



# Circulating tumor DNA as a prognostic indicator of colorectal cancer recurrence—a systematic review and meta-analysis

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## Abstract

**Purpose** Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide. After resection, patients need extensive follow-up to detect asymptomatic recurrences as early as possible to obtain optimal treatment. This study evaluated the prognostic value of circulating tumor DNA (ctDNA) for CRC recurrence.

**Methods** Two investigators independently conducted a systematic literature search of peer-reviewed studies that investigated the prognostic value of ctDNA in CRC. Fixed effects or random effects models were applied for all analyses based on the assessment of heterogeneity.

**Results** A total of 189 studies were initially retrieved from all databases; ultimately, eight studies with 879 CRC patients were included in this analysis. The pooled median recurrence-free survival was 11.36 months for ctDNA-positive patients. Meta-analysis of hazard ratio (HR) suggested that postoperative ctDNA-positive patients were more likely to experience cancer recurrence than ctDNA-negative patients (pooled HR: 5.41; 95% confidence interval (CI): 2.37–8.45).

**Conclusions** Successive monitoring of ctDNA status and follow-up with postoperative computed tomography (CT)/magnetic resonance imaging (MRI) are useful tools to detect early recurrence in postoperative ctDNA-positive patients.

**Keywords** Colorectal cancer · ctDNA · Prognostic indicator · Recurrence · Meta-analysis

## Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide, with approximately 1.3 million cases diagnosed annually [1, 2]. The recurrence rate of patients with no detectable tumor cells after first-line treatment is still up to 35% [3, 4]. Since most of these recurrences occur within 2 years, it is suggested that undetected residual disease or micro-metastases may occur [4]. The 5-year survival rate for patients with stage I CRC is 93%, while the

5-year survival rate for patients with stage IV CRC is only 14% [3]. Although the standard tumor staging method based on the depth of tumor invasion, lymph node involvement, and lesion metastasis is more effective for the diagnosis of stage I and IV CRC, it lacks predictive ability for stage II and III patients. Therefore, after radical resection, patients need extensive follow-up to detect asymptomatic recurrences as early as possible to obtain optimal treatment. There are known clinical pathological factors related to the poor prognosis of tumors, such as tumor stage, lymph node involvement, and depth of lesion infiltration, which can help guide adjuvant treatment and postoperative monitoring strategies. However, even in patients without high-risk factors, disease recurrence is common [1, 3, 5].

Carcinoembryonic antigen (CEA) is currently the only biomarker that is included in monitoring guidelines; however, its sensitivity to CRC recurrence is shown to be very low [5–9]. Therefore, it is crucial to find a novel biomarker that can not only assist in screening patients who will benefit from treatment but also be used as a means to detect disease recurrence early during the monitoring period so that patients can be treated in a timely and radical manner

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[5, 10, 11]. Studies have shown that circulating tumor DNA (ctDNA) detection, which occurs by genotyping the tumor itself and targeting mutations in ctDNA markers, can alert patients at risk of recurrence [12–23]. However, these somatic mutations associated with CRC progression lack commonality and have a low incidence [24, 25]. Additionally, as cancer cells progress, their heterogeneity becomes stronger, and the reliability of this detection method will be further reduced [26–28].

In recent years, an increasing number of studies have focused on the exploration of ctDNA for the prognosis of CRC, especially the prediction of recurrence after treatment. Our study aims to summarize the results of all relevant studies and use evidence-based medicine to determine the predictive value of ctDNA for CRC recurrence.

## Methods

### Data sources and searches

The PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were systematically searched by two investigators (Y.C. and M.W.) to identify published or unpublished studies. Additionally, the reference lists of the included studies recent reviews, editorials, and meta-analyses were manually searched. Peer-reviewed studies that investigated the prognostic value of ctDNA in CRC were selected. All studies were published in English. Studies with no extractable data were excluded from the analysis.

### Data extraction and quality assessment

A data extraction form was developed to collect data from each of the included studies. Two investigators independently extracted the following characteristics: study design, cancer type and stage, sample size, ctDNA positivity rate, and duration of follow-up. Extracted data were then compared, and disagreements were resolved by consulting a third person (X.C.).

### Data synthesis and analysis

Fixed effects or random effects models were applied for all analyses based on the assessment of heterogeneity, and pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were used to represent data. We quantified the statistical heterogeneity using  $I^2$  statistics. Publication bias was assessed through funnel plot asymmetry using Egger's and Begg's tests.

