Review Article

Clinicopathological and prognostic value of circulating tumor cells in esophageal carcinoma: a meta-analysis

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Abstract: The associations between circulating tumor cells (CTCs) in peripheral blood and prognosis of patients with esophageal carcinoma (EC) have been investigated by a number of studies, but the results are not consistent. Therefore, this study aimed to explore this controversial subject. A literature database search was performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. The risk ratio (RR), hazard ratio (HR) and their 95% confidence intervals (CIs) were retained as the effect measures. If necessary, subgroup analyses and meta-regression should also be performed to clarify the heterogeneity. Thirty-three studies, containing 3,236 patients with EC, were included in this meta-analysis. The results showed that overall survival (OS) (HR =2.14; 95% CI, 1.73–2.65) and progression-free survival (PFS) (HR =2.29; 95% CI, 1.69–3.11) were worse in CTCs-positive patients. CTC positivity is also significantly associated with depth of infiltration (RR =1.42; 95% CI, 1.10–1.82, P=0.21) and tumor-node-metastasis (TNM) stage (RR =1.36; 95% CI, 1.09–1.69, P=0.22). However, there was no significant relationship between CTC-positive and distant metastasis (RR =1.58; 95% CI, 1.00–2.50, P=0.65). Detection of CTCs had prognostic value for EC patients. Positive CTC is associated with poor prognosis and some prognostic factors, such as depth of infiltration and TNM stage, but not related to metastasis.

Keywords: Circulating tumor cells (CTCs); esophagus cancer; lymphatic metastasis; meta-analysis

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Introduction

Esophageal cancer (EC) is the eighth most common malignant tumor worldwide and the sixth leading cause of cancer-related death worldwide, with approximately 572,000 new cases and 509,000 deaths (1). There are two most common histopathological subtypes, squamous cell carcinoma and adenocarcinoma. Patients with EC, compared with those with other cancers, have poorer prognosis because of earlier metastasis or recurrence (2). Although new strategies including preoperative radio chemotherapy and three-field lymph node dissection have been implemented, the outcomes are still unsatisfactory. Therefore, biomarkers that can identify the recurrence or metastasis are needed to facilitate timely diagnosis and treatment strategies and thus improve the prognosis of EC

patients.

Circulating tumor cells (CTCs), which are defined as cancer cells that have escaped from the primary tumor into the circulation, have great promise as a "liquid biopsy", a noninvasive method of assessing tumor progression in real time. CTCs have several advantages over other technologies. Firstly, it is directly related to invasion and development of metastasis, and can even reflect the micrometastases status to a certain degree (3). Secondly, the collection of peripheral blood samples is convenient and simple, without radioactive pollution or risk of massive hemorrhage.

New research shows that a fraction of CTCs is capable of entering distant sites and progressing toward metastases. CTCs can remain non-proliferative state for a long period of time and resist the anti-tumor effect of chemotherapy drugs (4). In fact, the significance of CTCs in the peripheral blood of patients with various malignancies has been widely studied extensively in various malignancies. Previous studies have demonstrated that CTCs are closely related to tumor prognosis in breast cancer (5), lung cancer (6), gastric cancer (7), and pancreatic cancer (8). In the past two decades, a considerable amount of literature studied the relationship between CTCs and EC. Two previous meta-analysis (9,10) found that CTC status was related to TNM stage of cancer, but was not related to T stage or degree of differentiation in patients in esophageal patients. No significant relationship was found between CTCs and survival time of EC, definitely. Wang conducted a meta-analysis (11) providing strong evidence that detection of CTCs in the peripheral blood was an independent prognostic indicator of poor outcome for esophageal squamous cell carcinoma (ESCC) patients. Whereas Wang only based only on 13 studies and 715 patients, without specifying the correlation between clinicopathological parameters and CTCs status. Our meta-analysis will be the first systematic review to clearly investigate this issue and evaluate potential sources of heterogeneity that may affect some existing conclusions. We presented the following article in accordance with the PRISMA Checklist (available at http://dx.doi.org/10.21037/apm-20-590).

