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Review Article

Long noncoding RNA CCAT2 could serve as a novel prognostic biomarker in gastrointestinal cancers

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Abstract: Background: Numerous studies have shown that CCAT2, a newly discovered lncRNA, was aberrantly upregulated in gastrointestinal cancers. Its over-expression correlated with clinical progression and poor prognosis. However, the clinical application of CCAT2 in gastrointestinal cancer remains unclear. Materials and methods: A systematic search was performed in PubMed, Web of Science, Cochrane Library together with Chinese National Knowledge Infrastructure (CNKI) and Wanfang database, the retrieval time was up to March 1, 2017. We identified relevant publications that focused on the prognostic and clinicopathological significance of CCAT2 in gastrointestinal cancers. Results: We included eight studies comprising 1039 patients in this meta-analysis. We found a significant association between upregulation of CCAT2 expression and poor overall survival (OS) (HR=1.51, 95% CI=1.28-1.75, $p<0.001$) in gastrointestinal cancers, and shorter disease-free survival (DFS) (HR=1.83; 95% CI=1.37-2.29; $p<0.001$) in gastric cancer. For OS, subgroup analyses were also performed to confirm the prognostic significance of CCAT2. Upregulation of CCAT2 correlated with unfavorable features such as tumor size, depth of invasion, lymph node metastasis and TNM stage in gastrointestinal cancers. Conclusions: CCAT2 might serve as a promising tumor-marker for predicting poor prognosis and adverse clinicopathologic characteristics in gastrointestinal cancers.

Keywords: CCAT2, cancer, digestive system, prognosis, biomarker

Introduction

Gastrointestinal cancers are defined as malignancies of the gastrointestinal tract and accessory organs of digestion. These cancers account for the majority of all-cancer incidence and mortality worldwide [1]. For patients with these malignancies, prognosis and long-term survival rates are poor. To date there are no generally accepted prognostic biomarkers for these cancers, though they are urgently needed.

Long noncoding RNAs are a group of RNA transcripts, greater than 200 nucleotides in length but without protein-coding capacity [2]. LncRNAs account for more than 80% of the entire genome transcripts. For the past several decades they have been believed to constitute transcriptional "noise" or clonal artifacts [3-4]. Recent studies suggest that lncRNAs are involved in diverse biological processes and are closely associated with various diseases such as cancer [5-8]. Numerous studies suggest that lncRNAs play important roles in tumor initiation, progression, and metastasis. They may act as prognostic biomarkers as well as therapeutic targets in human cancers [9-10].

Colon cancer-associated transcript 2 (CCAT2) is a novel lncRNA located on chromosome 8q24 [11]. It was first found to be highly overexpressed in colon cancer by Ling et al [11]. Recently, studies have shown that CCAT2 plays an important role in carcinogenesis and tumor progression. Dysregulated expression of CCAT2 might promote tumor growth, invasion, and metastasis [12]. The potential prognostic value of CCAT2 as a biomarker in gastrointestinal cancers has recently drawn substantial attention. Many studies suggest that the expression of CCAT2 is related to prognosis of gastrointestinal cancers [13-14]. These findings also suggest that CCAT2 might be employed as a prog-

