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Review Article

Anemia is associated with poor outcomes of metastatic castration-resistant prostate cancer, a systematic review and meta-analysis

Dongjun Dai[1*], Shuting Han[1*], Ling Li[2], Yan Guo[2], Yuping Wei[1], Hongchuan Jin[2], Xian Wang[1]

[1]Department of Medical Oncology, Sir Run Run Shaw Hospital, Medical School of Zhejiang University, Hangzhou, China; [2]Laboratory of Cancer Biology, Key Lab of Biotherapy, Sir Run Run Shaw Hospital, Medical School of Zhejiang University, Hangzhou, China. [*]Equal contributors.

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Abstract: Androgen deprivation therapy (ADT) was an important management for metastatic prostate cancer. However, patients would finally progress to the metastatic castration-resistant prostate cancer (mCRPC) and lose sensitivity to ADT. In addition to lower testosterone level, ADT could cause anemia, which might impair the chemotherapy efficiency and worsen the outcomes of cancer patients. However, inconsistent results were found between anemia and mCRPC prognosis. Our study was the first systematic review to evaluate the influence of anemia in mCRPC prognosis. Thirteen studies with 6,484 samples were involved in this meta-analysis. We found anemia would worsen the Overall survival (OS) of mCRPC patients in both prognostic designed studies (HR = 1.55, 95% CI = 1.24-1.94) and retrospective designed studies (HR = 1.82, 95% CI = 1.52-2.18). Prognostic analyses also demonstrated that anemia associated with poor Progression free survival (PFS) (HR = 1.47, 95% CI = 1.22-1.75). In conclusion, we found that anemia was significantly associated with poor OS and PFS of mCRPC patients. Larger RCTs are needed for future study, especially for the evaluation of treatment value for anti-anemia in mCRPC.

Keywords: Systematic review, meta-analysis, metastatic castration-resistant prostate cancer, anemia, androgen deprivation therapy

Introduction

Anemia is one of the most common demonstrations of cancer, according to World Health Organization (WHO), hemoglobin <13 g/dL in males was defined as anemia. Almost 40% of cancer patients presented anemia, the proportion raised to 90% when patients were treated with chemotherapy [1]. The anemia was associated with shorter PFS and survival. It was also suggested to be a worse prognostic factor in many cancers, including prostate cancer [2, 3]. The deterioration of cancer caused by anemia may result from hypoxia. Low hemoglobin level would cause hypoxia [4], which contributes to chemotherapy and radiotherapy resistance [5]. As shown in the **Figure 1**, hypoxia could influence the chemotherapy by reducing the formation of reactive O_2 species and slowing down the cell cycle [6]. The hypoxia also induces the hypoxia-inducible factor 1 alpha (HIF-1α), which could dimerize with HIF-1β to activate the transcription of multiple oncogenic genes such as vascular endothelial growth factor, glycolytic enzymes, and glucose transporters [7].

Prostate cancer is the fourth most commonly diagnosed cancer and the second most commonly diagnosed cancer in men, with 1.1 million new cases per year worldwide [8]. The five-year relative survival rates dropped sharply when prostate cancer spreads to other organs such as bones [8]. Increasing incidence of metastatic prostate cancer was found recently [9]. The 5 year survival rate of metastatic prostate cancers is about 30% [10]. Since almost 75% of metastatic prostate cancers are hormone sensitive which make androgen deprivation therapy (ADT) established as a standard care for patients have metastatic prostate cancers. ADT refers to a variety of medical and surgical treatments such as bilateral orchiectomy and injections of estrogen that result in a reduction of androgens, or male sex hormones [11]. Up to nearly 90% of patients with metastatic prostate cancers witnessed serum prostate-Specific

