM staging, n	Age ≥60 years, n	T1/2 stage, n	HTS, n	TS>5, n	LD, n	M, n	(Refs.)
He *et al*, 2014	24	15	10	NA	15	17	NA	14	24	6	13	NA	5	8	NA	9	(30)
Zhu *et al*, 2015	43	NA	NA	NA	NA	NA	NA	NA	43	NA	NA	NA	NA	NA	NA	NA	(31)
Deng *et al*, 2015	33	NA	8	NA	NA	20	NA	27	33	NA	10	NA	NA	10	NA	25	(33)
McCleland *et al*, 2016	202	NA	107	NA	107	NA	NA	113	436	NA	233	NA	175	NA	NA	213	(37)
Wang *et al*, 2017	60	NA	29	NA	44	36	NA	40	37	NA	16	NA	9	15	NA	18	(36)
Zhang *et al*, 2017	45	29	26	17	29	NA	27	25	45	19	22	23	15	NA	22	24	(38)
Jiang *et al*, 2017	47	33	27	NA	34	NA	23	27	44	19	29	NA	19	NA	10	26	(34)
Ozawa *et al*, 2017	55	37	NA	11	38	20	3	35	70	32	NA	16	34	27	2	35	(35)
Liu and Shangguan, 2017	121	80	61	NA	73	80	63	45	119	54	70	NA	49	69	36	50	(32)
Zhang S *et al*, 2017	65	48	35	16	49	NA	NA	27	55	16	35	38	17	NA	NA	27	(39)
Li *et al*, 2017	41	31	35	9	19	16	23	17	27	12	25	10	23	11	22	23	(40)
Shang *et al*, 2020	NA	29	NA	NA	14	NA	NA	12	NA	8	NA	NA	7	NA	NA	13	(41)

HTS, high TNM stage (III/IV); LD, low differentiation; LNM, lymph-node-metastasis; M, male; T1/2, tumor stage 1/2; TS>5, tumor stage >5; NA, (data) not available.

Table III. Pooled ORs for the association between colon cancer associated transcript-1 expression levels and clinicopathological parameters in the meta-analysis.

Clinicopathological features	Number of studies	Number of patients	Pooled OR (95% CI)	P-value	Heterogeneity		Model used
					I^2 (%)	P-value	
Age	9	1,268	0.91 (0.73-1.12)	0.369	0.00	0.867	Random
Sex	11	1,633	1.16 (0.95-1.42)	0.156	9.30	0.355	Random
Depth of infiltration	4	403	1.95 (0.79-4.84)	0.147	75.90	0.006	Random
Tumor size	6	644	1.81 (1.31-2.48)	<0.001	49.60	0.078	Random
Differentiation	5	596	0.45 (0.31-0.64)	<0.001	0.00	0.750	Random
Lymph node metastasis	7	782	3.14 (2.34-4.21)	<0.001	9.80	0.354	Random
TNM stage	10	1,567	3.08 (2.07-4.59)	<0.001	62.00	0.005	Random

OR, odds ratio; CI, confidence interval.