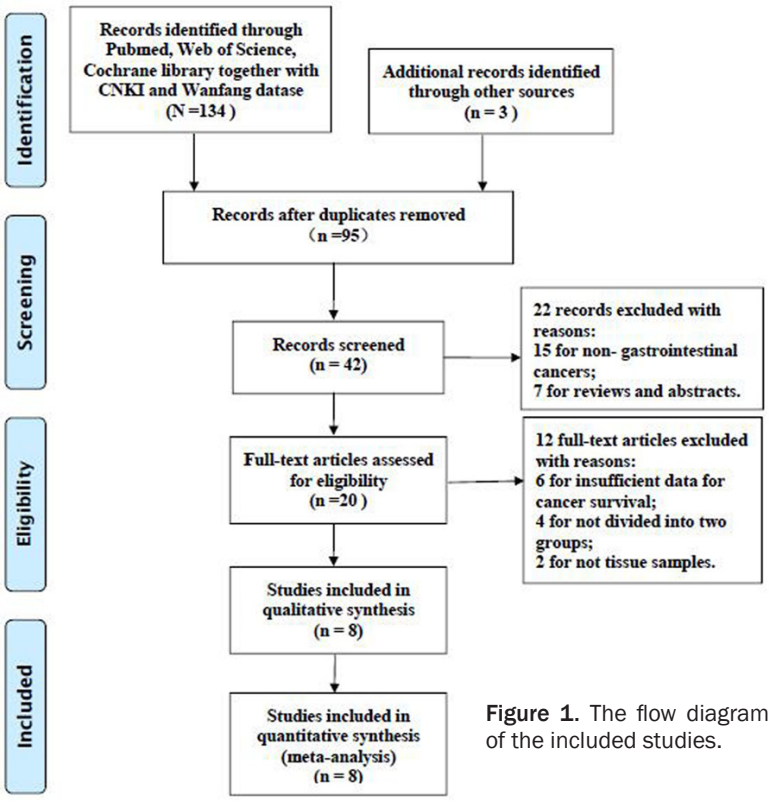

Figure 1. The flow diagram of the included studies.

nostic marker for gastrointestinal cancers. However, to date there has been no specific meta-analysis focused on the prognostic value of CCAT2 in digestive system cancers. Therefore, we performed this analysis to evaluate the relationship between CCAT2 expression level and prognosis in patients with digestive system cancers. The clinicopathological significance of CCAT2 was also analyzed.

Materials and methods

Literature search to identify relevant studies for meta-analysis

In order to obtain CCAT2-related studies, we performed a systematic search up to March 1, 2017 in the following online databases: PubMed, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Wanfang database. The combination of the following search terms was used: "colon cancer associated transcript 2" or "CCAT2" or "lncRNA CCAT2", "cancer" or "carcinoma" or "tumor" or "neoplasm", "prognosis" or "survival" or "clinical outcome". The retrieval strategy was correspondingly adjusted for particular databases. In addition, a manual search was performed against the reference lists of relevant articles. The publication languages were limited to English and Chinese.

Selection criteria for study inclusion

Studies were considered eligible for this meta-analysis if they met the following inclusion criteria: (1) studies was focused on the relationship between CCAT2 and human digestive system malignancies; (2) correlation of CCAT2 with prognosis or clinicopathological parameters was explored; (3) patients were divided into high- and low-expression groups according to the expression level of CCAT2 in tissue samples; (4) all digestive system cancers were confirmed by pathological or histological examinations.

The following studies were excluded: (1) studies involving benign tumors of the digestive system; (2) case reports, letters, reviews, or abstracts; (3) studies without available data; (4) studies with the molecular structure and functions of CCAT2 only; and (5) animal experiments.

Data extraction and quality assessment

Two investigators (ZY and LJ) extracted data and information from all included studies independently and reached consensus on all items: name of first author, publication year, country, cancer type, sample size, clinical stage, reference, outcome, cut-off value, determination method, HR and corresponding 95% CI for prognosis and relevant clinicopathological data.

For the association between CCAT2 and prognosis, we directly extracted the HRs with corresponding 95% CIs from the studies that reported such data. Otherwise, we extracted survival data from Kaplan-Meier survival curves via Engauge Digitizer V4.1.

Table 1. Main characteristics of all included studies

Author (Year)	Country	Cancer type	Total number	Clinical stage	Reference	Cut-off value	Detection method	Outcome	NOS score
Zhang X, 2015	China	ESCC	229	I-IV	RNU6B	Median	qRT-PCR	OS	8
Wang CY, 2015	China	GC	85	I-IV	GAPDH	Mean (4.3)	qRT-PCR	OS, PFS	6
Lan YZ, 2016	China	GC	62	*NA*	GAPDH	*NA*	qRT-PCR	OS	6
Wang YJ, 2016	China	GC	108	I-IV	GAPDH	Median	qRT-PCR	OS, DFS	7
Lu ZH, 2016	China	CRC	102	A-B-C-D	β-actin	Carcinoma/para-carcinoma >1	qRT-PCR	OS	7
Wu SW, 2017	China	GC	208	I-IV	β-actin	*NA*	qRT-PCR	OS, DFS	9
Kasagi Y, 2017	Japan	CRC	149	I-IV	β-actin	Exceeded 95% CI	qRT-PCR	OS, RFS	8
Xu YF, 2017	China	HCC	96	I-III	GAPDH	Median	qRT-PCR	OS	6

Abbreviations: ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; CRC: colorectal cancer; HCC: hepatocellular carcinoma; qRT-PCR: quantitative reverse-transcriptase polymerase chain reaction; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival. RFS: relapse-free survival; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; *NA*: not available.

