Prognostic Value of Circulating Tumor Cells in Castration Resistant Prostate Cancer: A Meta-analysis

Yuxiao Zheng**, Cheng Zhang**, Jie Wu**, Gong Cheng, Haiwei Yang, Lixin Hua*, Zengjun Wang

Purpose: The prognostic value of circulating tumor cells (CTC) detected in castration-resistant prostate cancer (CRPC) is currently under debate. The aim of our meta-analysis was to evaluate the prognostic effect of CTC and to elucidate whether the detection of CTC in the peripheral blood (PB) of patients diagnosed with CRPC can be used as an independent prognostic factor for survival.

Materials and Methods: The Pubmed, Science Citation Index, Cochrane Database, Embase Cell Research database and the references in relevant studies were systematically searched. Hazard ratios (HRs) for overall survival (OS) with 95% confidence intervals (CIs), subgroup analysis, sensitivity analysis, meta-regression analysis was pooled and publication bias were conducted.

Results: Ten eligible studies enrolling 1206 patients were identified for final analysis. To decrease the heterogeneity of this meta-analysis we excluded two studies after sensitivity analysis. Remained eight studies were enrolled in the pooled analysis and the result revealed that CTC positivity (presence of 5 or more CTCs per 7.5mL PB) was significantly associated with a poor OS (HR = 2.76, 95%CI: 2.28-3.34, P < .0001).

Conclusion: Our study demonstrated that CTC positivity indicates poor prognosis in patients with CRPC. CTC counts can be used as an independent prognostic factor of survival rate in patients with CRPC.

Keywords: castration-resistant prostate cancer; circulating tumor cells; hazard ratios; meta-analysis; prognosis

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer in men and is the fifth leading cause of cancer death worldwide[1]. Among all the cause of cancer-related death, metastasis plays a significant role undoubtedly. Cancer cells release only a small amount of the cells in the circulation which contributes to the formation and proliferation of new metastases in distant sites from the initial carcinoma. Tumor cells released by malignancies in the peripheral circulation of patients was firstly described by Ashworth in 1869[2]. These cells, which commonly known as circulating tumor cells (CTC), have been shown to play a significant role in the formation of metastases[3], and are considered prognostic biomarkers for various solid tumors including lung cancer, ovarian cancer, prostate cancer and breast cancer tumors[4]. Immunocytochemistry (ICC) and reverse transcriptase polymerase chain reaction (RT-PCR) are the two main methods for CTC detection in bloodstream. The CellSearch system (Veridex, Raritan, NJ, USA) is the only assay cleared by the U.S. Food and Drug Administration (FDA) for clinical use among all the ICC approaches[5]. The primary studies established that CTCs have prognostic value among patients with breast, colorectal, gastric, lung and pancreatic cancers[6-9] and can be used as a marker of metastatic breast cancer[10,11]. However, because of the lack of clinical data, the prognostic effects of CTC presence in patients with castration resistant prostate cancer (CRPC) remains controversial. Therefore, a comprehensive analysis of published literature on this topic is required to evaluate the prognostic relevance of CTC detection in the peripheral circulation of patients with CRPC. The purpose of our study was to use a meta-analysis to quantitatively and generally summarize the prognostic significance of CTC detected with the standardized Cell Search System in patients with CRPC.

MATERIALS AND METHODS

Search strategy

A literature search for relevant studies was performed systematically (from January 1950 to December 2015) on the Pubmed, Science Citation Index, Cochrane Database, EMBASE and Cell Research database. The reference lists of the relevant studies such as review studies and included studies were also checked for potentially relevant articles. Search term combinations were: “circulating tumor cell(s)”, “prognosis”, “castration resistant prostate cancer”. The detailed search

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Table 1. Key Words and Other Details for the Search

Database(Host)	Time span	Key words	NO. of citation in database
Pubmed	2016.1.11-16	CTC, prognosis, CRPC	34
Science Citation Index	2016.1.16-18	CTC, prognosis, CRPC, cohort	176
Cochrane Database	2016.1.18-21	CTC, prognosis, CRPC	231
EMBASE	2016.1.21-26	CTC, radical prostaectomy, prognosis, cohort	153
Cell Research Database	2016.1.26-30	CTC, prognosis, CRPC	98

Abbreviations: CRPC, castration-resistant prostate cancer; CTC, Circulating Tumor Cells

strategies and citations we found in such database are presented in **Table1**. Immunologic, immunocytochemistry and flow cytometric detection techniques were accepted detection approaches when we scaned the articles. Reviews, letters and irrelevant studies were excluded and the reference of the remaining articles were reviewed for supplementary of our initial search.