The median recurrence-free survival (RFS) time for those with positive postoperative ctDNA results was obtained from KM-Plot using DigitizeIT ([www.digitizeit.com](http://www.digitizeit.com)) if it

was available in full text, and it was pooled using method by McGrath et al. [29].

Subgroup analyses were performed as follows to explore the potential sources of heterogeneity: (1) whether stage IV patients were included in the study; (2) the study setting; (3) the year publication. Two-sided  $p$  values  $< 0.05$  were considered to be statistically significant. Statistical computations used the standard software STATA/SE v12.0 (StataCorp LP, College Station, TX, USA) and R software version 3.6.2 (R Foundation for Statistical Computing).

## Results

### Characteristics of the studies

In total, 189 citations were retrieved from all databases. After removing duplicates, 124 citations remained. After reading the abstracts, 26 studies were found to be relevant. Full studies were retrieved and examined. Subsequently, 8 of these met the inclusion criteria (Fig. 1).

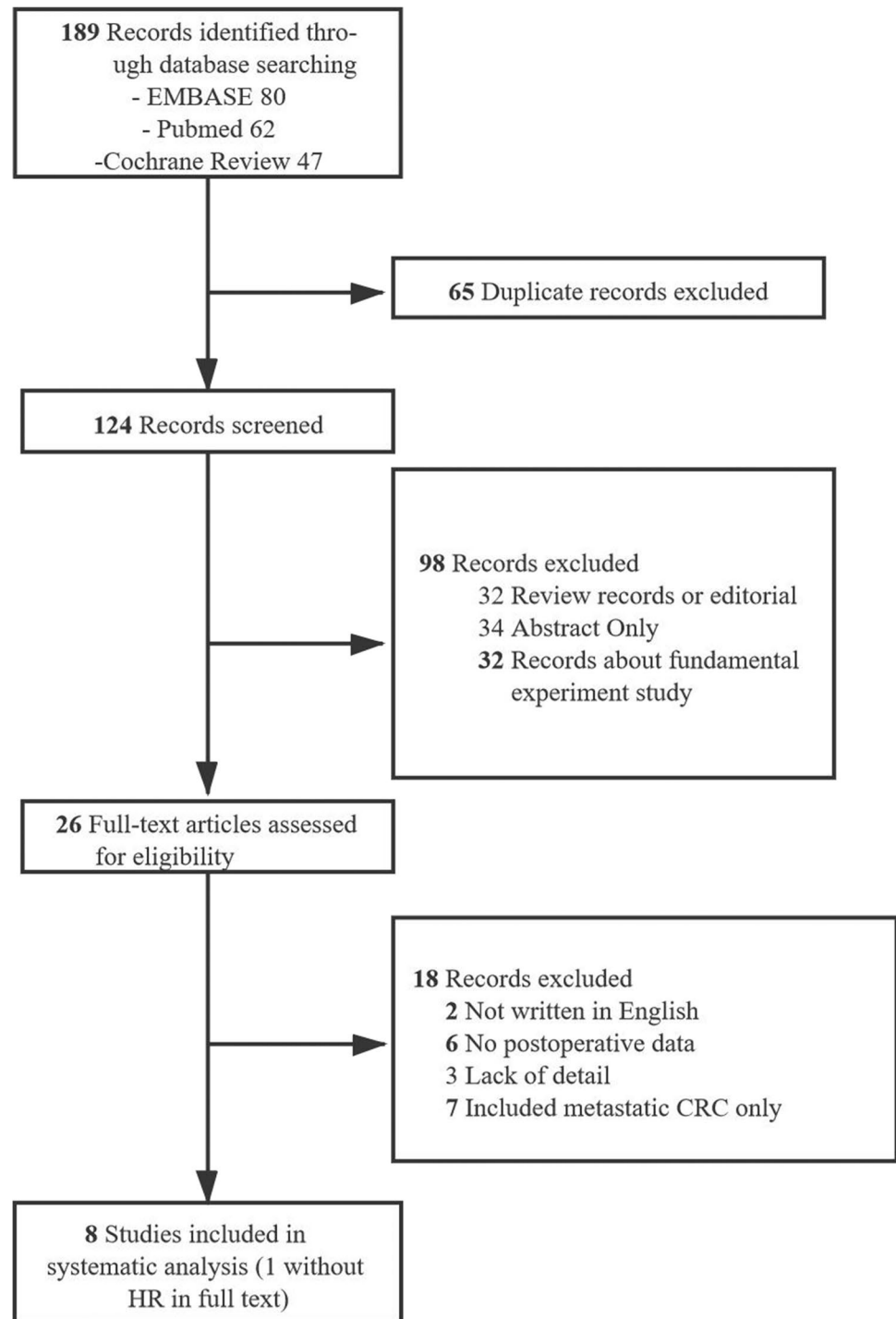
The characteristics of the 8 included studies are summarized in Table 1. A total of 879 CRC patients were included in the 8 studies. Three studies included 16 stage IV patients. The funnel plot suggested that there was no evidence of heterogeneity across studies (Fig. 2).