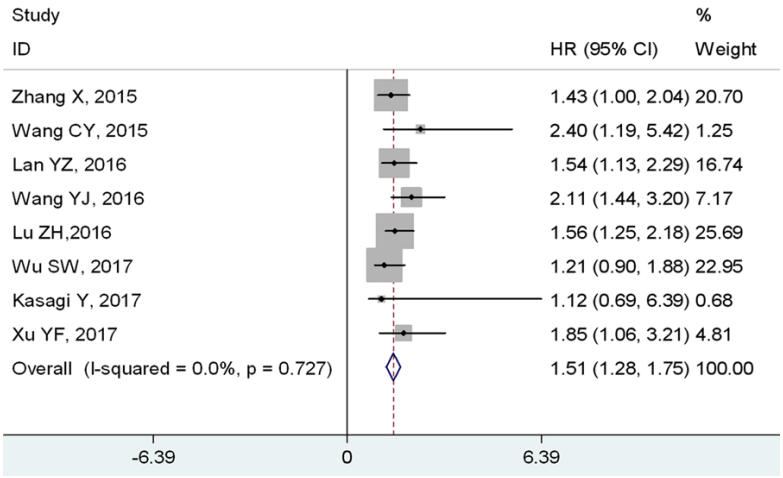

Figure 2. Forest plot of HR for the relationship between CCAT2 and OS in digestive system cancers.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies. NOS scores ranged from 0 to 9. A study with NOS score ≥6 was considered to be of high quality. The quality of all studies in this meta-analysis varied from 6 to 9, with a mean value of 7.1.

Statistical analysis

The pooled ORs for clinicopathological factors were calculated by RevMan5.3 software. Calculation of pooled HRs for OS/DFS was performed using Stata SE12.0.

We used the I^2 test and Q statistic test to determine heterogeneity among studies. Significant heterogeneity was defined as I^2>50% or P_Q< 0.05. In such cases, the random effects model was used. Otherwise, the fixed effects model was applied when no significant heterogeneity was observed across studies.

Subgroup analysis was performed to explore the prognostic value of CCAT2 in digestive system carcinomas. The Begg's test and Egger's test were used to screen for publication bias. Sensitivity analysis was also conducted. A *p* value less than 0.05 was considered statistically significant.

Results

Literature search analysis

According to the inclusion and exclusion criteria listed above, a total of eight studies [13-20] were considered in the meta-analysis. All studies reported prognostic value of CCAT2 in digestive system cancers. Detailed selection steps are shown in **Figure 1**.

A total of 1039 cases with survival data were included in this meta-analysis. Mean sample size was 129.9 with a minimum sample size of 62 and a maximum number of 229. Among those studies, four types of digestive system malignancies were, one for esophageal squamous cell carcinoma (ESCC), four for gastric cancer (GC), two for colorectal cancer (CRC) and one for hepatocellular carcinoma (HCC). All included patients were Asian. Seven studies were performed in the People's Republic of

Table 2. Summary of the meta-analysis results of pooled HRs of OS of patients with elevated CCAT2

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI)	*p*-value	Heterogeneity	
					I^2 (%)	P_Q
OS	8	1039	1.51 (1.28-1.75)	<0.001	0.0	0.727
Cancer type						
GC	4	463	1.49 (1.15-1.83)	<0.001	22.1	0.278
CRC	2	251	1.55 (1.09-2.01)	<0.001	0.0	0.765
ESCC	1	229	1.43 (1.00-2.04)	0.047	-	-
HCC	1	96	1.85 (1.06-3.21)	0.029	-	-
Country						
China	7	890	1.70 (1.40-2.00)	<0.001	0.0	0.786
Japan	1	149	1.12 (0.69-6.39)	0.48	-	-
Reference						
GAPDH	4	351	1.76 (1.33-2.19)	<0.001	0.0	0.668
β-actin	3	459	1.39 (1.06-1.73)	<0.001	0.0	0.595
RNU6B	1	229	1.43 (1.00-2.04)	0.047	-	-
Sample size						
≥100	5	796	1.47 (1.20-1.74)	<0.001	0.0	0.512
<100	3	243	1.65 (1.16-2.14)	<0.001	0.0	0.680
Analysis type						
Multivariate	5	726	1.49 (1.17-1.80)	<0.001	7.0	0.367
Non-multivariate	3	313	1.54 (1.19-1.90)	<0.001	0.0	0.956

