The Clinicopathological Characteristics of Androgen Receptor Splicing Variant 7 (AR-V7) Expression in Patients with Castration Resistance Prostate Cancer: A Systematic Review and Meta-Analysis

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Abstract

BACKGROUND Accumulating studies indicate AR-V7 may be related to the poor prognosis of castration resistance prostate cancer (CRPC), while the evidence of the clinicopathological characteristics of AR-V7 is rare.

METHODS To evaluate the clinicopathological features of AR-V7 in CRPC patients. A search of PubMed, Embase, and the Web of Science was performed using the keywords prostate cancer, prostate tumor, prostate neoplasm, prostate carcinoma; AR-V7, AR3, androgen receptor splicing variant-7, or androgen receptor-3. Twenty-four trials published due February 2020 were enrolled.

RESULTS The proportion of Gleason score ≥ 8 was significantly higher in AR-V7-positive CRPC (69.5%) than negative (54.9%) (OR 1.68, 95% CI 1.25–2.25, $P<0.001$), while the rate of T3/T4 stage (OR 1.16, 95% CI 0.60–2.24, $P=0.65$) and N1 stage (OR 0.99, 95% CI 0.65–1.51, $P=0.96$) were not statistically related to AR-V7 status. AR-V7-positive patients had a significantly higher proportion of any site metastasis (61.3% versus 35.0%) (OR 2.19, 95% CI 1.57–3.05, $P<0.001$) and bone metastasis (81.7% versus 69.0%) (OR 1.97, 95% CI 1.44–2.69, $P<0.001$), and a trend close to significance was expected in visceral metastasis (28.8% versus 22.1%) (OR 1.29, 95% CI 0.96–1.74, $P=0.09$). The percentage of pain presence in AR-V7-positive CRPC (54.6%) was prominently higher than negative (28.1%) (OR 4.23, 95% CI 2.52–7.10, $P<0.001$), line with worse ECOG performance status (56.7% versus 35.0%, OR 2.18, 95% CI 1.51–3.16, $P<0.001$). Limitations of the study include the differences in study sample size and design, AR-V7 detection assay, and disease characteristics.

CONCLUSIONS AR-V7 positivity was associated with higher Gleason score, bone or any site metastasis, presence of pain and worse ECOG performance score in CRPC, but not related to tumor stage or lymph node metastasis. More studies are needed to confirm these findings.

1 Introduction

Prostate cancer is the most common cancer among American men according to the recent study published in 2019 [1]. Unfortunately, most prostate cancer eventually experience progression to metastatic castration-resistant prostate cancer (mCRPC) [2, 3]. Predictive biomarkers are urgently warranted to identify the patients with worse prognosis and optimize more precise treatment selection. The androgen receptor (AR) signal pathway is the primary therapeutic target of prostate cancer because AR axis is still a major driver for tumor progression [4, 5]. Either blocking AR [6, 7] or inhibiting ligand production [8, 9] can suppress AR signaling and extends the survival of men with metastatic castration resistant prostate cancer (mCRPC). Whereas the appearance of Androgen receptor variants (AR-Vs), spliced isoforms of the AR and encode truncated AR proteins lacking the C-terminal ligand-binding domain but retaining the trans-activating N-terminal domain, may lead to the AR signal based therapy resistance [10, 11].

Accumulating evidence suggested that AR variant 7 (AR-V7), one of the most abundant AR-Vs in CRPC, are associated with prostate cancer aggressiveness, castration-resistant prostate cancer (CRPC) development [4, 12] and primary resistance to Enzalutamide and Abiraterone therapy in men with CRPC [13–15]. Despite incompetent to bind ligand, AR-V7 remains constitutively active in a ligand-independent manner and capable of driving CRPC growth [12, 16]. Therefore, AR-V7 may guide treatment decisions in CRPC patients and serve as a predictive biomarker [17, 18].