Eligibility criteria

The studies were screened by two reviewers and studies with the following criteria were considered eligible for inclusion: 1) Containing at least 30 patients and all the patients were diagnosed with CRPC, 2) the samples used in these studies should be peripheral blood, 3) evaluated the CTC levels with CellSearch System and the cutoff value of CTC level was 5 CTCs per 7.5mL PB, 4) evaluating association between specific markers of circulating tumor cells and overall survival (OS), 5) sufficient data to calculate a hazard ratio (HR) with a 95% confidence interval (95% CI), the HRs we have recruited were crude HRs, but not adjusted HRs. 6) letters to the editor, reviews, and articles published in non-English languages were excluded, 7) we included the most informative study when studies were based on the same patient population.

Table 2. Main characteristics of the eligible studies

References	Country	No. of patients	Age	Stage	Marker	CTC neg No.	CTC pos No.	Treatment	HR (95%CI)	NOS Score
Amir.Goldkorn	USA	212	62-76	CRPC	CD45-CK+	104	108	Docetaxel based chemotherapy	2014[13] (1.72-4.37)	2.74 7
D.Olmos 2009[14]	UK	119	48-86	CRPC	CD45-CK+	59	60	Chemotherapy	3.25 (1.4-7.4)	8
Daniel C.Danila 2013[15]	USA	97	47-90	CRPC	NR	52	45	NR	2.8 (1.79-4.36)	8
Howard I.Scher 2009[16]	USA	156	49-87	CRPC	CD45-CK+	71	85	Surgery/Chemotherapy	1.58 (1.41-1.77)	8
Johann S.de Bono 2008[17]	UK	219	45-92	CRPC	CD45-CK+	94	125	Chemotherapy	3.3 (2.2-5.1)	7
Kun Chang 2015[18]	China	70	55-85	CRPC	NR	40	30	Docetaxel based chemotherapy	2.44 (1.23-4.84)	7
Mark.Thalgott 2015[19]	Germany	33	53-82	CRPC	nucleic acid,	13	20	Docetaxel based chemotherapy	3.8 (1.4-10.3)	7
M.H.Strijobs 2010[20]	Netherland	154	45-92	CRPC	CD45-CK+	NR	NR	Docetaxel based chemotherapy	2.1 (1.4-3.2)	6
Rhonda L.Bitting 2015[21]	UK	89	42-94	CRPC	NR	30	59	Chemotherapy	0.41 (0.24-0.69)	7
Takatsugu Okegawa 2014[22]	Japan	57	61-82	CRPC	CD45-CK+	24	33	Docetaxel based chemotherapy	3.13 (1.3-6.3)	6

Abbreviations: CRPC, castration-resistant prostate cancer; NR, Not Reported; CTC, Circulating Tumor Cells; HR, Hazard Ratio; NOS, Newcastle-Ottawa Scale

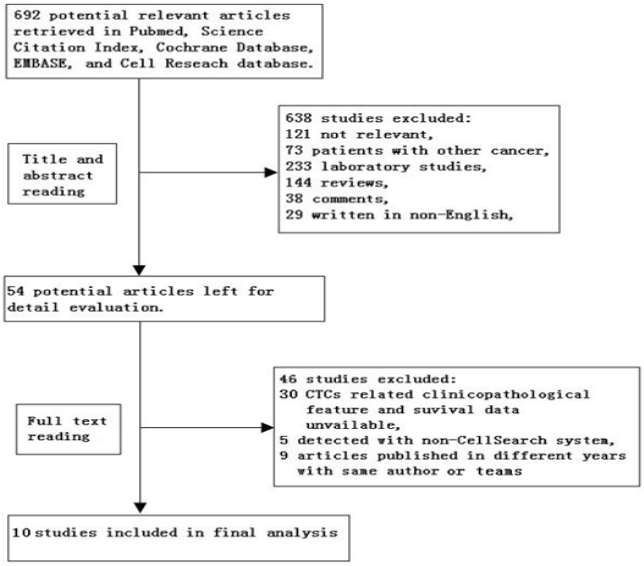

Figure 1. Flowchart of the strategy used for the selection of reports used in our analysis. (CTC, circulating tumor cells)