Methods

Search strategy

This systematic review and meta-analysis were registered at International Prospective Register of Systematic Reviews (CRD42019125600). PubMed, EMBASE, ISI Web of Science database and Cochrane Library were searched for eligible studies between January, 2000 and August, 2019. The following search terms were used for the literature search: (circulating tumor cells OR circulating cancer cells OR CTCs) AND (esophageal carcinoma OR esophageal cancer OR oesophageal cancer). The last search was conducted on January 17, 2020. The language was limited to English. Two authors independently retrieved the titles and abstracts of the primary studies identified in the electronic search. In addition, references of potentially relevant studies were also examined.

Inclusion and exclusion criteria

Articles, which met the following criteria, were included in the meta-analysis: (I) investigated the clinicopathological or prognostic of CTC detection in EC patients; (II) reported hazard ratio (HR) or a risk ratio (RR) with a 95% confidence interval (CI) of overall survival (OS) or/and progression-free survival (PFS) in the study or had sufficient data to calculate a RR of clinicopathological characteristic; (III) collected samples from PB; (IV) the study with observational design. Exclusion criteria were: (I) review articles, letters, comments and case reports; and (II) studies unable to retrieve or calculate data of interest. To avoid the inclusion of duplicated studies, all the included studies were carefully checked, including their authors, organization, accrual periods, and population of patients.

Data extraction and quality assessment

Two reviewers independently examined the included studies for eligibility and retrieved the information from all eligible studies. The following information was collected: first author, year of publication, country, characteristics of the study population (number, sex and age), TNM stage, adjuvant therapy, detection marker, CTCs-positive rate, treatment, follow-up period, the HR and its associated standard errors on prognostic outcomes (OS or/and PFS). If the HR and its 95% CI were not directly provided in the original articles, the method used was to incorporate summary time-to-event data into meta-analysis (12). In addition, if available, multivariate analysis was preferable because it also considered possible confounding factors (13). The methodological quality was assessed by two authors using the Newcastle-Ottawa Scale (NOS) with 0-3 scores defined as low quality, 4-6 scores as moderate quality, and

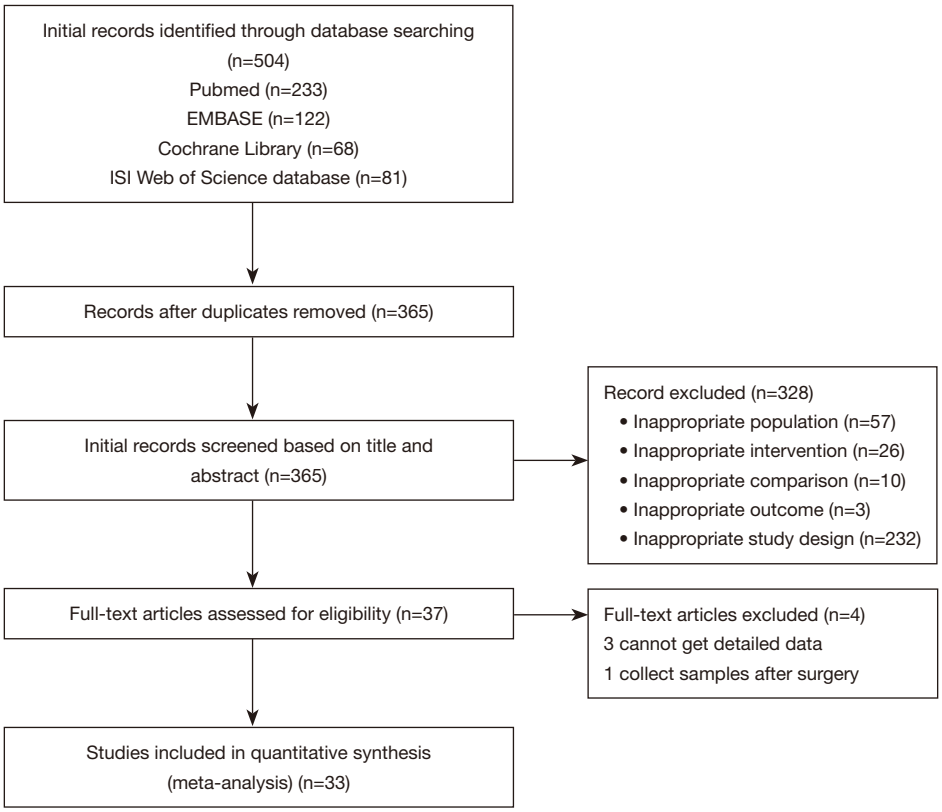

Figure 1 Flow diagram of included studies for this meta-analysis.