Although the prognosis value of AR-V7 has been revealed in CRPC, the clinicopathological characteristics of AR-V7 expression still remain unclear and controversial [13, 14, 19–21]. Some studies indicated AR-V7 positivity was associated with clinicopathological characteristics; however, others were not [13, 21–23]. To our knowledge, there is no systematic review investigating this topic which has been published so far and a meta-analysis is expected to a robust conclusion. Our study aimed to analysis the relation between AR-V7 expression and clinicopathological features including Gleason score, tumor stage, node stage, metastasis status, presence of pain and ECOG performance status score in CRPC. 24 studies were enrolled to evaluate the clinicopathological significance of AR-V7 expression in CRPC patients.

2 Methods

2.1 Search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24]. Search was completed before February 2020; published studies were retrieved from Embase, PubMed, and the Web of Science. Using prostate cancer or prostate neoplasm or prostate tumor or prostate carcinoma; AR-V7 or AR3 or androgen receptor splicing variant 7 or androgen receptor 3 as search terms. The references cited in the selected articles were also referred to identify more applicable studies. Two or three reviewers independently evaluated each study and identified whether they met the predefined inclusion criteria. Differences and disagreements in the studies that were selected were settled by discussion.

2.2 Selection criteria

Titles and abstracts of these searching studies were primarily screened and full papers were further retrieved to confirm eligibility. To be eligible, studies had to meet the following criteria. 1) The study reported on prostate cancer and AR-V7. 2) The results included the AR-V7 positive and patients' clinicopathological characteristics in castrated refractory prostate cancer (CRPC) including Gleason score, tumor (T) stage, node (N) stage, metastasis (M) status, presence of pain and/or Eastern Cooperative Oncology Group (ECOG) performance status score. 3) These outcomes were obtained from clinical trials, including prospective series or retrospective cohort studies or comparative series or case-series studies. Studies were excluded if they 1) only reported the AR-V7-positive proportion in hormone sensitive prostate cancer (HSPC) or other prostate neoplasm type; 2) did not report any clinicopathological features; or 3) were in vitro or animal studies. 4) were in languages other than English unless there is a translation. 5) Were case letters; reports; editorials; comments; and review papers. The most recent information was included in the analysis with longer follow-up and a larger patient population, when more than one report of a same trial was available.

2.3 Data collection and study quality

1) The patient feature extraction was performed with each included trial included age, Gleason score, tumor stage, node stage, metastasis status, presence of pain, ECOG performance status score, baseline prostate specific antigen (PSA) and alkaline phosphatase. 2) The description of the design of the study included the country in which performed the trial, the detection assay of AR-V7, the numbers of patients enrolled, the treatment received, and the median follow-up time. 3) The relationship between AR-V7 status and patients' clinicopathological features. 4) The number and percentage of patients with different AR-V7 status in various groups of clinicopathological characteristics.

2.4 Statistical methods

After data were extracted, comparison was processed using Review Manager Software (RevMan v.5.3; The Nordic Cochrane Center, Copenhagen, Denmark). The proportion of patients in different AR-V7 status in various groups of clinicopathological characteristics was evaluated. The main analysis grouped patients by different AR-V7 status and respectively compared Gleason score, tumor stage, node stage, metastasis status, presence of pain and ECOG performance status score in CRPC with OR (95% CI) as the summary measure. Statistical heterogeneity among studies was evaluated using the chi-square test and the I² statistic. A random-effects model had been adopted among significant heterogeneous studies (I² ≥ 50%). Odds ratio (OR) estimates were weighted and merged using the Mantel–Hansel random effect model. All statistical tests were two-sided; P < 0.05 was defined as statistically significant. No correction was made for multiple comparisons.

3 Results

3.1 Trial characteristics and quality

The enrollment process for the study is shown in Fig. 1. Results of the search were updated in February 2020, and 4409 of the 4433 full text of published papers were excluded. In short, 476 repeated studies were excluded, 3418 were ruled out for irrelevant to the research question, 477 were excluded for unable quality assessment such as conference abstracts, reviews, letters, and editorials, and 38 were excluded for irrelevant results. No additional studies in the reference lists. A total of 24 studies were selected in the present meta-analysis.