Data extraction

Descriptive and quantitative information from each literature were extracted by two reviewers and included: first author, publication year, nation, tested sample, patient and cancer characteristics such as cancer stage, age, treatment formula, tracking range, number of patients in the favorable (<5CTCs/7.5mL PB) and unfavorable (>5CTCs/7.5mL PB) groups, and overall survival rate and HR. Any disagreements on data extraction of the included studies were resolved through comprehensive discussion and checked by a third investigator.

Literature quality evaluation

The quality of the included studies was evaluated with the Newcastle-Ottawa Scale (NOS) criteria for cohort and case-control studies[12]. Nine points is the excellent score, the following aspects were included: the definition and selection of the observation group and the control group of the study, comparability of the two groups and exposed factors. Studies with more than six points were defined as high quality ones, and disagreements were resolved by joint discussion.

Statistical Methods

To statistically assess the prognostic outcomes of CTCs, we extracted Hazard ratios (HRs) and their associated standard errors (SE) on OS from the included studies. Hazard ratios (HRs) with 95 % confidence intervals (95% CIs) were determined using fixed and random models. Q and I2 tests were used to measure heterogeneity of these studies, and when heterogeneity was observed ($P \leq .05$ and I2 ≥ 50 %), only the random model was applied for the statistical analysis. We performed meta-regression analyses to explore the heter-

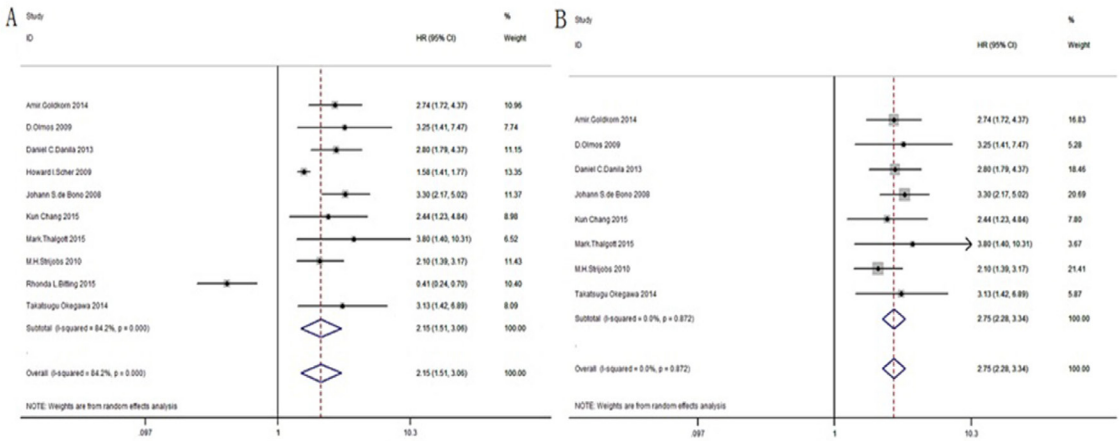

Figure 2. Hazard ratios summary for overall survival. Figure 2A: Pooled analysis of 10 studies and the result showed that CTC positivity was associated with poor OS and increased the risk of death (HR = 2.15, 95%CI: 1.51-3.06, $P < .0001$). Figure 2B: Pooled analysis of remain 8 studies after exclusion and the result showed that CTC positivity was noticeably associated with poor OS and increased the risk of death (HR = 2.76, 95%CI: 2.28-3.34, $P < .0001$)