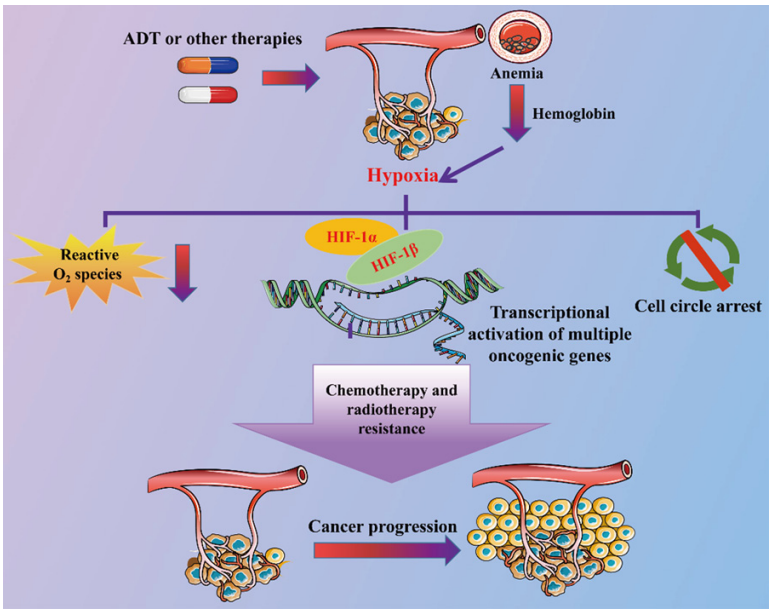

Figure 1. The mechanism of anemia promotes cancer progression. Androgen deprivation therapy and other therapies (such as chemotherapy) will cause hemoglobin decline which may finally lead to anemia and cause hypoxia in prostate cancer. Hypoxia can reduce the formation of active O_2 species and slow the cell cycle. Hypoxia also induces the dimerization of hypoxia-inducible factor 1 alpha (HIF-1 alpha) and HIF-1 beta to activate transcription of various oncogenes that finally leads to chemotherapy and radiotherapy resistance and cancer progression.

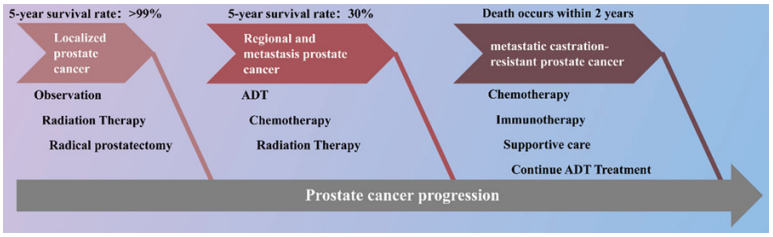

Figure 2. Brief introduction of treatment and prognosis of prostate cancer at different stages. ADT: Androgen deprivation therapy.

Antigen (PSA) level decrease after the using of ADT [12]. ADT could contribute to tumor regrssion and extend overall survival (OS) [13]. However, the average time for ADT therapy response is about 18 months, then the patients progress to the metastatic castration-resistant prostate cancer (mCRPC) [14, 15]. mCRPC patients have a poor prognosis with a fewer than 2 years survival from the initial time of progression [16, 17] (**Figure 2**).

ADT has several side effects such as adverse bone health, metabolic disorder, sexual dysfunction, cognitive effects, fatique and anemia [18-22]. In prostate cancer, ADT could cause anemia and anemia related fatique, reducing the quality of life (QoL) of patients, and this was more frequently and more severely occurred in metastatic prostate cancer patients [23]. A network meta-analysis showed that compared with other therapies, ADT had relative high surface under the cumulative ranking curve (SUCRA) value (82.8%) to induce anemia in the treatment of metastatic prostate cancer [24]. Furthermore, the ADT continued when metastatic prostate cancer patients progressed to mCRPC. The effects of anemia on mCRPC prognosis remains inconsistent, the majority of the studies showed that anemia could worsen the prognosis of mCRPC [25-34], yet others found that anemia was not associated with the prognosis of mCRPC [35-37].