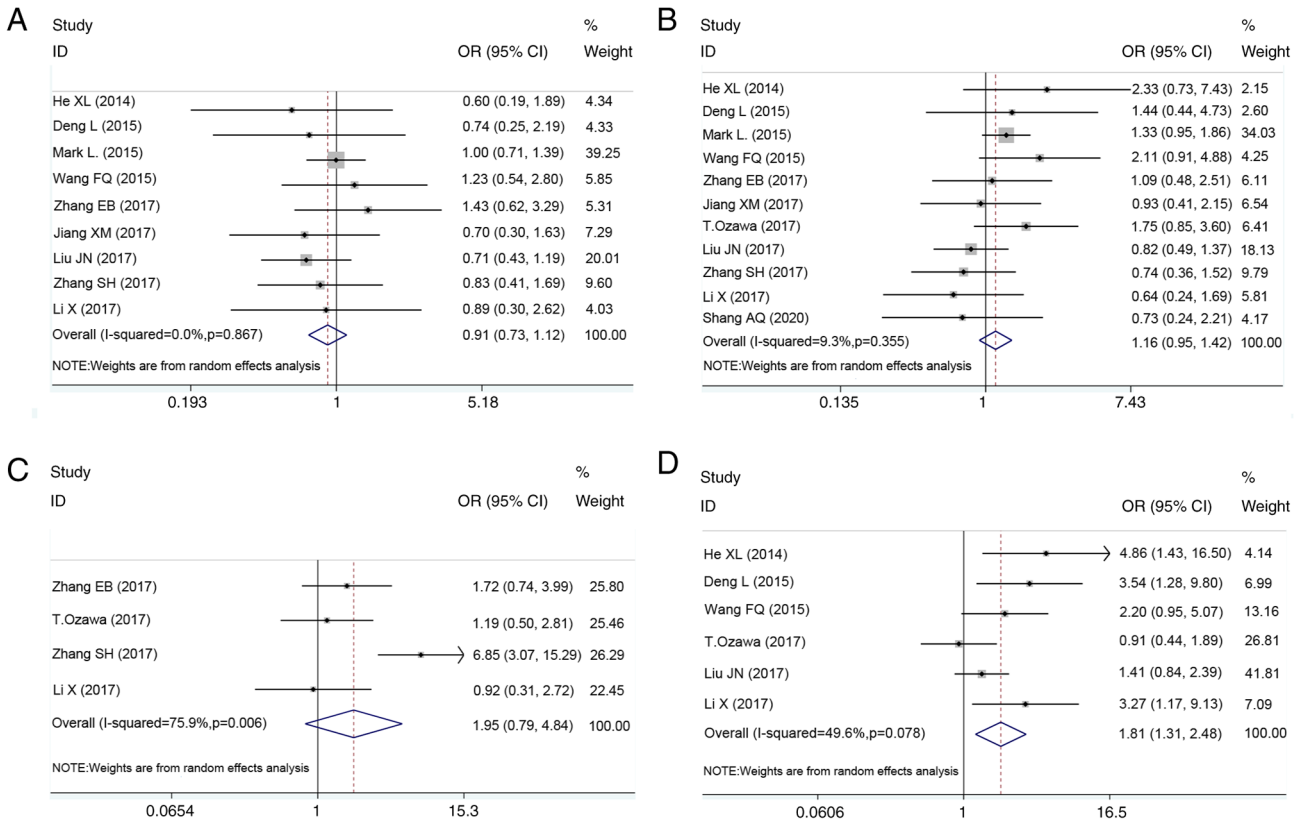

Figure 2. Forest plot of studies evaluating the relationship between colon cancer associated transcript-1 expression and clinicopathological variables. (A) Age, (B) sex, (C) depth of infiltration and (D) tumor size. CI, confidence interval; OR, odds ratio.

associated with larger tumor size (>5 cm vs. ≤5 cm; OR, 1.81; 95% CI, 1.31-2.48; P<0.001; Fig. 2D), poorer differentiation (high and moderate vs. low; OR, 0.45; 95% CI, 0.31-0.64; P<0.001; Fig. 3A), earlier lymph node metastasis (yes vs. no; OR, 3.14; 95% CI, 2.34-4.22, P<0.001; Fig. 3B) and advanced TNM stage (III+IV vs. I+II; OR, 3.08; 95% CI, 2.07-4.59, P<0.001, Fig. 3C). However, no significant association was found with age (≥60 vs. <60; OR, 0.91; 95% CI, 0.73-1.12; P=0.369; Fig. 2A), sex (male vs. female; OR, 1.16; 95% CI, 0.95-1.42; P=0.156; Fig. 2B) and depth of infiltration (T3+4 vs. T1+2; OR, 1.95; 95% CI, 0.79-4.84; P=0.147; Fig. 2C).

Association between CCAT1 expression and OS. The studies containing OS rate data covered 1,481 patients. A random effects model was applied to calculate the pooled HRs and the respective 95% CIs. Subsequently, the result suggested that CCAT1 expression had a significant effect on OS (pooled HR, 2.35; 95% CI, 2.08-2.63; Fig. 4 and Table IV), in which higher expression of CCAT1 was associated with a poorer OS outcome.

Association between CCAT1 expression and RFS. A total of 4 studies comprising 191 subjects reported the RFS based