3.2 Patient characteristics

Twenty-four trials enrolling 2431 patients were included in the clinicopathological features of AR-V7-positivity CRPC; their features were presented in Table 1. The target specimens and detection assays of AR-V7 were presented in Supplementary Table 1 in detail. Sixteen trials which enrolling 1699 patients were included in the Gleason score meta-analysis; six trials enrolling 169 patients in the T stage; ten trials enrolling 587 patients in the N stage; eighteen trials enrolling 1935 patients in the metastasis; a total of 418 patients were enrolled in the five trials in the presence of pain and seventeen trials enrolling 2047 patients were included in the ECOG performance status meta-analysis.

Table 1
– Characteristics of studies included in the clinicopathological features of different AR-V7 status CRPC

Study	Year	Country	Study design	AR-V7 detection assay	Patients characteristics						
					Treatment	Patients (n)	Age [42]	Gleason score (%)	Tumor stage at diagnosis (%)	Baseline PSA (ng/ml) median [42]	Baseline pH (U)
Antonarakis[14]	2017	USA	prospective	CTC mRNA	ABT or ENZ	53 CTC-	70	≥ 8 (68.0%)	-	13.7	80
						113CTC+/AR-V7-	71	≥ 8 (60.0%)	-	31.4	96
						36 CTC+/AR-V7+	70	≥ 8 (83.0%)	-	92.0	12
Del Re [43]	2017	Italy	prospective	Exosomal RNA	ENZ or ABT	36	66 (51–81)	≤ 7 (44%) ≥ 8 (53%)	T1/T2 (8.0%) T3/T4 (36.0%)	26.3 (0.63–4581)	18 (4)
Takeuchi T.[44]	2016	Japan	cohort study	Whole blood mRNA	ENZ or ABT	43	73 (59–88)	≤ 7 (20.9%) ≥ 8 (72.1%)		130 (5.3–9529)	
Lee[45]	2016	Korea	retrospective	IHC	ADT	3	70 (56–70)	≥ 8 (100%)	T3/T4 (100%)	8.78 (8.6-173.7)	
Sharp[38]	2019	USA	prospective	IHC	ENZ or ABT, Chemotherapy	160	68.5 IQR (63.9–73.1)		M1b (67%) M1c (21%)	230.5 IQR (77.0–591.5)	12 (7)
Wang[46]	2018	China	retrospective	CTC mRNA	ENZ or ABT	36	56.2 (SD = 8.6)		M0 (36%) M1 (64%)		
Tagawa [20]	2019	USA	prospective	CTC mRNA	Docetaxel or Cabazitaxel	54	71 (53–84)	≤ 6 (13.7%) 7 (25.5%) ≥ 8 (60.8%)	N1 (51.9%) M1b (90.7%) M1c (40.7%)	92.1 (2.4–1558)	21 (26)
Antonarakis[13]	2014	USA	prospective	CTC mRNA	ABT	31	69 (48–79)	≤ 7 (26.7%) ≥ 8 (73.3%)	T1/T2 (26.7%) T3/T4 (61.3%)	37.8 (2.2–2045.0)	11 (5)
					ENZ	31	70 (56–84)	≤ 7 (40%) ≥ 8 (60%)	T1/T2 (54.8%) T3/T4 (45.2%)	44.3 (4.3-3204.2)	10 (5)
Steinestel [47]	2015	Germany	prospective	CTC mRNA	ENZ or ABT	24	75 (53–87)	≤ 7 (41.3%) ≥ 8 (58.7%)	-	96.5 (0.1–4282)	-
Nakazawa [22]	2015	USA	prospective	CTC mRNA	NHT or chemotherapy	14	65 (50–82)	≤ 7 (92.9%) ≥ 8 (0%)		58.7 (2.2–895)	12 (5)
Antonarakis[32]	2015	USA	prospective	CTC mRNA	Docetaxel or cabazitaxel	37	67 (46–82)	≤ 7 (17%) ≥ 8 (83%)	T1/T2 (38.0%) T3/T4 (62.0%)	126 (0.1–2270)	16 (5)