Although the ADT was found to be a cause of anemia in prostate cancer, and inconsistent results were obtained when evaluated the prognostic value of anemia in the pretreatment mCRPC patients [25-37], there was no systematic review on the association of anemia with mCRPC prognosis. Therefore, we decide to perform this systematic review and meta-analysis to explore the association between anemia and mCRPC prognosis.

Methods

Data collection

This systematic review was conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [38] (Data not shown). We collected studies from online database PubMed without time limitation, only studies in English language were involved. The searching keywords were "(((((((Anemia[mesh]) OR Anemias)) OR ((Ferrous Hemoglobin) OR Hemoglobin))) AND

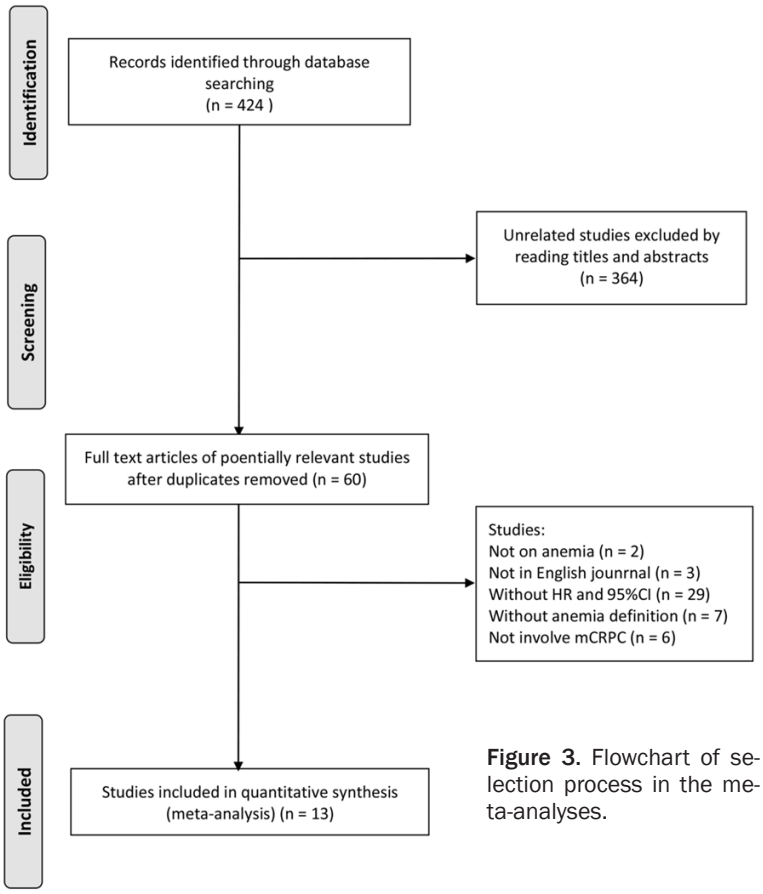

Figure 3. Flowchart of selection process in the meta-analyses.

((((((((((Prostate Cancer[mesh]) OR Cancer of Prostate) OR Cancers, Prostatic) OR Prostatic Cancer) OR Cancer of the Prostate) OR Prostate Cancers) OR Neoplasms, Prostatic) OR Prostatic Neoplasm) OR Prostate Neoplasm) OR Prostate Neoplasms)) AND ((((prognosis[mesh]) OR Factors, Prognostic) OR Prognostic Factors) OR Prognoses))) NOT (((animals[mh] NOT humans[mh])". The searching was updated until March 5, 2018. The included studies should meet the follow items: (1) it's a cohort study that involve mCRPC patients; (2) it contains definition of anemia by dimidiating the hemoglobin level; (3) it has sufficient information to calculate the Hazard Ratio (HR) and 95% Confidence Interval (95% CI) for outcomes such as OS, progression free survival (PFS). We chose HR as outcome data because of its time-independent nature. The study quality was assessed by two separate tools. The risk of bias was evaluated by Cochrane Risk of Bias Tool for randomized controlled trials (RCTs) [39]. In addition, the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (NOS) was used to evaluate the quality of each cohort study. The searching, study selection and study quality assessment were performed by two independent reviewers (LL and YW). If disagreements occur, decisions would be made by discussions and subsequent consensus. For the studies involved duplicate cohorts, the most recent, largest, or best-quality one would be selected.

