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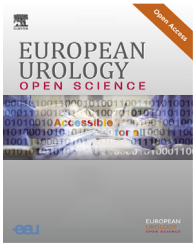

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Prostate Cancer

Evaluation of Survival Outcomes Among Black and White Patients with Metastatic Castration-resistant Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Data on racial disparities among patients with metastatic castration-resistant prostate cancer (mCRPC) are limited and there is no uniform conclusion on differences by race in this setting.
Objective: To provide the latest evidence on racial disparities in survival outcomes between Black and White patients receiving systemic therapies for mCRPC.
Evidence acquisition: Our study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. We systematically searched the PubMed, Web of Science, and Cochrane Library databases up to September 2023 to identify potentially relevant studies. Overall survival (OS) and progression-free survival (PFS) were the outcomes of interest. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were evaluated.
Evidence synthesis: Nine studies involving 9462 patients with mCRPC (2058 Black and 7404 White men) met the eligibility criteria and were included. Pooled estimates demonstrated significantly better OS for Black than for White men (HR 0.75, 95% CI 0.70–0.80; $p < 0.0001$). The results were similar in a subgroup of men receiving androgen receptor–targeted therapies (HR 0.72, 95% CI 0.66–0.78; $p < 0.0001$) and a subgroup of men receiving other treatments (HR 0.79, 95% CI 0.71–0.88; $p < 0.0001$). Likewise, significantly favorable PFS was observed for Black men receiving ARTs in comparison to their White counterparts (HR 0.84, 95% CI 0.71–0.99; $p = 0.0373$).
Conclusions: Overall, our meta-analysis of survival outcomes for men with mCRPC stratified by race revealed a significant survival benefit for Black men in comparison to their White counterparts, regardless of systemic therapeutic agent.
Patient summary: Both biological and nonbiological factors could account for racial differences in the efficacy of systemic treatments for metastatic prostate cancer that is resistant to hormone therapy. Our review provides the latest reliable evidence showing better survival outcomes for Black than for White men. The results

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will be helpful in further understanding the molecular mechanisms that might explain racial differences in this disease stage and in planning treatment.

1. Introduction

There is growing evidence regarding racial disparities in the onset and progression of prostate cancer (PCa) [1–4]. Population-level data show that Black men are more likely to develop and die from metastatic PCa than White men [5–8]. Many factors may be responsible for racial differences in PCa incidence and prognosis, such as variations in risk factors, socioeconomic status, genetic and molecular alterations, and other biologic factors [9]. Studies of genetic and biological differences among Black and White patients have revealed underlying causes and provided a promising theoretical basis for strategies to eliminate racial disparities in PCa [3,10]. These racial disparities are associated with a complicated interplay between social, environmental, and genetic factors. However, Black men are underrepresented in clinical trials in the metastatic castration-resistant PCa (mCRPC) setting, accounting for <3% of the global trial population, which fails to reflect real-world clinical practice [11–13]. More importantly, data on racial disparities in mCRPC are limited and there is no uniform conclusion on differences by race in this setting [14,15]. Previous studies did not reach an agreement on racial differences in the efficacy of androgen receptor–targeted therapies (ARTs) for mCRPC. Retrospective studies suggested superior overall survival (OS) outcomes for Black patients who received first-line abiraterone (ABI) [16,17], but prospective trials revealed no significant race-based difference in ABI effectiveness [18,19]. A real-world analysis including nearly 4000 patients with mCRPC showed that ABI was correlated with superior OS for African American men in comparison to non-Hispanic White men, but there was no racial difference among patients receiving first-line enzalutamide (ENZ), indicating a significant race-treatment interaction association [17]. Synthesis of these considerations prompted us to perform a systematic review and meta-analysis to compare the treatment efficacy of systemic therapies between Black and White patients with mCRPC using clinical data from comparative trials to inform decision-making.

2. Data acquisition

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [20], the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines [21], and the methods outlined in the Cochrane handbook [22]. The protocol was registered in the PROSPERO database (CRD42023481282).

2.1. Search strategy and selection criteria

We searched the PubMed, Web of Science, and Cochrane Library databases from inception to September 2023 to identify potentially relevant studies. The following search terms were used: "metastatic castration-resistant prostate cancer" OR "mCRPC" OR "castration-resistant prostate cancer" OR "CRPC". We included studies meeting the following criteria: (1) population: patients with mCRPC; (2) study design: prospective or retrospective studies; (3) intervention: systemic therapies such as chemotherapy, immunotherapy, and endocrinotherapy; and (4) outcomes: studies comparing the efficacy of systemic therapies between Black and White patients and reporting overall survival (OS) or progression-free survival (PFS) as the study endpoint. Studies were excluded if they were review papers, conference abstracts, editorials, preclinical articles, quality-of-life studies, or cost-effectiveness analyses.

2.2. Study selection and data extraction

Two independent reviewers screened the titles and abstracts and then the full texts for eligibility. Two reviewers extracted the following data from the studies included: first author; year of publication; type of study design; type of systemic therapies; sample sizes for Black and White patients; chemotherapy administered before the mCRPC stage; age; prostate-specific antigen (PSA) before systemic therapies; and relevant tumor control outcomes and treatment-associated adverse effects, including OS, PFS, PSA response (PSAR), skeletal-related events (SREs), and time to PSA progression (TTP). Any disagreements were resolved by a third reviewer.

2.3. Definition of outcomes

OS was defined as the time from treatment to death from any cause. PFS was defined as the time from treatment to the first clinical, radiographic, or biochemical progression event.

2.4. Risk-of-bias assessment

The risk of bias (RoB) was assessed using the ROBINS-I tool for evaluating RoB in estimates of the comparative effectiveness (harm or benefit) of interventions in observational studies [23]. A third reviewer was consulted to resolve any disagreements on decisions.