7-9 scores as high quality (14,15). Discrepancies between the two reviewers were resolved through discussion and consensus. If still no agreement was reached, an additional adjudicator was invited into the discussion.

Statistical analysis

HR, RR and their associated 95% CI were used as the effect indicators for summarizing the clinicopathological and prognostic significance of CTCs in EC. If available, multivariate-adjust risks were used for each study. All eligible studies were included in the analysis. The heterogeneity between studies was evaluated with Q and I^2 statistics (16). Studies with an I^2 statistics of 0%, 25%, 50% and 75% represented no, low, moderate, and high heterogeneity. According to the results of inter-study heterogeneity appraisal using Q and I^2 statistics, pooled RRs and HRs with 95% CI were calculated using a fixed-effect model (Mantel-Haenszel method) or random-effect model (DerSimonian-Laird method) (17). Sensitivity analysis was performed to assess the impact of a single study on the meta-analysis estimated by sequential omission of individual studies. If necessary, the heterogeneity was also explored by subgroup and meta-regression. The potential publication bias was further validated by the Egger's and Begg's test (18). The STATA version 12.0 (Stata Corp LP, College Station, Texas, USA) was used for statistical analysis. All statistical analyses were two sides. A P value less than 0.05 was considered statistically significant. The data-analysis started in February 10, 2020 and was completed in February 14, 2020.

Results

Study selection and characteristics

The PRISMA flow chart of this meta-analysis was shown in *Figure 1*. Duplicates and irrelevant studies or those without sufficient data were removed from a total of 504 publications. All investigators finally agreed to include 33 eligible studies in our meta-analysis (*Table 1*). Among these, Seventeen studies (19-35) were conducted on esophageal squamous cell carcinoma (ESCC), and nine (36-44) addressed esophageal adenocarcinoma cancer (EAC). Other

studies (45-51) addressed both. Three (22,28,29) only reported Clinicopathological parameters. The average age (median or mean) in the included studies was ranged from 58.9 to 65 years. The sample size was ranged from 18 to 410. All studies were of moderate or high quality.

Correlation between CTCs and OS

Data on OS were available in 25 studies (19-21,23,25-27,31,32,34,36-48,50,51). With considerable evidence of heterogeneity between studies (I^2=89.0%, P=0.000), the data from the subgroups within a single study was pooled using a random-effect model. The pooled results showed that OS of patients with CTCs-positive EC was significantly lower than that of CTCs-negative patients (HR =2.14; 95% CI, 1.73–2.65; *Figure 2*). We performed subgroup analysis to further assess whether the CTC positivity had prognostic value in different subsets (*Table 2*), and the stratified results showed that compared with CTCs-negative patients, CTCs-positive patients had a higher risk for poor OS in these subgroups. As to the difference of the detection methods, especially, the studies were divided into two subgroups (the PCR group and the non-PCR group). A significant difference in OS between CTC-positive and CTC-negative patients was found in both PCR and Non-PCR subgroups. The estimated HR was 3.27 (95% CI, 2.30–4.65) in the PCR subgroup and 1.58 (95% CI, 1.20–2.08) in the non-PCR subgroup. The meta-regression analysis showed no significant role of a variable to account for the heterogeneity (*Table 3*) and no single study markedly changed the overall effect on the sensitivity analysis.