### Impact of ctDNA detection on the prognosis of CRC

The pooled median RFS was 11.36 months for ctDNA-positive patients. We could not pool the median RFS for ctDNA-negative patients, as the event did not occur by the time of reporting. Considering that the pooled medium follow-up time of the included studies was 24 months, the pooled RFS for ctDNA-negative patients was no less than 24 months, which was already double that of ctDNA-positive patients (Table 1). Seven of the 8 included studies reported HR. Meta-analysis of HR suggested that postoperative ctDNA-positive patients were more likely to experience cancer recurrence than ctDNA-negative patients (pooled HR: 5.41; 95% CI: 2.37–8.45) (Fig. 3).

### Subgroup analysis and meta-regression analysis

Subgroup analysis showed that studies were published in the past 5 years. The prognostic value of ctDNA was recognized in all studies. Studies in different geographic locations (Europe and Australia) were consistent in the results. The inclusion of stage IV patients did not change the overall conclusion (Table 2). However, studies with stage IV CRC patients had a lower HR (3.96, compared to studies without stage IV patients, HR 8.25), which may indicate that ctDNA might be more reliable as a prognostic indicator for stage I–III patients.

**Fig. 1** Flowchart of literature search

## Discussion

Serial radiological examination is the most widely used CRC surveillance method, which subjects patients to significant cumulative radiation doses and has a significant false-positive rate [30]. However, the criterion for radiological assessment is often unclear and questioned [31]. The measurement of blood CEA levels is currently the only guideline recommended

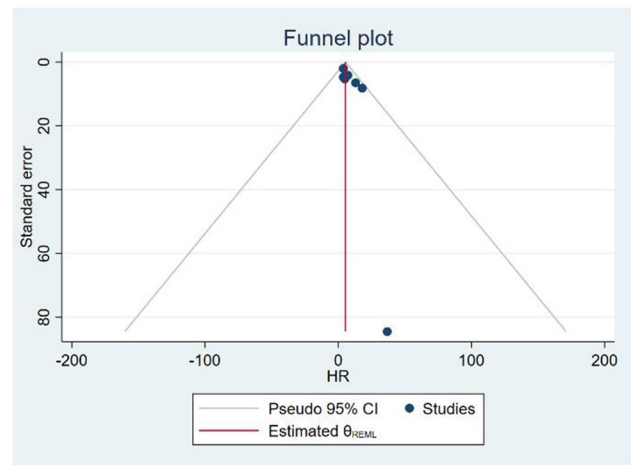
blood biomarker for postsurgical monitoring of CRC. A new monitoring method is needed to improve patient survival. Our study is the first systematic review that used meta-analysis to synthesize available data to evaluate the prognostic value of ctDNA in CRC patients after surgery. The main findings can be summarized as follows: (1) detectable ctDNA is a very meaningful indicator of CRC recurrence; (2) this finding was consistently observed in all studies; (3) the results did not