IQR = inter quartile range; SD = standard deviation; AR-V7 = androgen receptor splice variant 7; CTC = circulating tumor cell; PSA = prostate specific antigen; AD therapy; NHT = novel hormonal therapy; LHRH = luteinizing hormone releasing hormone; PCa = prostate cancer; CRPC = castration resistance prostate cancer; Enzalutamide; IHC = Immunohistochemistry;

Study	Year	Country	Study design	AR-V7 detection assay	Patients characteristics						
					Treatment	Patients (n)	Age [42]	Gleason score (%)	Tumor stage at diagnosis (%)	Baseline PSA (ng/ml) median [42]	Baseline pSAP (U/ml) median [42]
Onstenk [48]	2015	Netherlands	prospective	CTC mRNA	Cabazitaxel	29	70 (SD ± 7)	-	-	321 IQR (76–649)	16 (11–21)
Zhang [49]	2011	USA	retrospective	IHC	ADT	42	63 (42–93)			413.2 (0.15–7402)	
Saylor [50]	2016	USA	retrospective	RNA ISH	ABT or ENZ	12					
Zadra [23]	2019	USA	retrospective	Immune-fluorescence	ABT or ENZ	55	55				
Belderbos [41]	2019	Netherlands	prospective	CTC mRNA	ENZ, ABT or Cabazitaxel	94	69 IQR (65–75)			186 IQR (67–356)	
Cattrini [51]	2019	Italy	prospective	CTC mRNA	ENZ, ABT or Docetaxel	39	72 (56–84)		M1b (79.5%) M1c (17.9%)	35.2 (0.33–4688)	
Taplin [52]	2019	USA	prospective	CTC mRNA	Galeterone or ENZ	953	72 (62–77)	≤ 7 (43%) ≥ 8 (57%)	M0 (58%) M1 (42%)	15.5 IQR (8.98–31.70)	
Sharp [53]	2019	UK/USA	prospective	CTC mRNA /IHC	ENZ, ABT or Taxane	95 CTC-	71.0 IQR (66.8–75.6)		M1b (74.7%) M1c (17.9%)	110.0 IQR (29–300.5)	83 (6–110)
						86 CTC+ ARV7-	69.6 IQR (64.9–72.3)		M1b (86.1%) M1c (24.4%)	147.0 IQR (51.0–345)	11 (7–18)
						96 CTC+ ARV+	70.4 IQR (65.3–74.6)		M1b (84.4%) M1c (24.0%)	244.5 IQR (109.3–746.8)	18 (9–34)
Maillet [54]	2019	France	prospective	CTC mRNA	ENZ or ABT	41	73	≥ 8 (56%)	M1 (29%)	35	
Okegawa [55]	2018	Japan	retrospective	CTC mRNA	ENZ or ABT	49 CTC-	69	≥ 8 (81.6%)		75.7	31
						23 CTC+ AR-V7-	71	≥ 8 (91.3%)		71.5	32
						26 CTC+ AR-V7+	72	≥ 8 (96.2%)		79.1	37
Chung [19]	2019	USA	prospective	CTC mRNA	ENZ or ABT	37	72 (67–79)	≤ 7 (43.2%) 8 (8.1%) ≥ 9 (46%)	N1 (64.9%) M1b (89.2%) M1c (27%)	20.9 IQR (11.6–96.8)	10 (8–12)
Sieuwerts [56]	2019	Netherlands	prospective	CTC mRNA	Cabazitaxel	52	69 (SD = 7)			209 IQR (72–510)	17 (9–25)