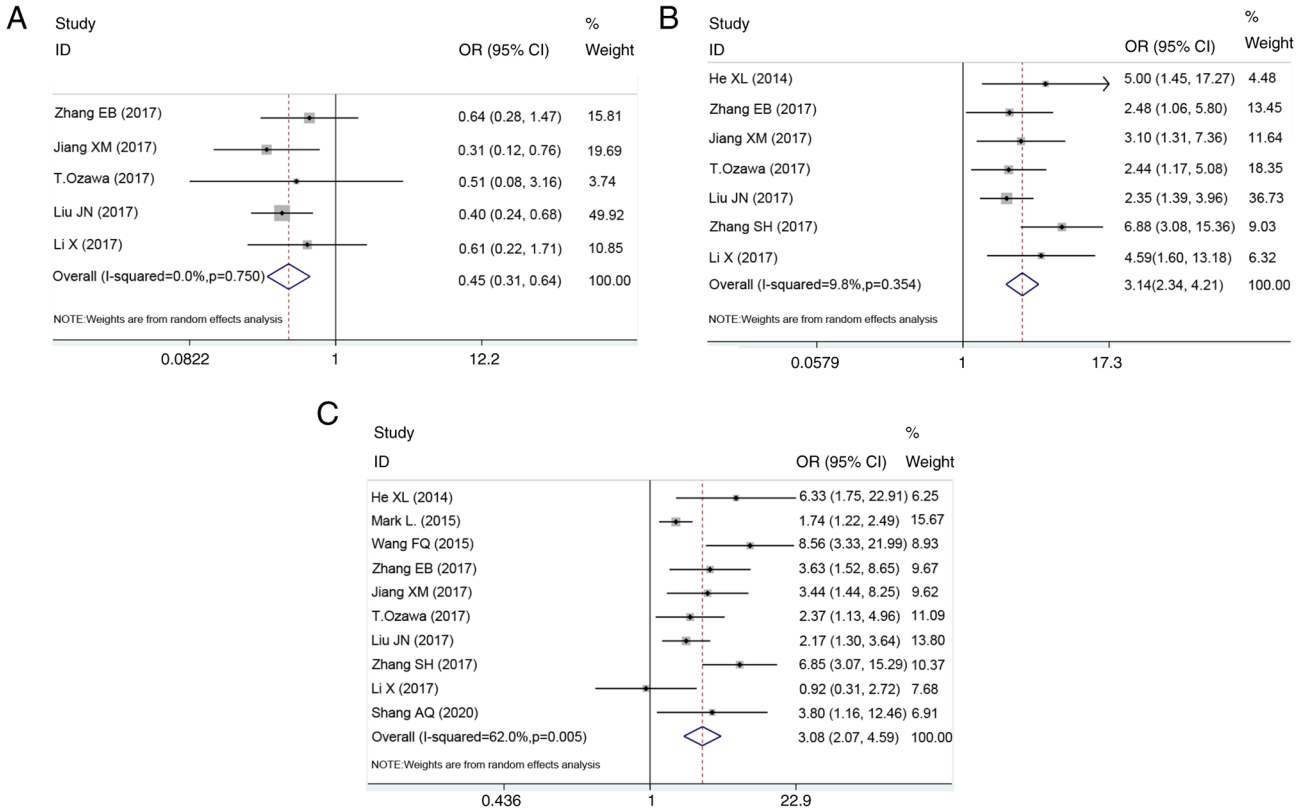

Figure 3. Forest plot of studies evaluating the relationship between colon cancer associated transcript-1 expression and clinicopathological variables. (A) Differentiation, (B) lymph node metastasis and (C) TNM stage. CI, confidence interval; OR, odds ratio.

on CCAT1 expression levels in patients with DSC (Fig. 4 and Table IV). The pooled HR was 2.27 (95% CI, 1.31-3.23) with no significant heterogeneity (I2=0.0%; P=0.932). This suggested that patients with high CCAT1 expression tended to have shorter RFS times compared with those patients with low CCAT1 expression.

Publication bias. To assess the potential publication bias, Begg's funnel analysis was performed. As shown in Figs. 5 and 6, there was no publication bias for age (P=0.602), sex (P=0.533), depth of infiltration (P=0.089), tumor size (P=0.060), differentiation (P=1.000), lymph node metastasis (P=0.072), TNM stage (P=0.210) and OS (P=0.076).

Sensitivity analysis. A sensitivity analysis was conducted to detect the influence of an individual study on the pooled results by omitting a single study each time (Figs. 7 and 8). The results verified that any individual study could not significantly change the pooled estimates, revealing that the results of the synthetic analysis were stable and credible.

Discussion

DSC, consisting mainly of esophageal cancer, gastric cancer, colorectal cancer, hepatocellular carcinoma, gallbladder cancer and pancreatic cancer, has become a health burden with high mortality worldwide, and a marked increase in incidence has been observed (42,43). Traditionally, clinicopathological variables, such as tumor size, depth of infiltration, differentiation, lymph node metastasis and TNM stage, are applied to predict the survival outcome of patients with DSC (7). Early stage DSC has a significantly improved survival outcome compared with advanced-stage DSC, in which tumor invasion and metastasis are common pathological characteristics of a poor prognosis (44). Thus, seeking new tumor biomarkers or therapeutic targets to increase the survival rate of patients with DSC has become the key to clinical work (45). Emerging evidence has revealed that lncRNAs have become a topic of interest due to their functions in a variety of biological processes, and the alteration of lncRNA expression could result in abnormal expression of gene products, cellular differentiation, protein localization and DNA damage response, leading to the occurrence and development of cancer (12,46). In a previous study, aberrant expression of lncRNAs was related to clinical outcomes for patients with cancer, and could be tracked in numerous malignant biological behaviors, including proliferation, invasion, migration, the cell cycle, apoptosis and angiogenesis, which indicated the potential roles of lncRNAs as biomarkers or therapeutic targets in cancer (47). Moreover, due to great specificity, sensitivity and convenient detection in bodily fluids, lncRNAs have significant potential to be a promising biomarker for the early detection and accurate survival outcome prediction of patients with DSC.

The lncRNA CCAT1 has been found to be upregulated in different types of cancer (17). Recently, emerging studies suggested that CCAT1 participated in multiple cellular processes involved in DSC, such as cell proliferation, invasion and drug resistance, by targeting mRNAs, regulating miRNAs or competing with endogenous RNAs (48-50). Zhang *et al* (51) demonstrated that CCAT1 could regulate the expression of

Table IV. Related survival data of enrolled studies in the meta-analysis.