**Table 1** Characteristics of the included 8 studies

Study ID	Setting	Type of cancer	Stage of cancer	Median follow-up*	N total	N positive	N negative	n recurrent + ctDNA +	n recurrent ctDNA-	Median RFS (+)*	Median RFS (-)*	HR
Tie et al. [19]	Australia	Colon cancer	Stage III	28.9	96	20	76	10	14	20.63	3.8	3.8
Reinert et al. [15]	Denmark	CRC	Stage I–III	12.5	94	10	84	7	10	12.13	7.2	7.2
Wang et al. [20]	Sweden	CRC	Stage I/II/III	49	58	13	45	10	0	9	NR	NR
Wong et al. [21]	Australia	CRC	Stage I–IV	24	43	14	29	11	10	3.46	4.94	4.94
Murray et al. [17]	German	CRC	Stage I–IV	22.9	172	28	144	7	16	33.62	3.8	3.8
Tie et al. [22]	Australia	Rectal cancer	Stage II/III	24	159	19	140	11	12	11.36	13	13
Scholer et al. [23]	Denmark	CRC	Stage I–IV	NR	27	14	13	14	0	9.42	36.77	36.77
Tie et al. [12]	Australia	Colon cancer	Stage II	27	230	20	210	11	16	7.42	18	18
<b>Overall</b>				<b>24</b>	<b>879</b>	<b>138</b>	<b>741</b>	<b>81</b>	<b>78</b>	<b>11.36</b>	<b>5.41</b>	<b>5.41</b>

CRC colorectal cancer, N, n number of patients, HR hazard ratio, RFS recurrence-free survival, NR not reported

\*Month



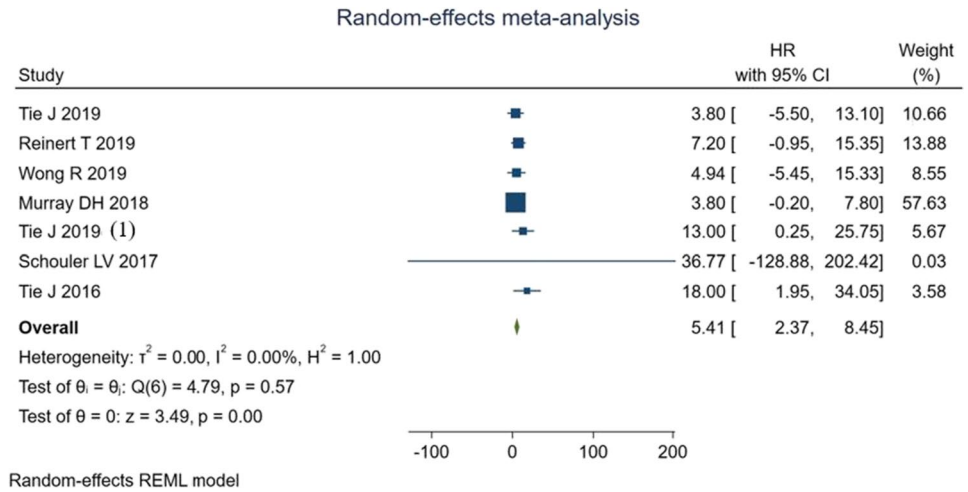
**Fig. 2** The Funnel plot demonstrating the heterogeneity of our meta-analysis

change with study time or location; and (4) ctDNA might be more reliable for predicting the prognosis of stage I–III CRC.

Approximately 2/3 of CRC patients were diagnosed at stage I–III, with localized and potentially curable disease. However, a large portion of patients still experience recurrence after curative surgery [32–34]. Therefore, it is crucial to identify patients at high risk of recurrence so that adjuvant therapy can be offered [35, 36]. Currently, TNM staging is the most widely used approach for estimating the risk of CRC recurrence. However, it has its limitations. ctDNA detection has become a mature technology in many clinical centers around the world. However, due to its higher testing costs and longer testing time, its clinical applications have been largely limited. The number of included studies and samples were relatively small and dispersed for the same reason. Our systematic review synthesized available data from different clinical centers and confirmed the prognostic value of ctDNA as a recurrence indicator of CRC to provide a theoretical basis for future prospective research. Our results support the clinical usage of ctDNA for CRC patients, especially those with stage I–III disease, after curative surgeries in the guidance of adjuvant therapies.

The pooled median RFS was 11.36 months for ctDNA-positive CRC. ctDNA-positive status was associated with shorter survival and disease recurrence in all 3 stages of CRC. As observed by Lecomte et al. [37], the survival time for CRC patients with ctDNA was 2 years shorter than that for those without ctDNA. Their study suggested that ctDNA analysis could distinguish CRC patients with a high risk of recurrence [37]. A significant correlation between ctDNA status and postoperative recurrence was also found by Wang et al. [38]. Tsikitis et al. [39] examined the postoperative recurrence rate by CRC stage and found that the estimated RFS rates at 5 years following surgery were 90% for stage II

**Fig. 3** The forest plot demonstrating recurrence-free survival in terms of ctDNA-positive vs ctDNA-negative



patients and 70% for stage III patients. For stage IV patients, the outcome is often poorer, as the 5-year survival rate is less than 10% [40], with a median survival time of approximately 6–12 months.