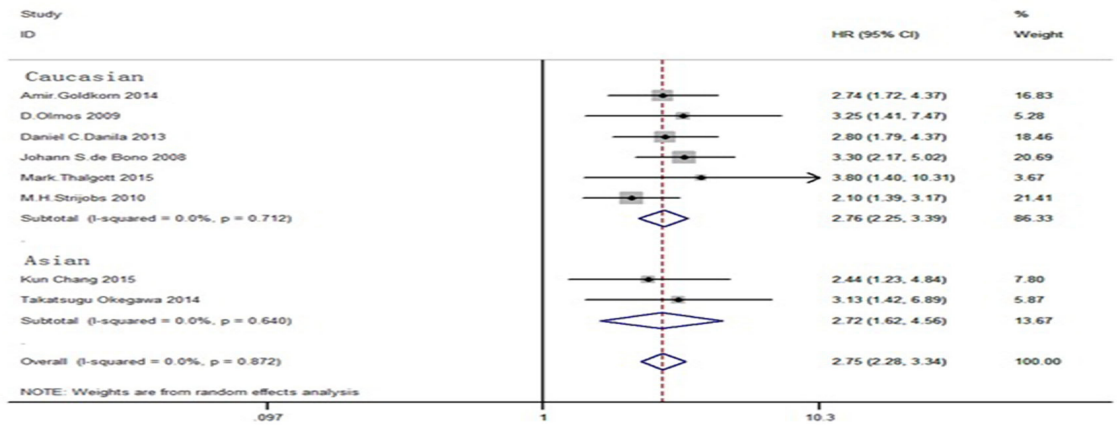

Figure 3. Subgroup analysis by races for the difference in OS between CTCs-positive and CTCs-negative CRPC patients.

ogeneity of potential cause, and publication bias was evaluated with Begg rank correlation method and the Egger weighted regression method. Significance was set at $P < .05$. STATA version 12.0 was employed to process all of the data, and all p-values were two-tailed.

RESULTS

Baseline study characteristics

Initially, 692 studies were identified in the literature search. However, based on their abstracts and titles, 638 studies were excluded because of laboratory studies, reviews, comments or written in a language other than English, and then 54 potential studies were further reviewed. 46 articles were excluded after detailed review because they did not examine the relationship between CTCs and clinicopathological features or survival data or because CTCs were detected by a method other than the CellSearch system. Additionally, 9 articles were excluded because they were published by the same author or teams. Finally, 10 studies were identified as eligible for inclusion in the meta-analysis (**Fig. 1**)[13-22].

Characteristics of eligible studies

The 10 studies analyzed in this report included a total of 1206 CRPC patients, and their sample size ranged from 33 to 219 patients with a median sample size of 121. 3, 5 and 2 studies were conducted in the USA, Europe and Asia respectively and were issued between 2008 and 2015. The baseline characteristics and the quality of the included studies evaluated with the NOS were summarized in **Table 2**. The Cell Search System was applied to detect the tumor cells in all 8 studies. 8 studies identified CTCs by testing for anti-cytokeratin antibodies but 2 studies did not mention the method. The cutoff value for positive CTC status was 5 cells per 7.5mL PB in all 8 studies.

Correlations between CTC number and overall survival in CRPC

HR and their associated standard errors on relapse and overall OS from the included studies were extracted. We used HR to compare the CTC positive and CTC negative, and defined a poor prognosis in the CTC positive group when HR>1. Pooled analysis of all studies revealed that CTC positivity was noticeably associated