Correlation between CTCs and PFS

Nineteen studies (19-21,23,24,26,27,30-35,39,40,43,44,49,51) were included in this meta-analysis. High heterogeneity was shown among the studies (I^2=83.4%, P=0.000). Therefore, the data was pooled in a random-effect. The pooled data revealed that compared with CTCs-negative EC patients, the CTCs-positive patients had a higher risk of disease progression (HR =2.29; 95% CI, 1.69–3.11, *Figure 3*). The meta-regression was further performed to explore the source of heterogeneity on PFS. As showed in *Table 3*, only the method of CTC detection was significantly correlated with intra-study variability (P=0.021), which explained 92.42% of the heterogeneity in the analysis. Furthermore, we conducted subgroup analysis to evaluate the prognostic value of CTCs detected by two most common methods respectively. The pooled HR, in random-effect, for the studies based on RT-PCR that assessed the association between CTCs and the PFS of EC (HR =1.67; 95% CI, 1.19–2.34, *Figure 3*), with high heterogeneity (I^2=84.7%, P=0.000). However, when studies on non-PCR were combined, no high heterogeneity was found (I^2=2.4%, P=0.415), with high HR (HR =3.32; 95% CI, 2.43–3.53, *Figure 3*) in fixed-effect. In other subgroup analysis, the overall effect did not change significantly in the subgroup. In the sensitivity analysis, the exclusion of any single study did not remarkably change the overall effect.

Association between CTCs and clinicopathological parameters

Thirteen studies including 15 sets of data were evaluated to determine the relationship between CTC-positive and TNM stage. With moderate heterogeneity (I^2=59.8%, P<0.05), the results showed, TNM stage was associated with CTC positivity (RR =1.36; 95% CI, 1.09–1.69, P=0.22). The depth of tumor infiltration was associated with the CTC positivity (RR =1.42; 95% CI, 1.10–1.82, P=0.21), with low heterogeneity (I^2=48.0%, P=0.027), but the regional lymph nodes metastasis was not statistically associated with the CTC positivity (RR =1.31; 95% CI, 0.96–1.80, P=0.76), with high heterogeneity (I^2=75.4%, P<0.05). Studies assessed by pooled analyses showed no significant association between CTC-positive and distant metastasis (RR =1.58; 95% CI, 1.00–2.50, P=0.65), with high heterogeneity (I^2=84.4%, P=0.000). Similarly, the data from eight studies demonstrated that tumor grade was not associated with the CTC positivity (RR =0.88; 95% CI, 0.71–1.09, P=0.15). Low heterogeneity was shown among studies (I^2=29.2%, P=0.195). And all analyses were conducted in random-effect. In addition, the EC adjusted survival rates did not differ by anatomic location of the tumor. Moreover, sensitivity analysis confirmed that no individual study influenced affected the overall results.

Publication bias

The publication bias in this meta-analysis were indicated by Egger's test and Begg's test. The results were shown in *Table 4*. Notably, a significant publication bias was revealed by Egger's test (P=0.033) on the association between regional lymph nodes metastasis and CTC-positive, but not by the Begg's test (P=0.732). The conclusions were not changed after adjustment for publication bias by using the