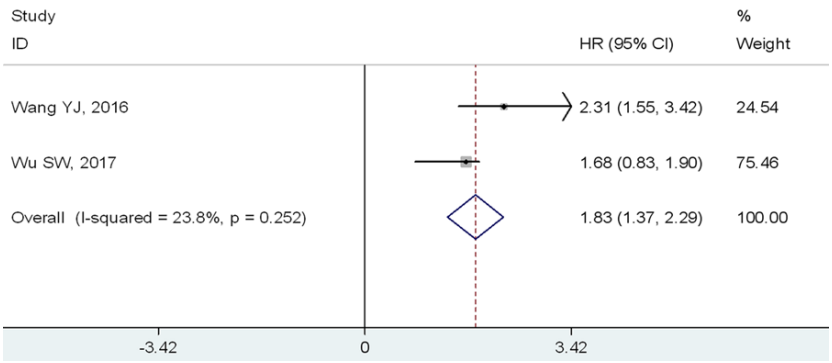

Figure 3. Forest plot of HR for the relationship between CCAT2 and DFS.

China, and one was performed in Japan. The publication period ranged from 2015 to 2017.

Among those studies, five studies directly reported the HRs and 95% CIs in multivariate analyses. The others provided Kaplan-Meier survival curves. The expression of CCAT2 in tissue samples was measured in every case by qRT-PCR. All recruited patients had pathologically or histologically confirmed cancers of the digestive system. The main characteristics are displayed in **Table 1**.

Association between lncRNA CCAT2 expression and prognosis

Increased CCAT2 expression and OS: To determine the relationship between CCAT2 and OS in digestive system cancers, we pooled all included studies with 10-39 patients. Pooled results showed that there was a significant negative association between the levels of CCAT2 and OS (HR=1.51, 95% CI= 1.28-1.75, p<0.001) (**Figure 2**). No significant heterogeneity was observed among studies (I^2=0.0 %, P_Q=0.727).

We conducted subgroup meta-analysis to further assess the prognostic value of CCAT2. Detailed results are displayed in **Table 2**. Pooled results revealed that a negative effect of elevated CCAT2 expression on OS was seen in patients with GC (HR=1.49; 95% CI=1.15-1.83; p<0.001) and CRC (HR=1.55; 95% CI=1.09-2.01; p<0.001). These data suggested that lncRNA CCAT2 was a promising prognostic marker for Chinese patients with digestive system cancer (HR=1.70; 95% CI=1.40-2.00; p<0.001). Statistically-significant pooled HR values >1 for OS were seen consistently in subgroup meta-analyses stratified by the reference, sample size and analysis type (**Table 2**).

Increased CCAT2 expression and DFS: Two studies, comprising a total of 316 GC patients, explored the association between the expression of CCAT2 and DFS. No significant cross-study heterogeneity was observed using the fixed-effects model (I^2=23.8%; P_Q=0.252).

Table 3. Meta-analysis of the association between CCAT2 and clinicopathologic parameters

Variable	Studies (n)	Number of patients	OR (95% CI)	*p*-value	Heterogeneity		
					I^2 (%)	P_Q	Model
Age (≥60 vs. <60)	5	732	1.05 (0.78-1.42)	0.73	0	0.42	Fixed
Gender (Male vs. Female)	7	977	1.06 (0.80-1.39)	0.70	0	0.99	Fixed
Tumor size (≥5 cm vs. <5 cm)	5	599	1.43 (1.03-1.99)	0.03	8	0.36	Fixed
Tumor invasion (T3-T4 vs. T1-T2)	3	342	1.68 (1.01-2.81)	0.05	0	0.81	Fixed
Tumor differentiation (Poorly/others vs. Well/moderately)	4	647	1.30 (0.67-2.54)	0.44	0.02	71	Random
Lymph node metastasis (Yes vs. No)	5	671	2.48 (1.22-5.04)	0.01	76	0.002	Random
Distant metastasis (Yes vs. No)	3	336	1.53 (0.40-5.85)	0.53	76	0.02	Random
TNM stage (III-IV vs. I-II)	5	775	2.25 (1.65-3.08)	<0.00001	49	0.10	Fixed

Overall result demonstrated that DFS was significantly worse in GC patients with high CCAT2 expression in cancerous tissues (HR=1.83; 95% CI=1.37-2.29; $p<0.001$) (**Figure 3**).