IQR = inter quartile range; SD = standard deviation; AR-V7 = androgen receptor splice variant 7; CTC = circulating tumor cell; PSA = prostate specific antigen; AD therapy; NHT = novel hormonal therapy; LHRH = luteinizing hormone releasing hormone; pSAP = prostate cancer; CRPC = castration resistance prostate cancer; AR-V7 = androgen receptor splice variant 7; IHC = Immunohistochemistry;

Study	Year	Country	Study design	AR-V7 detection assay	Patients characteristics						
					Treatment	Patients (n)	Age [42]	Gleason score (%)	Tumor stage at diagnosis (%)	Baseline PSA (ng/ml) median [42]	Bone metastases (U)
El-Heliebi [21]	2018	Austria	prospective	CTC FISH	ENZ, ABT or Taxane	31	70.5	≤ 7 (38.7%)	T1/T2 (22.6%)	48.81	
		Germany					(42–83)	≥ 8 (51.6%)	T3/T4 (45.2%)	(0.8–4623)	
		Netherlands									
		Sweden									
IQR = inter quartile range; SD = standard deviation; AR-V7 = androgen receptor splice variant 7; CTC = circulating tumor cell; PSA = prostate specific antigen; AL therapy; NHT = novel hormonal therapy; LHRH = luteinizing hormone releasing hormone; PCa = prostate cancer; CRPC = castration resistance prostate cancer; A Enzalutamide; IHC = Immunohistochemistry;											

3.3 Gleason score

The proportion of Gleason scores ≥ 8 between the group of AR-V7-positive and negative CRPC was compared in sixteen studies including 1699 patients. As shown in Fig. 2, 242 of 348 (69.5%) AR-V7-positive men had Gleason scores ≥ 8 , whereas 742 of 1351 (54.9%) AR-V7-negative men were Gleason scores ≥ 8 . Gleason score was significantly higher in AR-V7-positive than in AR-V7-negative CRPC (OR 1.68, 95% CI 1.25–2.25, $P < 0.001$). Significant heterogeneity was not found among studies ($I^2 = 0.0\%$, $P = 0.57$) and fixed-effects model was adopted.

3.4 T stage

The rate of higher tumor stage (T3/T4) in different AR-V7 status CRPC was analyzed in six studies, 169 patients. Figure 3A presented that 39 of 74 (52.7%) AR-V7-positive men had higher T stage, and the proportion in AR-V7-negative CRPC was 49.5% (47 of 95). There was no significant difference of T stage in CRPC grouped by different AR-V7 status (OR 1.16, 95% CI 0.60–2.24, $P = 0.65$). There is no evidence for heterogeneity between the studies ($I^2 = 28\%$, $P = 0.23$) and fixed-effects model was applied.

3.5 N stage

Lymph node metastatic rate was evaluated in ten studies including 587 CRPC patients, grouped by AR-V7-positive and negative. As shown in Fig. 3B, 104 of 283 (36.7%) AR-V7-positive men had lymph node invasion, and the rate in AR-V7-negative CRPC was 28.0% (85 of 304). There was no significant difference of N stage in CRPC of different AR-V7 status (OR 0.99, 95% CI 0.65–1.51, $P = 0.96$). Significant heterogeneity was not found ($I^2 = 46\%$, $P = 0.07$) and fixed-effects model was used.

3.6 M stage

The proportion of metastases was assessed in ten studies including 1448 CRPC patients, grouped by different AR-V7 status. As shown in Fig. 4A, 144 of 235 (61.3%) AR-V7-positive men had metastases, while the rate in AR-V7-negative CRPC was 35.0% (424 of 1213). The rate of metastases in AR-V7-positive CRPC was significantly higher than that in AR-V7-negative (OR 2.19, 95% CI 1.57–3.05, $P < 0.001$). Fixed-effects model was applied to evaluate OR and 95% CI due to there is no heterogeneity between the studies ($I^2 = 3\%$, $P = 0.41$).