Table 1 Baseline characteristics of the included studies

Article	Country	Number	Rate%	Treatment	Detection method	Markers	Survival measure	Quality scores
Qiao *et al.* 2017	China	59	56%	Surgery non-surgery	IHC	CK8/18/19, CD45, DAPI	OS, PFS	7
Li *et al.* 2016	China	140	54%	Surgery	IHC	CK19, CD45, DAPI	OS, PFS	7
Tanaka *et al.* 2010	Japan	244	14%	Surgery	RT-PCR	CEAA, SCCA	PFS	8
Li *et al.* 2015	China	61	32%	Surgery	Cell search	CK, EpCAM, CD45, DAPI	–	8
Cao *et al.* 2009	China	108	47%	Surgery	RT-PCR	Survivin, SCC	OS, PFS	6
Reeh *et al.* 2015	Germany	100	43%	Surgery	Cell search	CK8/18/19, EpCAM, CD45,	OS	9
Ling *et al.* 2012	China	209	37%	Surgery	IHC	MSH2	PFS	8
Matsushita *et al.* 2015	Japan	90	28%	Non-surgery	Cell search	CK8/18/19, EpCAM, CD45, DAPI	OS	6
Setoyama *et al.* 2007	Japan	125	62%	Surgery	RT-PCR	CEA	OS, PFS	7
Yin *et al.* 2012	China	72	69%	Non-surgery	RT-PCR	CEA, CK19, Survivin	PFS	8
Choi *et al.* 2018	Korea	73	90%	Non-surgery	Immunofluorescence	CK, EpCAM, CD45, DAPI	–	8
Hiraiwa *et al.* 2008	Japan	38	52%	Non-surgery	Cell search	CK, EpCAM, CD45	OS	7
Hoffmann *et al.* 2009	Germany	59	61%	Non-surgery	RT-PCR	APC, DAPK	OS	8
Hoffmann *et al.* 2010	Germany	62	61%	Non-surgery	RT-PCR	Survivin	OS	8
Hoffmann *et al.* 2017	Germany	112	84%	Surgery	RT-PCR	ERBB2	OS	8
Brung *et al.* 2018	Australia	43	47%	Non-surgery	Cell search	CK, EpCAM, CD45	OS	7
Han *et al.* 2019	China	110	55%	Non-surgery Surgery	BIOPSY system	CK, EpCAM, CD45, DAPI	PFS	7
Honma *et al.* 2006	Japan	46	43%	Surgery	RT-PCR	SCCA	OS	6
Sclafani *et al.* 2014	USA	18	56%	Non-surgery	Cell search	CK, EpCAM, CD45, DAPI	OS	6
Kaganoi *et al.* 2004	Japan	70	33%	Non-surgery	RT-PCR	SCCA, GAPDH	–	7
Kubisch *et al.* 2015	USA	69	83%	Non-surgery	RT-PCR	KRT19, MUCI, EPCAM, CEACAM5	OS, PFS	8
Pernot *et al.* 2017	France	89	55%	Non-surgery	Cell search	CK8/18/19, EpCAM, CD45, DAPI	OS, PFS	8
Qiao *et al.* 2015	China	139	45%	Surgery	RT-PCR	CK19	PFS	8
Qiao *et al.* 2017	China	129	77%	Surgery	RT-PCR	CK19, CEA	OS	9
Matsusaka *et al.* 2010	Japan	52	90%	Non-surgery	Cell search	CK, EpCAM, CD45	OS, PFS	9
Schumacher *et al.* 2017	Germany	73	81%	Surgery	RT-PCR	CK18, EpCAM,	OS, PFS	6

Table 1 (*continued*)

Table 1 (*continued*)

Article	Country	Number	Rate%	Treatment	Detection method	Markers	Survival measure	Quality scores
Shim *et al.* 2015	Korea	53	45%	Non-surgery	RT-PCR	FGFR4	OS, PFS	7
Song *et al.* 2012	China	85	59%	Non-surgery	RT-PCR	STC-1	PFS	7
Su *et al.* 2016	China	57	85%	Non-surgery	RT-PCR	CEA	OS, PFS	8
Tachezy *et al.* 2011	Germany	410	91%	Non-surgery	Immunofluorescence	CK, ALCAM, CD166	OS,	8
Zhang *et al.* 2019	China	63	79%	Surgery	Cell search	CK18, EpCAM, CD45, CEP8	PFS	6
Macguil *et al.* 2007	Ireland	146	59%	Non-surgery	IHC	CK	OS, PFS	7
Kolodziejczyk *et al.* 2007	Poland	32	78%	Non-surgery	Cell search	CK18, EpCAM, CD45	OS	7

IHC, immunohistochemistry; RT-PCR, reverse transcription-polymerase chain reaction.

trim and fill method (52).

Discussion

In this meta-analysis, we discussed the prognostic value of CTCs in EC, including 3,271 patients with 33 publications. Survival outcome could be obtained from 31 studies including 3,073 patients. The pooled data demonstrated that CTC-positive patients had poorer OS and DFS than CTC-negative patients, suggesting that CTCs is a useful biomarker for the clinical prognosis of patients with EC. In addition, this meta-analysis assessed the correlation between clinicopathological parameters of EC patients and the results showed that the depth of tumor and later TNM stage were significantly correlated with CTC positivity.

A meta-analysis discussed clinicopathological and prognostic value of CTC-positive patients for both PFS and OS in patients with EC. However, due to the significant heterogeneity in PFS, they only confirmed the clinical value for OS (10).