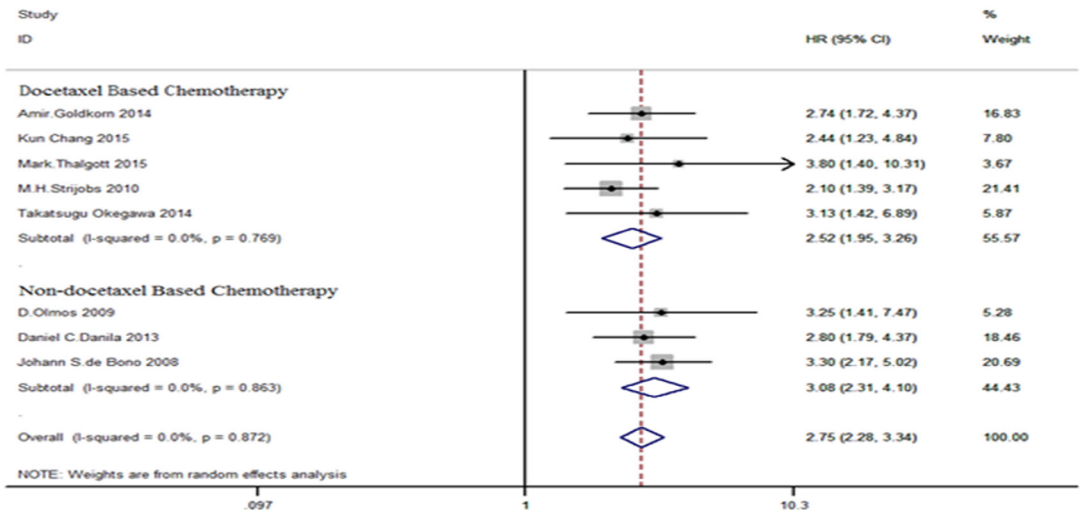

Figure 4. Subgroup analysis by treatment method for the difference in OS between CTCs-positive and CTCs-negative CRPC patients.

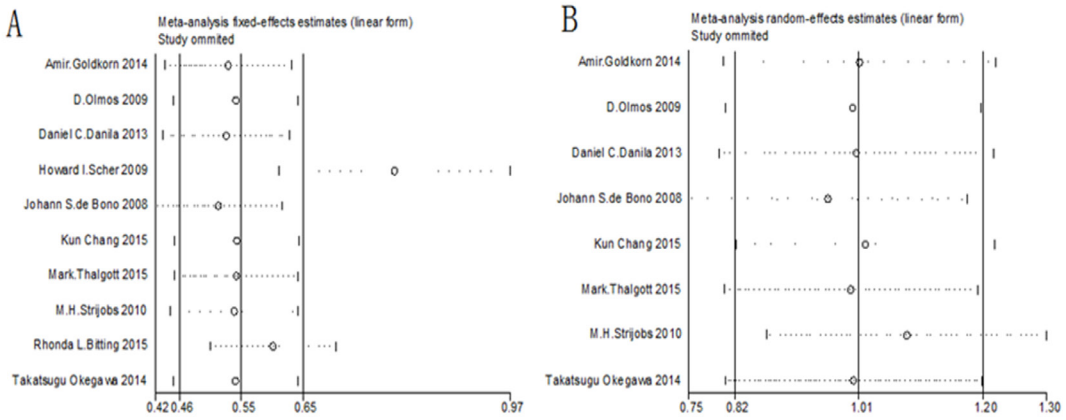

Figure 5. Sensitivity analysis of the influence of each single study on the pooled HRs by omitting single studies. Figure 5A: We performed sensitivity analysis by estimating the average HR in the absence of each study in order to assess the influence of single study on the pooled HRs. The result indicated that two studies dominated the pooled HRs. Figure 5B: We excluded these two studies subsequently and perform sensitivity analysis again. The result showed that no single study dominated the pooled HRs.

with poor OS and increased the risk of death, (HR = 2.15, 95%CI: 1.51-3.06, $P < .0001$; **Figure 2A**) and the heterogeneity among studies was moderate ($P < .0001$, $I^2 = 84.2\%$). In order to evaluate the influence of single studies on the pooled HRs, we performed sensitivity analysis by estimating the average HR in the absence of each study in order to assess the influence of single study on the pooled HRs. The result indicated that two studies dominated the pooled HRs (**Figure 5A**). We excluded these two studies subsequently and perform sensitivity analysis again. The result showed that no single study dominated the pooled HRs (**Figure 5B**). We performed pooled analysis on the remained 8 studies and showed that CTC positivity was noticeably associated with poor OS and increased the risk of death, (HR = 2.76, 95%CI: 2.28-3.34, $P < .0001$; **Figure 2B**) and the heterogeneity among studies was moderate ($P < .0001$, $I^2 = 87.2\%$).