We further compared the proportion of bone metastases between the group of AR-V7-positive and negative CRPC in seventeen studies including 1935 patients. Figure 4B indicated that 375 of 459 (81.7%) AR-V7-positive men had bone metastases, whereas the rate in AR-V7-negative was 69.0% (1018 of 1476). Significantly higher rate of bone metastases was determined in AR-V7-positive CRPC (OR 1.97, 95% CI 1.44–2.69, $P < 0.001$). Significant heterogeneity was not found ($I^2 = 21\%$, $P = 0.22$), and a fixed effect model was performed to calculate the OR and 95% CI.

Meanwhile, the visceral metastatic ratio was also evaluated in eighteen studies including 1137 CRPC patients, grouped by different AR-V7 status. Figure 4C indicated that 124 of 430 (28.8%) AR-V7-positive men had visceral metastases and 156 of 707 (22.1%) AR-V7-negative had visceral metastases. There was a barely detectable statistically significant difference of visceral metastatic ratio in different AR-V7 status (OR 1.29, 95% CI 0.96–1.74, $P = 0.09$). No significant study heterogeneity was detected ($I^2 = 19\%$, $P = 0.24$) and fixed-effects model was adopted.

3.7 Presence of pain

The proportion of presence of pain was compared in five studies including 418 CRPC patients, grouped by different AR-V7 status. As shown in Fig. 5A, 59 of 108 (54.6%) AR-V7-positive men suffered pain, while the rate in AR-V7-negative CRPC was 28.1% (87 of 310). Significantly higher rate of presence of pain was

determined in AR-V7-positive CRPC (OR 4.23, 95% CI 2.52–7.10, $P < 0.001$). Fixed-effects model was used to calculate OR and 95% CI because there is no heterogeneity between the studies ($I^2 = 0\%$, $P = 0.68$).

3.8 ECOG performance status score

In total, seventeen trials 2047 CRPC patients were enrolled in the comparison of the relation between high ECOG score (ECOG score ≥ 1) and AR-V7 status. Figure 5B showed 275 of 485 (56.7%) AR-V7-positive men were ECOG score ≥ 1 , whereas the rate in AR-V7-negative was 35.0% (546 of 1562). AR-V7-positive CRPC patients had performed significantly higher ECOG score than AR-V7-negative (OR 2.18, 95% CI 1.51–3.16, $P < 0.001$). A random effects model was used to calculate the OR and 95% CI because significant heterogeneity was found ($I^2 = 40\%$, $P = 0.05$).

4 Discussion

We processed a meta-analysis to verify the hypothesis that AR-V7 positivity was associated with worse clinicopathological features. Biomarker of clinical utility should provide reliable information to the doctors with the potential to optimize precision treatment for patients. AR-V7 is taken for the most common AR splice variant, which was first found in advanced stage patients [25–29]. AR-V7 positive may be a particular type of prostate cancer subtype due to its worse clinicopathological characteristics. As various researches have indicated that AR-V7 was a novel AR splice variant which was capable of initiating and promoting CRPC progress [6, 7, 9], the AR-V7 positive CRPC needs to be considered as a novel subtype of CRPC with specific clinicopathological characteristics and resistance to AR signal targeted therapy.

AR-V7 positive has been associated with unfavorable baseline characteristics; therefore, it may reflect a larger neoplasm burden [20, 30, 31]. We compared the association between Gleason score and different AR-V7 status. Gleason score was obviously higher in AR-V7-positive than negative CRPC. We concluded that AR-V7 status is associated with clinicopathological characteristics for CRPC patients. However, recent trials showed insignificant relation between AR-V7-positive and higher Gleason score [14], some even implied AR-V7-negative patients had higher Gleason score [13]. Our results indicated AR-V7 positive patients had significant higher Gleason score, which was inconsistent with the previous findings that AR-V7 positivity was not related to higher Gleason score in metastatic CRPC [13]. Further researches about the relation between AR-V7 and Gleason score are still urgently expected.