			Related information on survival					
			Overall survival		Recurrence-free survival			
First author, year	Cancer type	Sample size	Univariate	Multivariate	Univariate	Multivariate	HR estimation method	(Refs.)
He *et al*, 2014	CC	48	2.34 (1.32-4.17)	NA	NA	NA	KM	(30)
Zhu *et al*, 2015	HCC	86	3.33 (1.60-6.96)	3.33 (1.60-6.96)	NA	NA	Rep	(31)
Deng *et al*, 2015	HCC	66	2.11 (0.88-5.15)	NA	1.97(1.04-3.70)	NA	KM	(33)
McCleland *et al*, 2016	CRC	638	2.31 (2.01-2.65)	NA	NA	NA	KM	(37)
Wang *et al*, 2017	HCC	97	3.27 (1.62-6.27)	2.98 (1.32-3.95)	NA	NA	Rep	(36)
Zhang *et al*, 2017	ESCC	90	2.22 (1.35-3.66)	NA	NA	NA	KM	(38)
Jiang *et al*, 2017	CCA	91	3.14 (1.97-5.01)	2.25 (1.40-3.63)	NA	NA	Rep	(34)
Ozawa *et al*, 2017	CRC	125	NA	5.90 (2.09-24.70)	NA	2.52 (1.07-5.56)	Rep	(35)
Liu and Shangguan, 2017	GC	240	2.16 (0.98-6.65)	2.41 (1.13-5.94)	NA	NA	Rep	(32)

CC, colon cancer; CCA, cholangiocarcinoma; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; KM, Kaplan-Meier; NA, not applicable; Rep, reported.

CCNE1 by acting as a competing endogenous RNA to sponge miR-30c-2-3p, thereby regulating the cell proliferation and metastasis of hepatocellular carcinoma (HCC), indicating that CCAT1 might be a novel therapeutic target for HCC. An investigation by Fang *et al* (52) found that the expression of CCAT1 in gastric cancer tissues was higher than that in adjacent tumor tissues, and CCAT1 could promote the metastasis of gastric cancer by epithelial-mesenchymal transition. Similarly, a study by Li *et al* (53) revealed that CCAT1 upregulation could promote cell proliferation and migration by affecting Bmi-1 expression in gastric cancer. In addition, Hu *et al* (54) demonstrated that CCAT1 could influence the cell proliferation and drug resistance of esophageal cancer by inhibiting the miR-143/PLK1/BUBR1 axis, and that CCAT1 could be a potential biomarker for esophageal cancer. Together, these studies revealed that CCAT1 could be a potential prognostic biomarker for DSC.

In order to clarify the association of CCAT1 expression levels with clinicopathological features and patient survival in DSC, the present meta-analysis was performed. A previous meta-analysis reported that CCAT1 expression was related to certain clinicopathological variables (tumor size, lymph node metastasis, TNM stage, distant metastasis, microvascular invasion and capsular formation) in all types of cancer, and had a predictive value for a poor prognosis of cancer (55), which was consistent with the present study conclusions. In contrast to the previous study, digestive system tumors were analyzed in the present study rather than all tumor types. In the present meta-analysis, a total of 1,719 patients from 12 studies were enrolled. The random effects model was applied for analyzing the relationship between CCAT1 expression and clinicopathological variables, including age, sex, tumor size, differentiation and lymph node metastasis. Due to the presence of moderate heterogeneity among the studies in terms of depth of infiltration (P=0.006; I^2=75.9%) and TNM stage (P=0.005; I^2=62.0%), a random effects model was used to pool data. It was observed that 4 studies had significant statistical heterogeneity for depth of infiltration and 10 studies for TNM stage. This heterogeneity might be the result of design discrepancies for depth of infiltration among the studies. The heterogeneity for TNM stage might be due to the different staging criteria being used by the studies. Most studies did not introduce the staging criteria they used. The results demonstrated that increased expression of CCAT1 was significantly related to larger tumor size (OR, 1.81; 95% CI, 1.31-2.48), poorer differentiation (OR, 0.45; 95% CI, 0.31-0.64), earlier lymph node metastasis (OR, 3.14; 95% CI, 2.34-4.22) and advanced TNM stage (OR, 3.08; 95% CI, 2.07-4.59). However, no significant association was observed between the expression of CCAT1 and other clinicopathological features, including age, sex and depth of infiltration. In addition, considering the survival rate of patients, the association between the expression level of CCAT1 and the prognosis of patients with DSC was clarified. The results showed that elevated CCAT1 expression was associated with poor OS (HR, 2.37; 95% CI, 2.11-2.67) and RFS (HR, 2.16; 95% CI, 1.31-3.57). Moreover, Begg's funnel analysis was conducted to estimate the underlying publication bias. The result indicated that there was no significant publication bias for age, sex, depth of infiltration, tumor size, differentiation, lymph node metastasis, TNM stage and OS.