Data extraction

Data extraction was performed by two independent investigators (DD and YG). The extractions included the name of first author, the year of publication, the NOS score, the region of where the cohort from, ethnicity of cohort, type of the study (prognostic or retrospective cohort), outcome types, sample size, definition of anemia, median follow-up time for outcomes, and the result that whether the anemia is a significant risk factor for metastatic prostate cancer prognosis.

Data analyses

All the analyses were performed by Stata software 11.0 [40]. The pooled HR and 95% CI were calculated for OS and PFS. Only the multivariate results were pooled. I^2 test [41] was used to calculate statistical heterogeneity. The random effect model was used in current meta-analyses for random and fix model present similar results when heterogeneity is low [42]. Funnel plots, Begg and Egger were performed to evaluate potential publication bias [43, 44]. Subgroup stratification and sensitive analysis would be performed if any heterogeneity occurred. A p value of less than 0.05 was considered significant.

Results

Study selection

As shown in **Figure 3**, we collected 424 studies from PubMed, after reading titles and abstra-

Table 1. The characteristic of each involved study

Author/Year	Ethnicity	Type	Outcomes	Sample size	Definition of anemia (g/dL)	Median follow-up time (months)	Results
[25] C Ryan/2017	Mixed	Prognostic	PFS	1088	<12.7	28	S
[26] C Praet/2017	Caucasian	Retrospective	OS	368	<12	14	S
[35] C Buttigliero/2016	Caucasian	Retrospective	OS	179	<13	32	N.S
[27] O Caffo/2014	Caucasian	Retrospective	OS	260	<11	11	S
[28] K Fizazi/2014	Mixed	Prognostic	OS	1901	<12.8	20	S
[36] H Matsuyama/2014	Asian	Retrospective	OS	279	<11.3	26	N.S
[37] N Kamiya/2014	Asian	Retrospective	CSS	145	<12.2	16	N.S
[29] Y Qu/2012	Asian	Retrospective	OS	115	<11	17	S
[30] M Ito/2011	Asian	Retrospective	OS	80	<11	15	S
[31] J Shamash/2011	Caucasian	Prognostic	OS	270	<11	19	S
[32] A Armstrong/2009	Mixed	Prognostic	OS	1006	<13	15	S
[33] R Wyatt/2004	Mixed	Retrospective	OS	379	<12	14	S
[34] R Abratt/2004	Caucasian	Prognostic	PFS	414	<13	4	S

OS, Overall survival; PFS, Progression free survival; S, significant; N.S, Non-significant.

Table 2. RCTs were evaluated by the Cochrane Risk of Bias assessment tool

Item \ Study	[25] C Ryan/2017	[28] K Fizazi/2014	[31] J Shamash/2011	[32] A Armstrong/2009	[34] R Abratt/2004
Random sequence generation	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Low risk	Low risk	Low risk	Low risk	Unclear risk
Blinding of participants and personnel	Low risk	Low risk	Low risk	High risk	Unclear risk
Blinding of outcome assessment	Low risk	Low risk	Low risk	High risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

Table 3. NOS scale for cohort studies

Author/Year	Selection	Comparability	Outcomes	NOS score
[26] C Praet/2017	4	0	2	6
[35] C Buttigliero/2016	4	1	2	7
[27] O Caffo/2014	4	0	2	6
[36] H Matsuyama/2014	4	0	2	6
[37] N Kamiya/2014	4	0	2	6
[29] Y Qu/2012	4	1	2	7
[30] M Ito/2011	4	0	2	6
[33] R Wyatt/2004	4	1	2	7

NOS, Newcastle-Ottawa Quality Assessment Form for Cohort Studies.