Recent researches indicated that AR-V7-positive men would suffer higher T stage and lower N stage respectively [20, 21]. In this analysis, we assess the relevance between AR-V7 expression and clinicopathological features of CRPC patients. According to the merged results, we offered trustworthy evidence that the correlations between AR-V7 with T stage and lymph node metastasis were not statistically significant.

Bone or any site metastasis, presence of pain and ECOG performance score were compared in CRPC respectively with different AR-V7 status. AR-V7-positive patients had an elevated risk of any site metastasis, pain sufferance and worse ECOG performance score compared with AR-V7-negative CRPC. Although there were few studies about the clinicopathological features of AR-V7, it has been a hot-spot role of clinical decision-making and potential therapeutic target of CRPC. Existing evidence validated that expression of AR-V7 protein in circulating tumor cells nuclear was related with superior survival on taxane therapy in clinical practice as a specific treatment biomarker in men with mCRPC [18]. Accordingly, AR-V7 targeted therapy strategies are necessary and AR-V7 should be continuously surveilled during treatment. Same conclusion as before, AR-V7 is related to faster disease progression in CRPC [32–35]. Considering the prognosis value and the specific clinicopathological characteristics of AR-V7 in CRPC, AR-V7-positive CRPC should be taken as a novel subtype of prostate cancer which requires more aggressive, personalized and AR-V7 targeted therapy strategy. Further prospective studies are certainly needed to validate the role of AR-V7 positive as a particular type of prostate cancer subtype in CRPC.

There are several advantages in our systematic review. First of all, this is the first meta-analysis that indicates the clinicopathological characteristics of AR-V7 in CRPC patients to our knowledge. Second, our research offers a scientific basis to support for individualized estimations of clinicopathological features for CRPC patients, identifies more aggressive CRPC patients. In this way, doctors may conduct precision medicine and individualized treatment for CRPC patients. A challenge in the near future will be to correctly classify patients according to AR-V7 status within a suitable time for clinical practice [36]. In addition, this study may promote researchers to design additional clinical studies with larger sample sizes to validate these findings.

Notably, we did the best to perform this meta-analysis but there were still a few limitations in this systematic review. The sample size is rather small and limits its statistical power, which ranged from 3 to 953 participants. And the number of published studies was not sufficiently large for more accurate results due to the limited number of studies included. It is certain that smaller sample sizes were less reliable and tended to have publication bias. Thus, more large-cohort clinical trials are warranted to more accurate provide evidence for the clinicopathological features in CRPC patients. Second, the standards of study designs were not unified. Many studies caused an uncertain selection bias due to enrolled patients from a single center. Others reported patients in single or multicenter clinical trials, where patients enrolled might be highly selected by different criteria. Third, only references published in English were included in our meta-analysis. Fourth, the cut-off values distinguishing positive and negative AR-V7 expression differed in studies. And the various detection assays and antibodies used in the included researches might impact the sensitivity and specificity of AR-V7 positivity [37–40]. Therefore, consensus on the analytical method of testing and cut-off value are needed [41], generalized to more large multicenter researches, will provide more precise and credible results. Moreover, the clinicopathological features of CRPC patients including T stage, N stage and M stage, the definition of PSA and alkaline phosphatase response, and Gleason score vary among different studies, which might be responsible for the heterogeneity. Last but not the least, we admitted that AR-V7 was not extensively and sufficiently studied in CRPC patients, which would most likely draw controversial conclusions.

Several important efforts we made to deal with these drawbacks. Firstly, we performed a comprehensive, systematic, and repeatable search strategy for the most relevant references in multiple online databases which based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. To be honest, selection bias couldn't be eliminated, but could be minimized by our strict screening of inclusion eligibility in the meta-analysis. Secondly, details of the study design, method of AR-V7 detection, types of therapy, Gleason score, tumor stage, node stage, metastasis status, presence of

pain and ECOG performance status score in CRPC, and follow-up period were tabulated and available for further analysis and reference. Thirdly, fixed or random effect model was arranged according to different heterogeneity for more authentic and credible results. Additionally, the publication bias was evaluated and small-study effect was assessed by funnel plot listed in the supplement.