Curative-intent surgery has become amenable to more CRC patients due to advances in surgical, radiological, and therapeutic options over the past decade. How to monitor patient prognosis after surgery is being widely investigated. Our meta-analysis of HR suggested that postoperative ctDNA-positive patients were more likely to experience cancer recurrence than ctDNA-negative patients (pooled HR: 5.41; 95% CI: 2.37–8.45). Therefore, for postoperative ctDNA-positive patients, successive monitoring of ctDNA status and follow-up with more frequent postoperative computed tomography (CT)/magnetic resonance imaging (MRI) are necessary for early detection of CRC recurrence. Clinical application of ctDNA can be an excellent supplement to the current disease monitoring methods. Personalized assays can be created based on gene

mutations that are detected within a tumor biopsy or panel of ctDNA genes to facilitate ongoing ctDNA measurement. Positive or negative ctDNA status can be identified by the presence of a particular gene alteration. Thus, ctDNA measurement can be used as a noninvasive method of tumor monitoring and assessment of therapy response.

Levels of ctDNA dropped following surgery, suggesting preoperative ctDNA correlates with macroscopic tumor burden [41]. Patients with residual disease were significantly more likely to have a positive postoperative ctDNA status. One study that was included in this systematic review specifically focused on the postchemotherapy ctDNA level and risk of disease recurrence and found that assessment of ctDNA at the end of adjuvant therapy showed that a positive result was predictive of disease recurrence [12]. Since ctDNA status is proven to be useful as a surrogate marker for the presence of residual disease, the postchemotherapy ctDNA level could potentially be a more important marker for patient prognosis monitoring.

Additionally, it is worth noting that, given COVID-19, much surveillance imaging has been deferred due to the risk of coming to the hospital/clinics to get a scan [42, 43]. Noninvasive blood ctDNA monitoring, which can also be performed at home, may be one additional method of surveillance and decreasing contact and exposure during the COVID-19 pandemic [44, 45].

Our study has several limitations. First, because of the limited clinical application, the number of included studies was relatively small, although no significant heterogeneity was found among the studies. Several studies were still in the follow-up period; hence, the medium recurrence-free survival was not fully reported. The testing methods of ctDNA also varied among studies. Second, our studies are mainly from Europe and Australia, and studies from other geographic locations may also be needed in future updates. Third, we analyzed the prognostic value of ctDNA by cancer stage. However, the individual studies that were included did not report such data.

**Table 2** Subgroup analyses

Subgroup	No. of studies	HR	95% CI		P value
Year of publication					
2016	1	18.00	1.95	34.05	0.028
2017	1	36.77	(128.88)	202.42	0.664
2018	1	3.80	(0.20)	7.80	0.063
2019	4	6.62	1.74	11.49	0.008
Setting					
Australia	4	7.76	2.07	13.45	0.008
Denmark	2	7.27	(0.87)	15.41	0.080
German	1	3.80	(0.20)	7.80	0.063
Include IV stage					
No	4	8.25	3.02	13.47	0.002
Yes	3	3.96	0.23	7.70	0.037
Overall	7	5.41	2.37	8.45	<0.001

CI confidence interval, HR hazard ratio

## Conclusion

In brief, successive monitoring of ctDNA status and follow-up with postoperative CT/MRI are useful tools to detect early recurrence in postoperative ctDNA-positive patients.

**Author contribution** J.J.P. contributed to conception and design; Y.K.C., S.B.M., and Y.Q.L. contributed to development of methodology; Y.K.C., S.B.M., M.D.W., Y.Q.L., and X.C. contributed to acquisition of data; Y.K.C., M.D.W., and X.C. contributed to analysis and interpretation of data; Y.K.C., S.B.M., M.D.W., and X.C. contributed to writing of the manuscript; Y.Q.L. and J.J.P. contributed to review and revision of the manuscript; J.J.P. contributed to study supervision. All authors approved the final version of the manuscript, including the authorship list.

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**Availability of data and materials** The dataset used during the study are available from the corresponding author on a reasonable request.

## Declarations

**Consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.

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