cts, sixty full-texts were obtained for further selections. We further excluded 2 studies that are not on anemias, 3 non-English language studie. 29 studies without HR and 95% CI value, 7 studies without anemia definition, and 6 studies not involving mCRPC patients. Finally, thirteen studies with 6,484 samples were involved in final meta-analysis (**Table 1**). Among them, there were 5 prognostic cohorts and 8 retrospective cohorts, different population were selected that including Caucasians (n = 5), Asians (n = 4), and mixed population (n = 4). And there were 10 studies [25-34] showed that the anemia significantly associated with a worse prognosis of mCRPC and 3 studies [35-37] showed that anemia had no association with mCRPC. Relative high quality of involved studies were observed by Cochrane Risk of Bias Tool and NOS scale (over 5 stars) (**Tables 2**, **3**).

Anemia is a risk factor for prostate cancer prognosis

Considering that the mix of prognostic and retrospective cohorts might cause heterogeneity, we separately calculated the pooled HR and

Table 4. The meta-analyses of associations between anemia and mCRPC

Group	Subgroup	Studies number	Sample size	HR (95% CI)	I^2 (%)	Begg	Egger
Prognostic (OS)	NA	3	3177	1.55 (1.24, 1.94)	60.6	0.456	0.792
Prognostic (PFS)	NA	2	1502	1.47 (1.22, 1.75)	0	NA	NA
Retrospective (OS) Before sensitivity analysis	Total	7	1666	1.63 (1.25, 2.13)	75	1	0.011
	Caucasian	3	807	2.00 (1.56, 2.56)	0	1	0.31
	Asian	3	474	1.64 (1.27, 2.13)	0	1	0.768
	Mixed	1	379	1.15 (1.07, 1.24)	NA	NA	NA
Retrospective (OS) after sensitivity analysis	NA	6	1287	1.82 (1.52, 2.18)	0	1	0.653
Retrospective (CSS)	NA	1	145	1.47 (0.55, 3.99)	NA	NA	NA

HR, hazard ratio; OS, Overall survival ; PFS, Progression free survival; CSS, Cause-Specific Survival; NA, Not available.

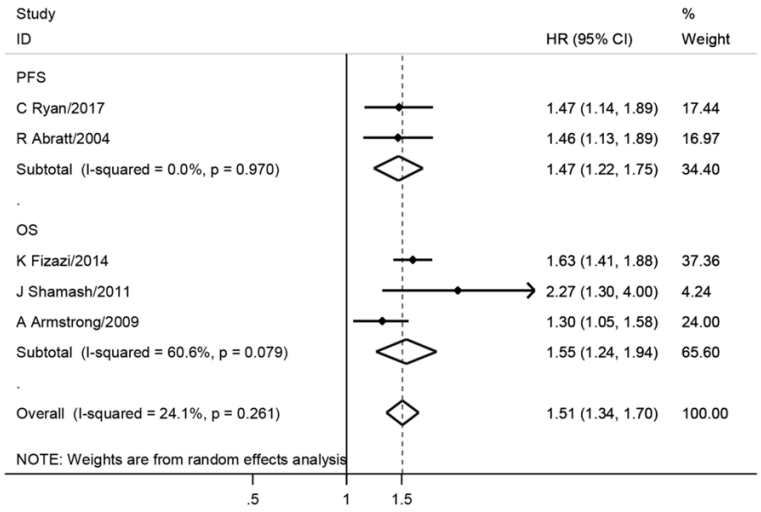

Figure 4. Forest plots of anemia with mCRPC outcomes among prognostic studies. The large diamond at the bottle of the table represents the pooled hazard ratio of all studies. The width of the diamond represents with 95% CI.