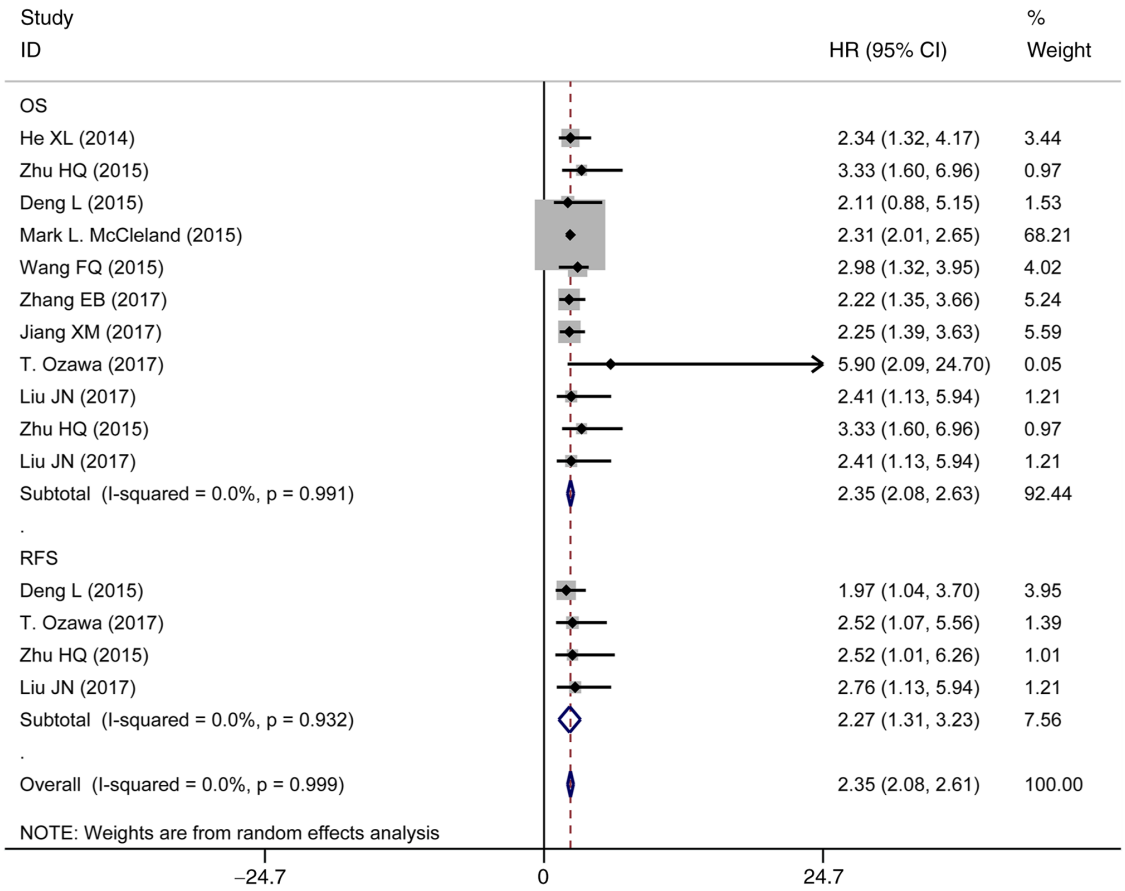

Figure 4. Forest plot for the correlation between colon cancer associated transcript-1 expression and survival outcomes. CI, confidence interval; OR, odds ratio; OS, overall survival; RFS, recurrence-free survival.