Therefore, this meta-analysis took peripheral blood samples of patients with EC and analyzed the clinicopathological and prognostic value of CTCs. We included high quality studies with sufficiently large sample. At present, the prognosis outcome of EC patients is still guided by the TNM stage, which is influenced by clinicopathological parameters such as vascular invasion, poor differentiation, tumor size and serum tumor markers. In terms of cost and simple operation, CTC analysis has the advantages to serve as a monitoring tool pre- or/and post-treatment. Several studies suggested that CTCs detection could provide important prognostic information for patients with EC (53). Many factors may influence the CTCs status. The sampling time, pre- or post-treatment, also seemed to play an important role in CTC analysis. In endometrial cancer, the relationship between prognosis and post-treatment CTC status was more convincing because post-treatment CTCs status contained pre-treatment CTCs and released CTCs during therapy, especially operation (54). However, rapid apoptotic death of pre-treatment CTCs may release massive tumor genes or antigens due to the change of the survival microenvironment in the process of operation, which might cause detection bias. Hence, uncertainties still remained, and the sampling time could provide more prognostic information, which needs further research work to confirm this relationship.

Several limitations of this study must be acknowledged. First, although several subgroup analyses were performed,

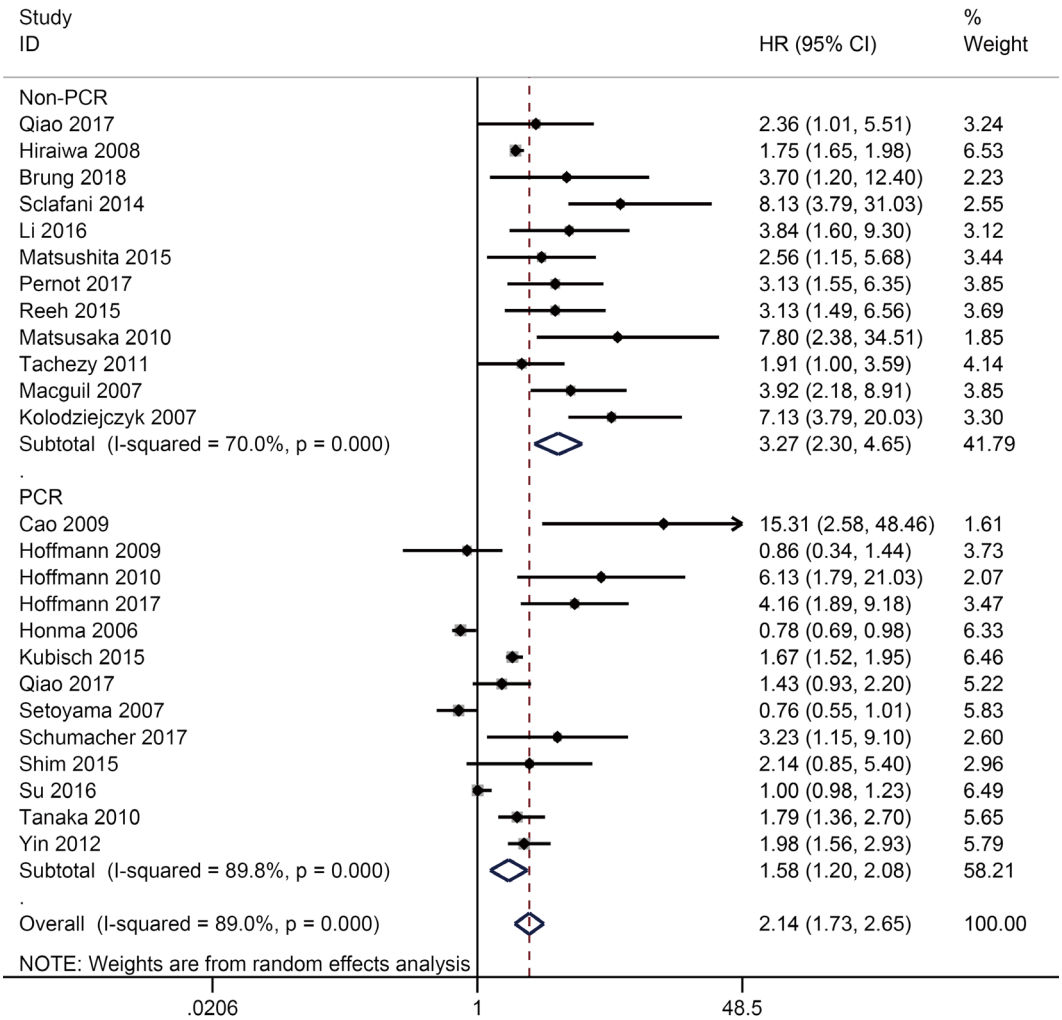

Figure 2 Hazard ratio (HR) for overall survival (OS) of the included studies. PCR, polymerase chain reaction; non-PCR, non-polymerase chain reaction.