Association between lncRNA CCAT2 expression and clinicopathological features

We found that increased CCAT2 expression was significantly associated with larger tumor size (OR=1.43, 95% CI: 1.03-1.99), deeper tumor invasion (OR=1.68, 95% CI: 1.01-2.81), positive lymph node metastasis (OR=2.48, 95% CI: 1.22-5.04) and higher TNM stage (OR=2.25, 95% CI: 1.65-3.08). However, no significant correlation was observed between CCAT2 expression and age, gender, tumor differentiation and distant metastasis. Detailed description of CCAT2 expression and clinicopathological features are displayed in **Table 3**.

Publication bias

For the association between CCAT2 expression and OS, Begg's funnel plot was shown in **Figure 4**. The results from Begg's test and Egger's test suggested no significant publication bias across studies (for Begg's test: Pr>|z|=1.000; for Egger's test, P>|t|=0.613).

Sensitivity analysis

Sensitivity analysis was performed to assess the effect of any single study on OS. It showed that the combined result was not significantly altered after exclusion of any individual study (**Figure 5**).

Discussion

CCAT2, a novel long non-coding RNA transcript, was recently reported to be implicated in human diseases, especially in tumors. It was identified as an oncogenic lncRNA which was found frequently to be upregulated and associated with tumor progression in various malignancies [21-24]. Several studies have explored the correlation of CCAT2 expression with clinicopathologic features and prognosis. In ESCC, Zhang et al [13] suggested that up-regulation of CCAT2 was positively correlated with LNM and TNM stage, but not with age, sex or degree of differentiation. ESCC patients with high expression of CCAT2 had poorer overall survival. In GC, Wang et al [14] showed that high CCAT2 expression was closely associated with lymph node metastasis, distant metastasis and poor prognosis. However, there were no significant correlations between CCAT2 expression and tumor size, TNM stage, or depth of invasion. In a study of HCC, Xu et al [20] found that high CCAT2 expression group correlated with more frequent vessel invasion and advanced stages, in addition to poor prognosis. However, in a study of CRC, Kasagi et al [19] reported no significant correlations between CCAT2 expression and depth of invasion, lymph node metastasis, distant metastasis, pathological stage, overall survival and relapse-free survival rate.

The precise function and regulatory mechanism of CCAT2 in gastrointestinal cancers remains largely unknown. Several studies suggested that CCAT2 might play a pivotal role in gastrointestinal cancers. Initially, the role of CCAT2 as a tumor promoter was confirmed in colon cancer. It was reported that CCAT2, as a novel lncRNA encompassing the rs6983267 SNP, was highly overexpressed in human microsatellite-stable CRC [11]. It was suggested that CCAT2 might influence *MYC* levels and interact with TCF7L2 to enhance the activities of the WNT signaling pathway, which may result in tumor growth, metastasis and chromosomal instability [11]. Kasagi et al [19] also reported the CCAT2

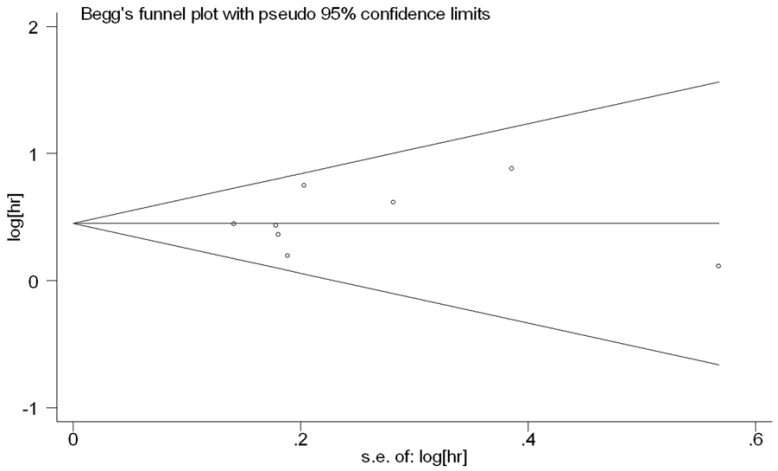

Figure 4. Funnel plot analysis of potential publication bias.