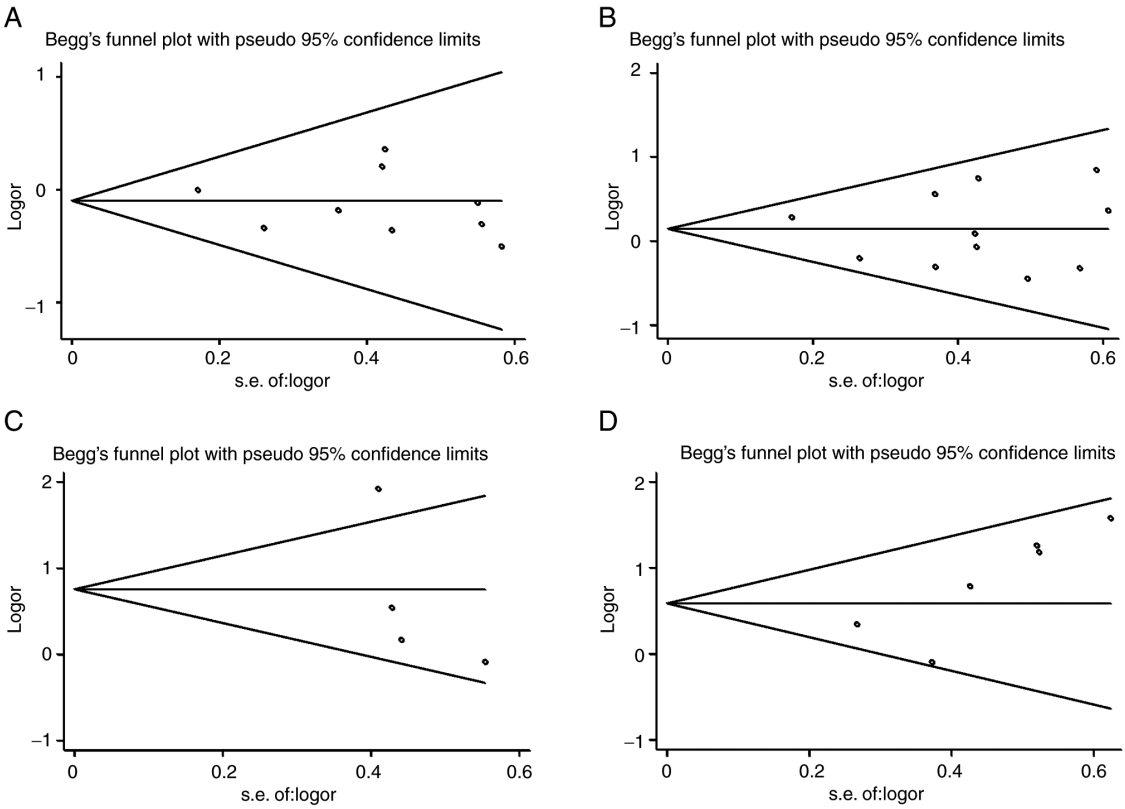

Figure 5. Funnel plot analysis of potential publication bias in the present study (Begg's test) regarding (A) age, (B) sex, (C) depth of infiltration and (D) tumor size. s.e. of: logor, standard error of OR logarithm; s.e. of: lnhr, standard error of HR logarithm.

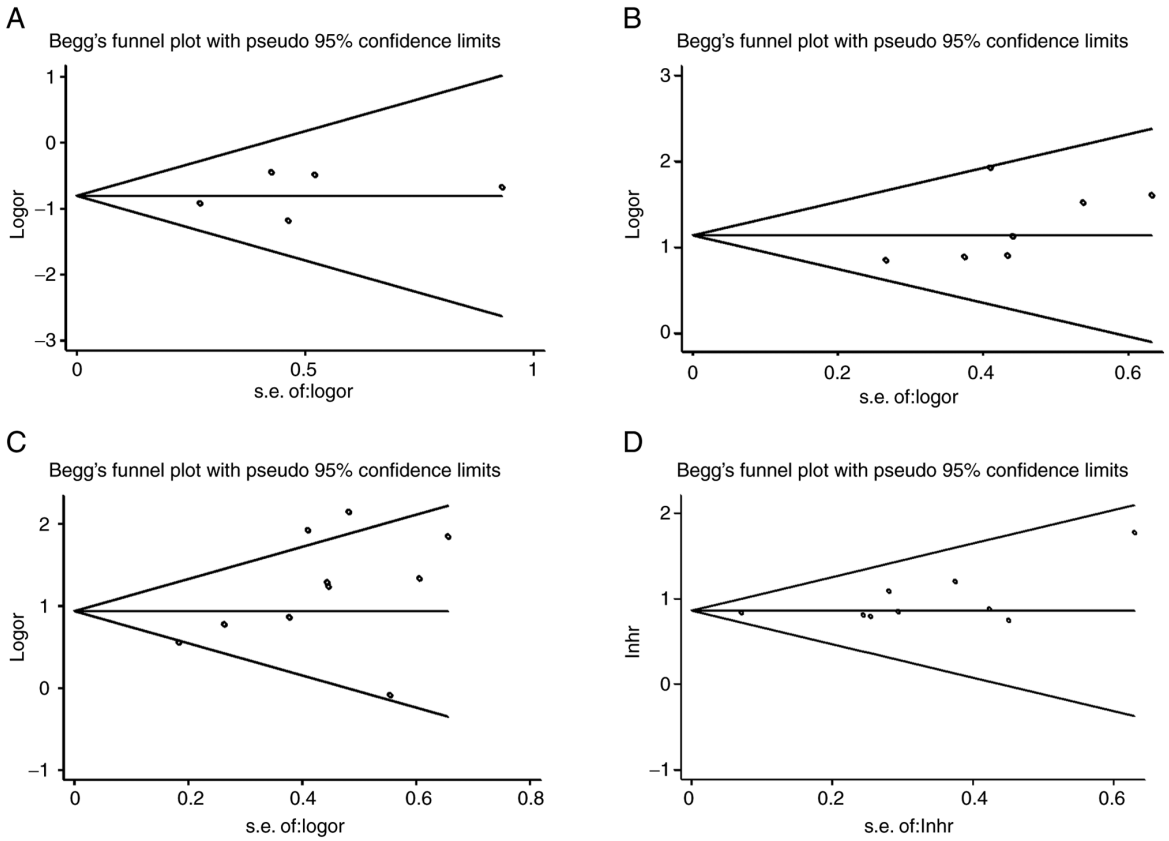

Figure 6. Funnel plot analysis of potential publication bias in the present study (Begg's test) regarding (A) differentiation, (B) lymph node metastasis, (C) TNM stage and (D) overall survival.