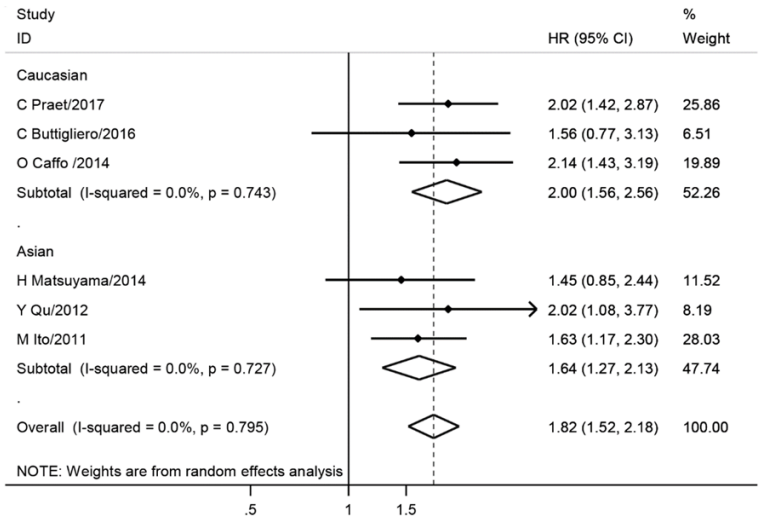

Figure 5. Forest plots of anemia with mCRPC OS among retrospective studies after sensitivity analysis. The large diamond at the bottle of the table represents the pooled hazard ratio of all studies. The width of the diamond represents with 95% CI.

95% CI for different study types. Meta-analyses based on prognostic studies showed that the anemia significantly lead to a worse prognostic for both OS (HR = 1.55, 95% CI = 1.24-1.94, I^2 = 60.6%, **Table 4**; **Figure 4**) and PFS (HR = 1.47, 95% CI = 1.22-1.75, I^2 = 0, **Table 4**; **Figure 4**). Meta-analyses based on retrospective studies also showed that the anemia promote prostate cancer progression (HR = 1.63, 95% CI = 1.25-2.13, I^2 = 75%, **Table 4**). However, the heterogeneity was relatively high in this analysis. Since different populations were involved in current meta-analyses, we further performed meta-analyses in different populations. Surprisingly, no heterogeneity was found in sub-group population-based meta-analyses, and consistently, the meta-analyses showed that the anemia lead to a worse prognosis in Caucasians (HR = 2.00, 95% CI = 1.56-2.56, I^2 = 0, **Table 4**; **Figure 5**) and Asians (HR = 1.64, 95% CI = 1.27-2.13, I^2 = 0, **Table 4**; **Figure 5**). Meanwhile, sensitivity analysis was performed. After excluding one potential heterogeneity-causing study [33], no heterogeneity was found in the new meta-analysis and the results sh-