5 Conclusions

In conclusion, this meta-analysis clearly indicated that AR-V7 expression was significantly associated with Gleason score, bone or any site metastasis, pain presence and ECOG performance status, but not statistically related to tumor stage or lymph node metastasis. Specific clinicopathological features of AR-V7-positive CRPC were expected with higher Gleason score, more metastasis and pain presence, and worse ECOG performance status. Considering the prognostic value of AR-V7 in resistance to Abiraterone and Enzalutamide treatment for CRPC patients, our results may guide clinicians in identifying patients with more aggressive cancers, and selecting suitable patients that would derive durable clinical benefit from more active anti-tumor therapy. However, heterogeneous among study sample size and design, assays for AR-V7 detection assessment, and cut-off values definition for positive versus negative expression were evident within the included studies. More cross-institutional large-cohort prospective studies are warranted to confirm these findings and the clinical utility of AR-V7 as a biomarker in CRPC are expected.

Abbreviations

AR-V7: Androgen receptor splicing variant 7

CRPC: Castration resistance prostate cancer

mCRPC: Metastatic castration-resistant prostate cancer

AR: Androgen receptor

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

T: Tumor

N: Node

M: Metastasis

ECOG: Eastern Cooperative Oncology Group

HSPC: Hormone sensitive prostate cancer

PSA: Prostate specific antigen

OR: Odds ratio

CI: Confidence interval

IQR: Inter quartile range

SD: Standard deviation

CTC: Circulating tumor cell

ADT: Androgen deprivation therapy

NHT: Novel hormonal therapy

LHRH: Luteinizing hormone releasing hormone

PCa: Prostate cancer

ABT: Abiraterone

ENZ: Enzalutamide

IHC: Immunohistochemistry;

Declarations

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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None.

Authors' contributions

Project administration: ZW. Data curation: HS. Formal analysis: CW. Writing original draft: QL. Investigation: ZW. Writing revised: ZW and LX. All authors read and approved the final manuscript.

Ethics Statement

The studies involving human participants were reviewed and approved by First Affiliated Hospital of Zhejiang University.

Consent for publication

All authors have authorized the publication of this manuscript.

Conflicts of interest

Authors declare no conflicts of interest in this study.

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Figures

Figure 1

Study selection process.

Figure 2

Forest plots of the proportion of Gleason scores ≥ 8 between the group of AR-V7-positive and negative CRPC from sixteen studies. The bars indicate 95% CIs. AR-V7 = androgen receptor splicing variant 7; CI = confidence interval; OR = odds ratio.

A. T3/T4 stage

B. N1 stage

Figure 3

Forest plots of T stage and N stage in CRPC between the group of AR-V7-positive and negative. (A) The ratio of T3/T4 stage in different AR-V7 status CRPC. (B) The ratio of N1 stage in different AR-V7 status CRPC. The bars indicate 95% CIs. AR-V7 = androgen receptor splicing variant 7; CI = confidence interval; OR = odds ratio.

A. Any site metastasis

B. Bone metastasis

C. Visceral metastasis

Figure 4

Forest plots of metastasis in CRPC between the group of AR-V7-positive and negative. (A) The rate of any site metastasis in different AR-V7 status CRPC. (B) The rate of bone metastasis in different AR-V7 status CRPC. (C) The rate of visceral metastasis in different AR-V7 status CRPC. The bars indicate 95% CIs. AR-V7 = androgen receptor splicing variant 7; CI = confidence interval; OR = odds ratio.

A. Presence of pain

B. ECOG score ≥ 1

Figure 5

Forest plots of performance status in CRPC between the group of AR-V7-positive and negative. (A) The rate of pain sufferance in different AR-V7 status CRPC. (B) The rate of ECOG score ≥ 1 in different AR-V7 status CRPC. The bars indicate 95% CIs. AR-V7 = androgen receptor splicing variant 7; CI = confidence interval; OR = odds ratio.

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