Subgroup analyses

Correlation between CTC number and race :

We investigated the prognostic value of CTCs for patients with different races. Asians were enrolled in two studies and Caucasian were enrolled in the other six studies. Results shown in **Figure 3** demonstrate that the prognostic value of CTC for OS was significant in the "Asians" subgroup (HR = 2.76, 95%CI: 2.25-3.40, $P < 0.0001$) and it was also significant in the "Caucasian" subgroup (HR = 2.72, 95%CI: 1.62-4.56, $P < .0001$). Statistical heterogeneity was not found in both "Asians" subgroup and "Caucasian" subgroup (I2 = 0.00%, $P = .712$ and I2 = 0.00%, $P = .640$, respectively). Correlation between CTC number and treatment method Prognostic value of CTCs for patients with different treatment methods were also investigated in our study. Patients received docetaxel based chemotherapy in five studies and other treatment (chemotherapy or not mentioned) in the other three studies. The results shown in **Figure 4** demonstrate that the prognostic value of CTCs for OS was significant in the "docetaxel based chemotherapy" subgroup (HR = 2.52; 95%CI: 1.95-3.26, $P < .0001$) and it was also significant in the "non-docetaxel based chemotherapy" subgroup

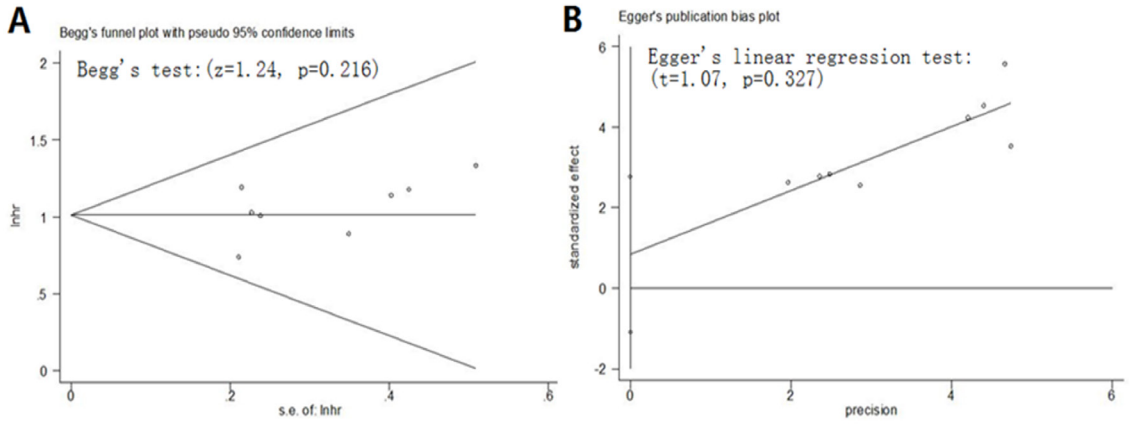

Figure 6. Begg's funnel plot (A) and Egger's linear regression test (B) of overall survival in patients with castration resistant prostate cancer.

(HR = 3.01; 95%CI: 2.31-4.10, $P < .0001$). Statistical heterogeneity was found in neither the "docetaxel based chemotherapy" subgroup nor the "non-docetaxel based chemotherapy" subgroup (I2 = 0.00%, $P = .769$ and I2 = 0.00%, $P = .863$, respectively). Sensitivity analysis and publication bias Sensitivity analysis was performed and the result was explained before and depicted in **Figure 5B**. Furthermore, Begg's test and Egger's test was performed to assess the publication bias of OS in this meta-analysis. No evidence for publication bias was found in the pooled analysis of OS tested by Begg's test (z=1.24, $P = .216$, **Figure 6A**) or Egger's linear regression test (t=1.07, $P = .327$, **Figure 6B**).