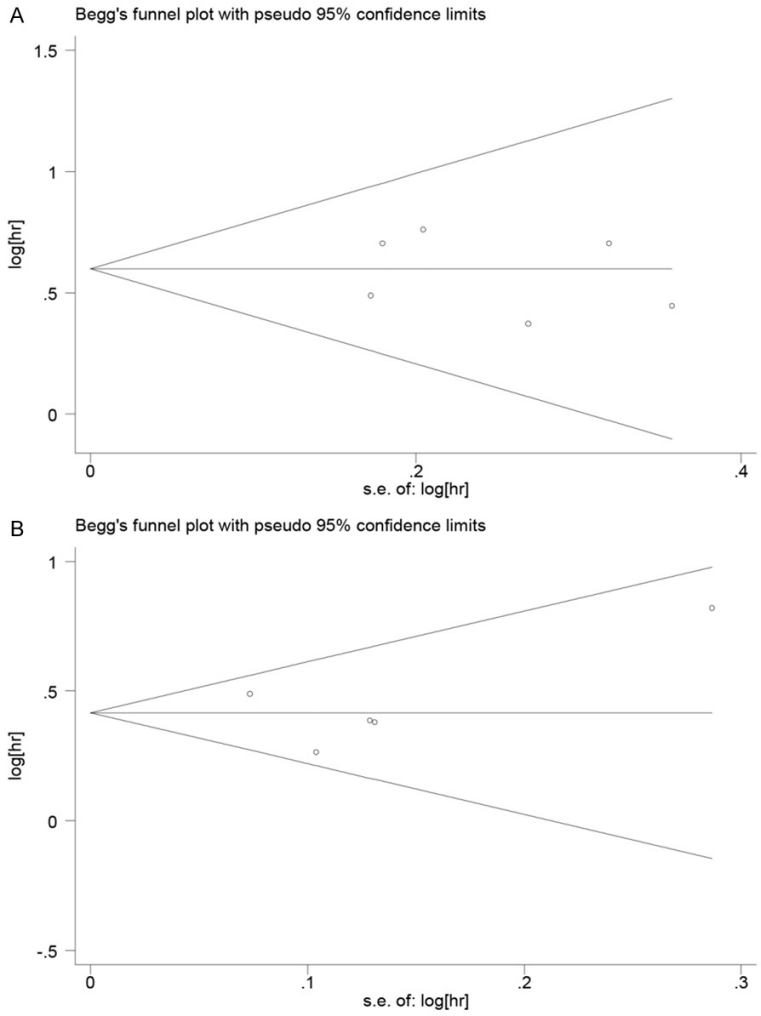

Figure 6. Funnel plots of anemia with mCRPC. A: Funnel plots of association between anemia and mCRPC OS among retrospective studies after sensitivity analysis; B: Funnel plots of association between anemia and mCRPC OS among prognostic studies. Hr: hazard ratio; SE, standard error; One cycle represents one individual study.

owed the anemia still promote the prostate cancer progression (HR = 1.82, 95% CI = 1.52-2.18, I^2 = 0, **Table 4**; **Figure 5**). We speculated the heterogeneity might result from the population, as the excluding study was the only study involving African-Americans and Hispanics patients. Besides, one study [37] with cancer specific survival (CSS) endpoint showed no significant association between anemia and mCRPC prognosis (**Table 4**).

Publications bias

As shown in **Table 4**, after sensitivity analysis of retrospective group, the Begg and Egger text showed no publication bias in all analyses (Begg >0.05, Egger >0.05). The funnel plots also showed symmetrical shapes that suggested no publication bias (**Figure 6**).

Discussion

Our meta-analysis showed that the anemia was significantly associated with a worse prognosis in mCRPC, and sub-group analyses by ethnicity found the anemia was a hazard factor both in Asians and Caucasians. Both prognostic and retrospective studies were involved in current meta-analysis. And the positive result was obtained from both types of studies.

Anemia frequently occurs in advanced prostate cancer [45]. ADT is the most common reason for anemia in advanced prostate cancer [23]. Testosterone could promote the generation of renal erythropoietin which could promote the differentiation of bone marrow erythroid stem cells to erythrocytes. Men with untreated hypogonadism commonly have mild anemia [46]. With no doubt, ADT would lower the level of testosterone and therefore impair the erythropoiesis. In non-metastatic prostate cancer patients without anemia, the use of gonadotropin-releasing hormone agonist therapy or orchiectomy would lead to a 1-2 g/dl fall in hemoglobin, which could cause a mild normochromic and normocytic anemia that was often not associated with bad clinical consequence. However, in metastatic prostate cancer patients, the use of ADT was more likely to lead to a more severe anemia, and the duration of ADT use was correlated with the severity of anemia [23]. Among the 15 studies included in current study, there were 12 studies [25-34, 47, 48] showed that the anemia was significantly associated with worse outcome of mCRPC while 3 studies [35-37] found no significant association between mCRPC prognosis and ane-