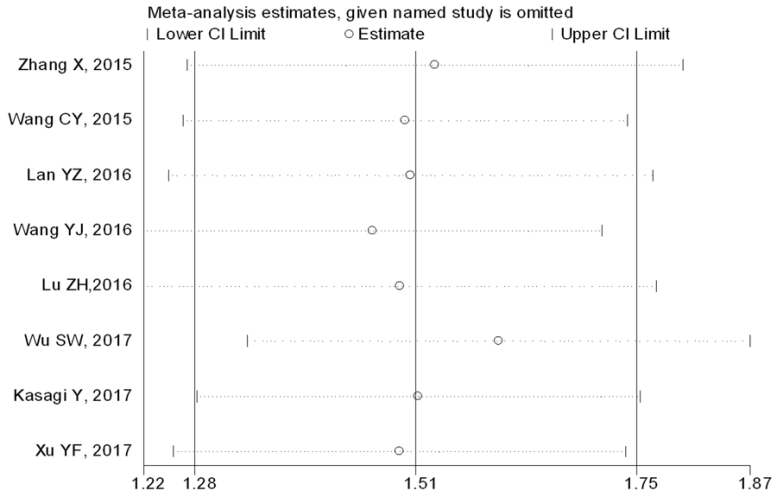

Figure 5. Sensitivity analysis of the pooled HRs of CCAT2 and OS.

expression was markedly higher in CRC tissue. CCAT2 expression was associated with microsatellite-stable CRC. In other types of gastrointestinal cancers, functional analysis demonstrated that silencing CCAT2 expression could inhibit some malignant biological properties, such as migration, invasion and metastasis. However, overexpression of CCAT2 could lead the opposite results *in vitro* and *in vivo*. In GC, the expression of CCAT2 was found to be significantly elevated in tumor tissues or GC cell lines, and up-regulation of CCAT2 promoted tumor proliferation and invasion [15, 18]. CCAT2 my function as an oncogene in GC, by promoting epithelial-mesenchymal transition via downregulation of E-cadherin and LATS2 and upregulation of ZEB2, Vimentin and N-cadherin [16]. In HCC, Zhou et al [25] investigated the physiological function of CCAT2 and suggested that enhanced CCAT2 could significantly promote cell migration and proliferation, and could inhibit apoptosis. Xu et al [20] showed that high CCAT2 expression may promote tumor metastasis by regulating Snail2-mediated epithelial-mesenchymal transition in HCC. In ESCC, the expression profile of CCAT2 was up-regulated in cancerous tissues [26]. Another study by Wang et al [13] suggested that the effect of CCAT2 on prognosis in ESCC was at least in part mediated by the CCAT2-miR-20a pathway.

To the best of our knowledge, this is the first meta-analysis to comprehensively assess the prognostic value of CCAT2 in gastrointestinal cancers. In this present study, a total of eight studies encompassing 1039 patients were included, including four major types of gastrointestinal cancer. We found that CCAT2 expression was negatively associated with OS in gastrointestinal cancers and DFS in gastric cancer. In particular, a significant prognostic value for OS was observed in Chinese patients with digestive system cancers. CCAT2 could act as a prognostic marker for GC and CRC. According to the subgroup analysis results for OS, pooled HR values >1 were also seen in the reference, sample size and analysis types. The clinical relevance of CCAT2 in gastrointestinal cancers was also investigated in this meta-analysis. From the pooled results, we found that there were significant associations between CCAT2 expression and some clinicopathological features, including tumor size, depth of invasion, lymph node metastasis and TNM stages. Taken together, these data suggest that CCAT2 expression correlates with development and progression of gastrointestinal cancers, and may serve

as a promising predictive biomarker in gastrointestinal cancers.

There were some limitations in our meta-analysis. Firstly, only eight studies with 1039 patients were included. The total number of studies and sample sizes were relatively small. Secondly, the evaluation standard for high CCAT2 expression in tissues varied across studies. Thirdly, most of patients were Chinese, introducing some question as to the generalizability of our findings. Additionally, the clinicopathological data provided in different studies varied and was limited. Finally, positive results were generally easier to publish than negative results, generating a source of potential publication bias.

Our meta-analysis synthetically provided evidence that high CCAT2 expression correlates with unfavorable prognosis and advanced clinical progression in gastrointestinal cancers. CCAT2 is a novel prognostic factor and may act as a potential marker for therapeutic regimens. Well-designed studies with larger sample sizes and greater ethnic diversity are warranted to further confirm the prognostic value of CCAT2 in gastrointestinal cancers.

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Disclosure of conflict of interest

None.

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