DISCUSSION

Recently, many studies have reported that the presence of CTC was significantly associated with prognosis or other clinicopathologic parameters in prostate cancer[23]. At present, considering the lack of primary studies, studies about prognostic value of CTC detection in CRPC were usually enrolled in meta-analysis focused on CTC in PB of PCa patients[24]. The limitation of individual clinical value with the prognostic effect of CTC positivity was caused by the lack of statistical power with their different study designs and results, and whether CTC can be treated as a predictive marker for prognosis of CRPC is controversial. This is the first meta-analysis targeted CTC in PB of patients with CRPC and evaluated the prognostic value of CTC detection in CRPC patients. At first we enrolled 10 studies including 1206 CRPC patients. We used HR to compare the CTC positive and CTC negative, and defined a poor prognosis in the CTC positive group when HR>1. Pooled analysis was provided and results showed that CTC positivity was noticeably associated with poor OS and increased the risk of death. In order to evaluate the influence of single studies on the pooled HRs, we performed sensitivity analysis and the results demonstrated that two studies dominated the pooled HRs. So we excluded these two studies subsequently and perform sensitivity analysis again. The result of second sensitivity analysis showed that no single study dominated the pooled HRs. The remained 8 studies were enrolled in pooled analysis again and the result showed that CTC positivity was noticeably associated with poor OS and increased the risk of death and the heterogeneity among studies was moderate, which confirmed the stability of our results. Subgroup analysis revealed that the "Asian" subgroup and the "Caucasian" subgroup both presented significant association between CTCs and OS. In addition, subgroup analysis focused on the correlations between CTC number and treatment methods showed that the prognostic value of CTCs for OS were significant in both "docetaxel based chemotherapy" subgroup and "non-docetaxel based chemotherapy" subgroup. These results suggest that the detection of CTC expression in PB of CRPC patients may be valuable in the determination of prognosis. Although the predictive value of CTC was statistically supported by this meta-analysis, our conclusions should be carefully interpreted. Heterogeneity is a potential problem universally present in interpreting the results of any meta-analysis. We thought the potential source of heterogeneity for this meta-analysis might include following factors: 1) The most commonly applied three methods for detecting CTCs in PB are immunochemistry, RT-PCR and Cell Search System. Approaches that rely on nucleic acid detection such as immunochemistry and RT-PCR possess the greatest sensitivity, but also possess relatively low specificity, which reduces their overall accuracy. In some situations, a minority of non-cancerous cells can release false signals which can enter into the circulating immune cells, which have been reported to express CK, a marker of CTC[25]. To avoid the drawbacks of other CTC detection methods, we only included studies that used the Cell Search System, which combines image cytometry technology and immunomagnetic sample enrichment, and is the only FDA-approved approach for the detection and enumeration of CTC in prostate cancer patients[26,27]; 2) The optimal cutoff value of CTC for predicting the clinical outcome in ovarian cancer is controversial. Although other cutoff value of CTC such as 3 or 4 CTCs per 7.5mL PB were used by some studies (28-30), we set cutoff value as 5 CTCs per 7.5mL PB because it is the most widely used cutoff value in CTC detection in patients with CRPC. Further studies are required to assess prognostic relevant CTC cutoff levels; 3) The markers of CTC detection in studies enrolled in our meta-analysis were not uniform, which may influence the result of CTC detection and increase the limitation of our study; 4) A meta-analysis demonstrated that the prognostic and predictive significance of CTC was relevant to CTC sampling time in colorectal cancer (31). So we hypothesized that a similar result may appear in CRPC. However, sampling time of the studies enrolled in our meta-analysis was not mentioned accurately, which may lead to heterogeneity and influence the prognostic value of CTC positivity; 5) HRs enrolled in our meta-analysis partly used the primary data provided from studies, but some HRs were estimated from the available data according to the method reported by Tierney J.F.[32] because some studies did not provide HRs directly. Although publication bias and sensitivity analysis in this meta-analysis showed no significant results, we think that our meta-analysis may suffer from the following limitations: 1) The number of studies included in our meta-analysis was limited, and studies introduced to pooled analysis have relatively small sample sizes. It is necessary to enroll larger-size and better designed studies to confirm our results; 2) Studies included in our meta-analysis were all published in English, which means the omission of studies published by other language can contribute to publication bias; 3) We tried to identify all relevant data about CTC detection and prognostic clinical statistics, but it is unavoidable that some data could still be missing. The prognostic power of CTC could reduce by negative results reflected by missing information. In conclusion, the results of our meta-analysis suggest that presence of unfavorable numbers of CTCs in PB (≥5 CTCs/7.5mL PB) detected with the Cell Search System is associated with a relatively shorter OS in patients with CRPC. In addition, CTC detected in PB is a statistically significant prognostic factor for patients with CRPC. Future large-size, high-quality, well-designed multicenter studies are required to assess the clinical values and clinical utility of CTCs detected by Cell Search System in CRPC patients.

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CONFLICT OF INTEREST

No potential conflicts of interest were disclosed.

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