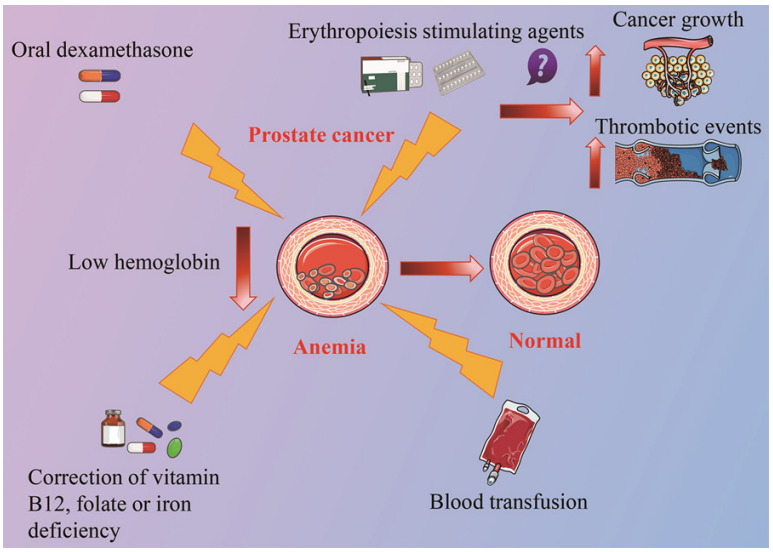

Figure 7. Treatment for anemia caused by ADT. For prostate cancer patients with symptoms of severe anemia, corrections of vitamin B12, folic acid or iron deficiency is needed. Erythropoiesis stimulants agents are also effective in controlling anemia. However, it could promote angiogenesis that might stimulate cancer growth and it might also cause thrombotic events. For anemia in hormone-refractory prostate cancer, low dose oral dexamethasone is found to be effective. For patients with more severe conditions, blood transfusion may be the only effective treatment.

mia. And our meta-analysis finally showed that the anemia indeed could promote the worse outcomes of mCRPC.

Most prostate cancer patients with ADT-induced anemia do not need anti-anemia treatment. However, treatments for symptomatic patients with more severe anemia are required (**Figure 7**). Any deficiencies in vitamin B12, folate or iron should be corrected. Erythropoiesis stimulating agents (ESAs) are effective in managing anemia and were demonstrated to reduce transfusion requirements and improve QoL in cancer patients with symptomatic anemia. However, the use of ESAs in cancer related anemia was controversial, as the ESAs could also promote angiogenesis that might stimulate cancer growth. In addition, ESAs might increase the risk of thrombotic events [49], despite the influence of ESAs in OS of cancer patients was uncertain [50-54]. Low doses of oral dexamethasone were found to decrease the severity of anemia for hormone-refratcory prostate carcinoma [55]. For the prostate cancer patients with limited bone marrow reserve, or symptomatic patients with less than 10 g/dl Hb, or asymptomatic patients with comorbidities such as congestive heart failure, blood transfusions may be the only effective treatment [56, 57]. The treatments for ADT-induced anemia still need further studies to confirm their impacts on QoL and survival [23].

There were some limitations in this systematic review. First, certain heterogeneity was found in prognostic group, while the sensitivity analysis failed to identify the potential heterogeneity (data not shown). We speculated that the heterogeneity was from the different diagnostic criteria of anemia and the ethnic diversity. Second, effects of confounding factors could not be assessed, which might influence the reliability of study. Third, no record was found about the treatment of anemia for mCRPC, considering the impacts of ADT on anemia incidence and the relationship of anemia and worse outcome of mCRPC, more studies on the anti-anemia treatments in mCRPC patients are required. Fourth, only one study involved CSS endpoint and showed no significant result, which indicated that anemia might be the direct cause for death, more studies are needed to draw a more solid result. On the other hand, focusing on OS is more important for the effect of anemia in mCRPC patients.

In conclusion, we found the anemia played a hazard role in mCRPC patients' prognosis. We speculated that anemia was likely to be caused by ADT treatment. Larger RCTs are required to evaluate the effect of anti-anemia treatment on mCRPC patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xian Wang, Department of Medical Oncology, Sir Run Run Shaw Hospital, Medical School of Zhejiang University, Hangzhou, China. Tel: +86 571 8600 6929; Fax: +86 571 8600 6929; E-mail: wangx118@zju.edu.cn

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