significant heterogeneity was generally observed. Given the differences of the studies in age, subjects' lifestyle, information collection method, sample size and so on, the heterogeneity was inevitable. We addressed the heterogeneity by using a random effects model to obtain a more conservative result. Second, the number of stratified analysis was so limited that might cause a result in invalid statistical analyses in those groups. Our overall results lead to imprecision in the results. Besides, several sources of bias would be crude. Third, although we used multivariate statistical models to calculate the estimated RR, the number and content of the adjusted confounders varied in each trial, as inherent limitations, unmeasured confounding, and the typical bias in observational studies, may influence the observed results.

Our meta-analysis systematically assessed the prognostic significance of CTCs in EC patients. Our results suggested that standardized testing method, optimized sampling time, complete analysis and report of results played an important role in deriving more accurate prognostic significance of CTCs in EC patients.

Conclusions

Our meta-analysis suggested the CTCs testing has high prognostic value in EC and confirmed that CTC-positive patients were associated with poor PFS and OS. In addition, we found that CTC-positive patients were significantly

Table 2 Result of subgroup analyses on OS and PFS

Variables	OS					PFS				
	HR [95% CI]	Number	Model	I^2	P value	HR [95% CI]	Number	Model	I^2	P value
Method										
Non-PCR	3.27 [2.30–4.65]	12	Random	70.0%	0.000	1.86 [0.87–3.15]	9	Random	2.4%	0.415
PCR	1.58 [1.20–2.08]	13	Random	89.8%	0.000	3.66 [1.25–7.41]	10	Random	84.7%	0.000
Pathology										
ESCC	1.73 [1.25–2.38]	11	Random	87.7%	0.000	3.29 [1.72–6.29]	4	Random	61.3%	0.051
EAC	2.18 [1.71–2.77]	8	Random	73.1%	0.001	2.18 [1.71–2.77]	12	Random	84.4%	0.000
EAC+ESCC	2.67 [1.56–4.57]	6	Random	65.3%	0.013	2.18 [1.71–2.77]	3	Random	79.6%	0.007
Marker number										
Single	3.54 [1.54–4.11]	7	Random	80.6%	0.000	3.92 [3.25–7.32]	7	Random	46.5%	0.181
Multiple	1.34 [1.01–4.02]	18	Random	25.3%	0.062	3.01 [1.57–6.92]	12	Random	74.5%	0.000
Treatment										
Surgery	3.69 [2.54–4.34]	18	Random	78.0%	0.001	3.91 [3.57–6.75]	10	Random	72.9%	0.001
Non-surgery	2.96 [1.68–3.51]	6	Fixed	0%	0.672	3.01 [1.57–6.92]	8	Random	61.5%	0.004
Detection rate (≥0.6)										
>60%	3.23 [1.54–4.39]	15	Random	53.6%	0.012	3.36 [1.57–6.64]	5	Random	74.2%	0.001
≤60%	3.44 [1.68–3.96]	10	Random	65.3%	0.007	3.25 [1.41–6.30]	4	Random	87.2%	0.000
Quality of study										
Moderate	4.23 [1.68–4.68]	5	Fixed	0%	0.678	3.36 [1.57–6.64]	3	Fixed	1.8%	0.732
High	3.08 [1.07–3.66]	20	Random	82.1%	0.000	3.36 [1.57–6.64]	16	Random	80.7%	0.000

HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 3 Result of meta-regression analyses on OS and PFS

Variables	OS			PFS		
	Cofe.	Std. Err.	P value	Cofe.	Std. Err.	P value
Method	−0.1532	0.4145	0.7270	−1.7561	0.3263	0.0020
Marker	0.0354	0.6080	0.9560	−0.8783	0.5981	0.1850
Treatment	0.0354	0.6080	0.9560	−0.8784	0.5981	0.1850
Detection rate (60%)	−0.7282	0.5035	0.2080	−0.6236	0.6035	0.3360
Quality of study	0.0010	0.2145	0.9960	−0.1780	0.2679	0.4965

OS, overall survival; PFS, progression- free survival.