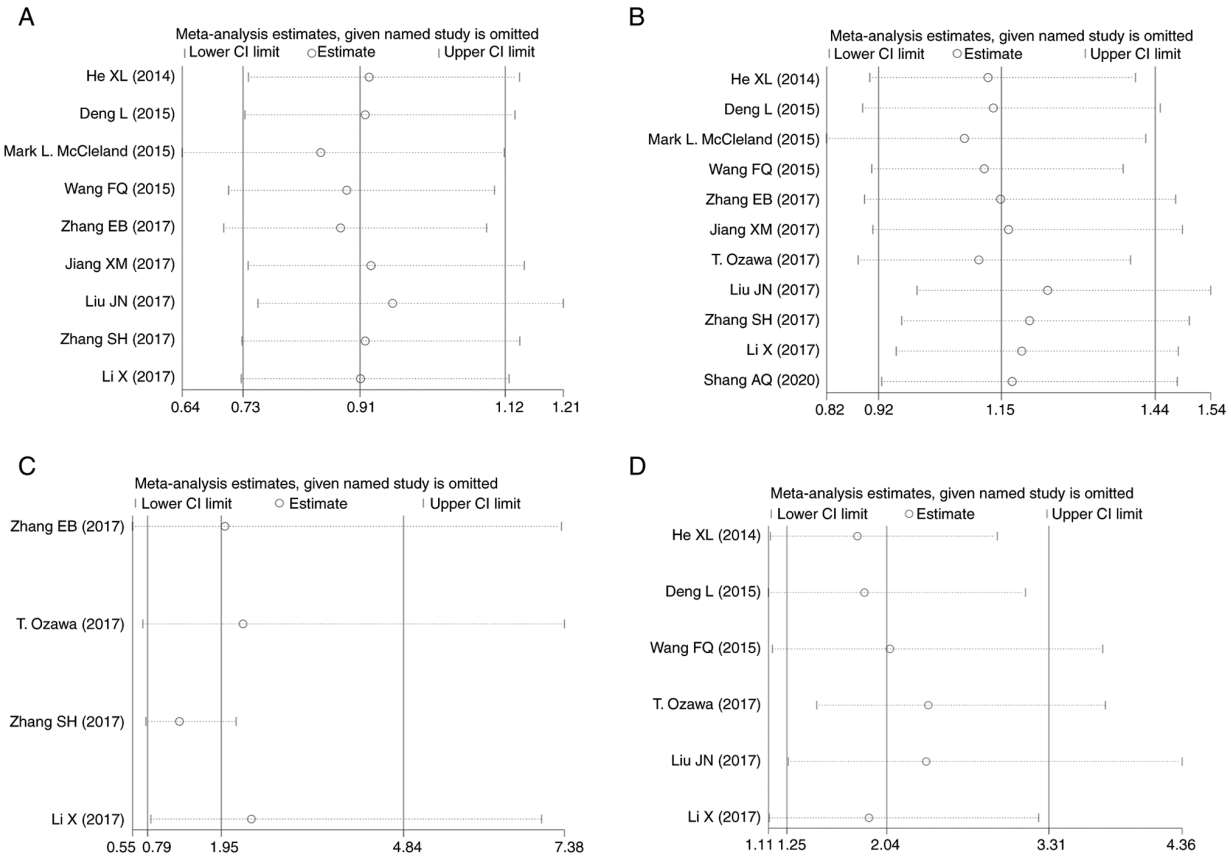

Figure 7. Sensitivity analysis to determine whether an individual study influenced the (A) age, (B) sex, (C) depth of infiltration or (D) tumor size pooled results. CI, confidence interval.

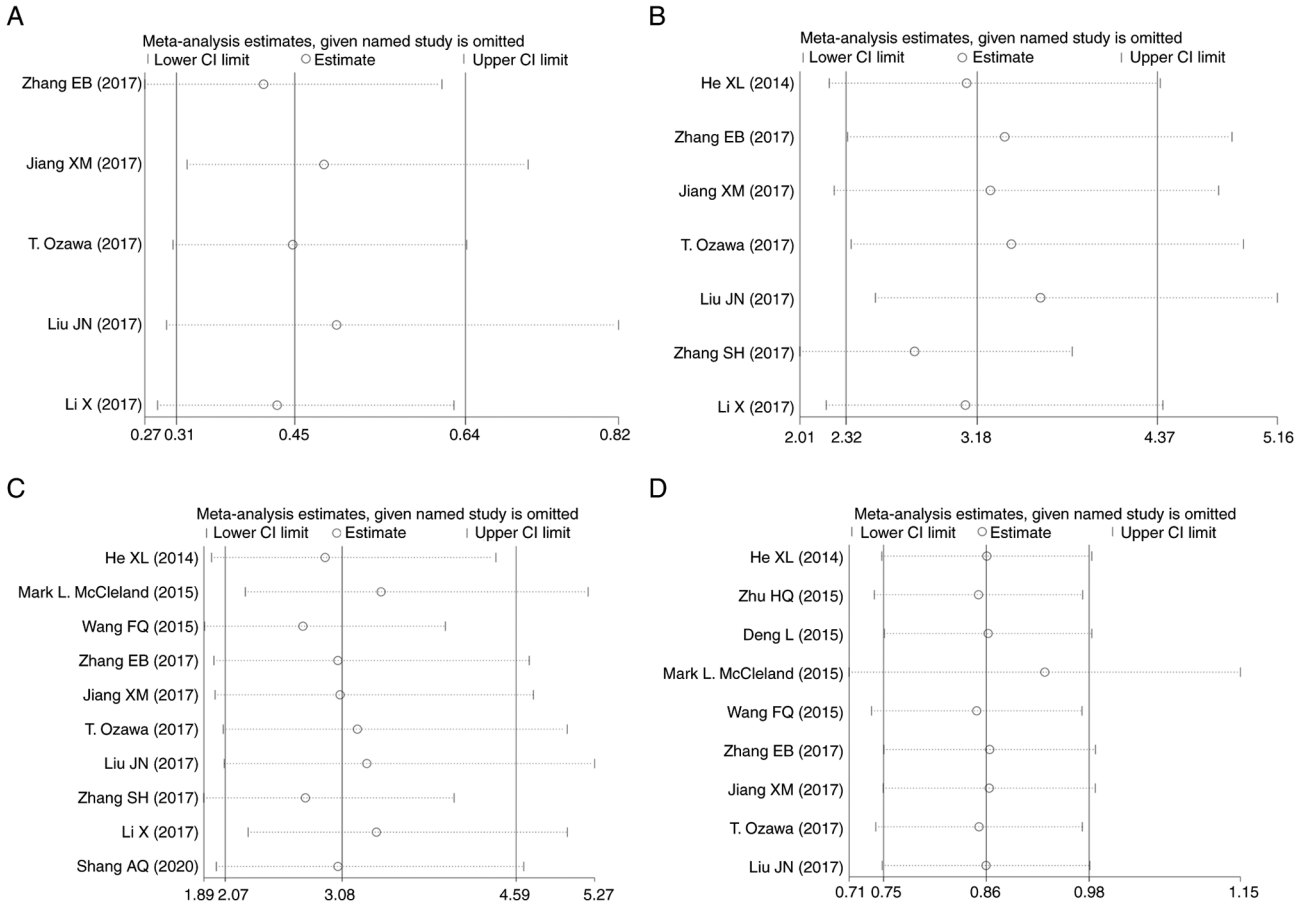

Figure 8. Sensitivity analysis to determine whether an individual study influenced the (A) differentiation, (B) lymph node metastasis, (C) TNM stage or (D) overall survival pooled results. CI, confidence interval.

The sensitivity analysis suggested that each individual study could not influence the conclusions significantly, indicating the robustness of the results.

Although the association between CCAT1 expression and the prognosis of patients with DSC was comprehensively evaluated, there were still some limitations in the present meta-analysis. Firstly, the lack of further refinement in the research strategy due to the digestive system tumors being analyzed as a whole, and not also as separate cancer entities (e.g., colorectal, gastric and esophageal cancer), was a major limitation of the present study. Secondly, most studies were from China, and only 2 articles were from the USA, which may not fully represent the conclusions of all countries, and diminished the overall effect of the results. On the one hand, it might be that through the inclusion and exclusion criteria, only articles published in English were used, which led to relevant studies in other countries not being included. On the other hand, in recent years, the incidence of DSC in China has gradually increased (56). It is possible that some eating habits are high-risk factors for the occurrence of DSC, leading to more articles on DSC in China than in other countries. Thirdly, the number of patients enrolled in some studies was relatively small, and the studies could not cover all types of DSC. Fourthly, some of the HRs were calculated by reconstructing survival curves rather than being directly obtained from the primary data. Fifthly, most enrolled studies presented positive results, and those with negative results were less likely to be published. Sixthly, the cut-off value of CCAT1 expression levels in each study had its own criteria (median or mean), which meant that there was no consensus on the cut-off estimates for differentiating high or low CCAT1 expression. Finally, the biological features and molecular mechanisms associated with different types of DSC may generate potentially inconsistent results. However, in the present study, there was still scope to analyze the existing CCAT1 articles and explore the clinical significance of CCAT1 in DSC. It is hoped that there will be more relevant studies of CCAT1 from other countries and high-quality studies involving large numbers of patients in the future, which will further strengthen the present findings and will enhance the understanding of CCAT1 in DSC and its possible mechanisms.

CCAT1 could serve as a potential biomarker for the prognosis of patients with DSC and potentially participate in DSC development and progression. Importantly, the present study sheds some light on the clinical and molecular mechanisms underlying the pathogenesis of DSC and facilitates the understanding of novel therapeutic targets in DSC. Therefore, more relevant studies that meet the requirements should be included in future studies to further evaluate the value of CCAT1 in the prognosis of DSC, so as to provide more sufficient and powerful evidence-based medical results and guide clinical medical work. A comprehensive prognosis should be based on a combination of multiple prognostic

approaches to improve the accuracy. Furthermore, more well-designed studies involving all types of DSC are needed to verify the prognostic value of CCAT1 in DSC. In future, the mechanism of CCAT1 expression from the perspective of molecular and epigenetics should be explored, and the tissue specificity of CCAT1 expression in different histological types of tumors should be validated.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZHX conceived and designed the study. YY collected and analyzed the data, and drafted the paper. CD and MXJ helped with the data analysis and manuscript revision. YY and HN analyzed the data and revised the final paper. ZHX and CD confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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