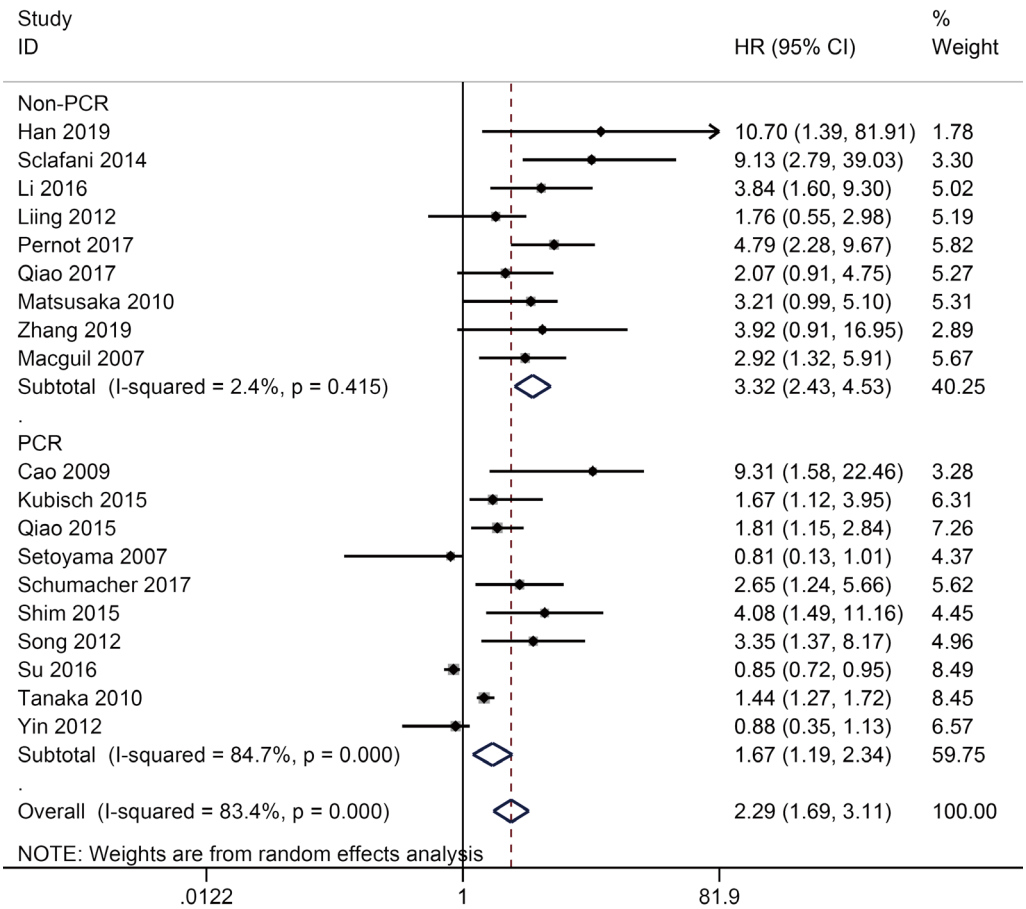

Figure 3 Hazard ratio (HR) for progression-free survival (PFS) of the included studies. PCR, polymerase chain reaction; non-PCR, non-polymerase chain reaction.

associated with depth of infiltration and clinical pathologic staging. However, CTCs status was less supportive as an indicator of the risk of more lymph node metastasis or distant organ metastasis. Further studies are warranted to address these issues as an attempt to bring CTCs from the lab bench to the hospital bedside in EC.

Table 4 Result of publication bias

Item	Egger's test	Begg's test
OS	0.511	0.764
PFS	0.220	0.448
TNM	0.403	0.322
T	0.864	0.760
N	0.033	0.732
M	0.392	0.929
Histology	0.666	0.902

OS, overall survival; PFS, progression- free survival; T, tumor; N, lymph node; M, metastasis.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-590

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-590). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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