2.5. Statistical analysis

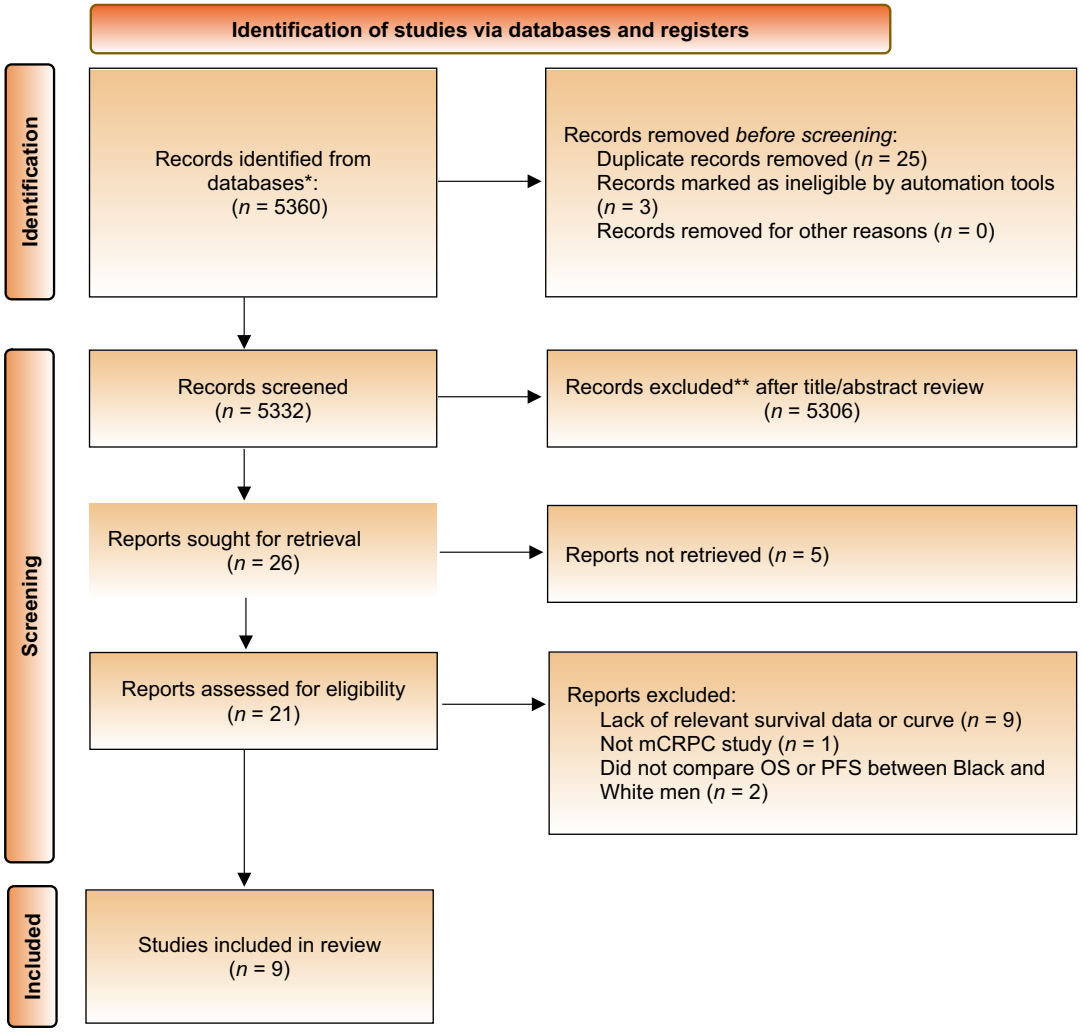
Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated for OS and PFS using pairwise meta-analysis. Before pooling, each HR was log-transformed and standard errors were calculated for the HR and 95%

CI. We applied a fixed-effect model because of the heterogeneity among studies. Heterogeneity was formally evaluated using a χ^2 test ($p \leq 0.10$) and the I^2 statistic. Considering the potential impact of different therapy types, preplanned subgroup analyses were conducted for two systemic therapy classes: (1) ARTs and (2) others, which included chemotherapy, ^{223}Ra, sipuleucel-T, and others. Publication bias was tested by applying the Egger test for funnel plot symmetry. A p value <0.01 indicates a statistically significant risk of publication bias. The *meta* and *metafor* packages in R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) were used to perform all the statistical analyses and generate forest plots.

3. Data synthesis

3.1. Inclusion of studies

A total of 5360 studies were initially identified via preliminary searches. After removing duplicate articles and initial assessment of titles and abstracts, 21 publications were selected for subsequent full-text evaluation. Of these, 12 were excluded as they did not provide relevant survival data or curves, did not compare the effectiveness or efficacy of systemic therapies between Black and White men, or the study participants did not have mCRPC. Nine studies [17,18,24–30] met the eligibility criteria and were included in the quantitative analysis. A PRISMA flow diagram [20] of the study selection process is presented in Figure 1.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of the study selection process. Reproduced from [20]. mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PFS = progression-free survival.

3.2. Characteristics of the studies included

The main characteristics of the studies included are summarized in Table 1. Of the nine studies, one was a prospective study and the remaining eight were retrospective studies. Overall, 9462 patients with mCRPC were involved, including 2058 Black and 7404 White patients. The median age ranged from 60 to 76 yr and median PSA from 10.5 to 57 ng/ml. Eight studies reported on chemotherapies received before enrolment and only one study did not report this information [29]. Among the 9462 patients with mCRPC, 766 (8.1%) had received chemotherapy before study enrolment, which was docetaxel in 84% of cases. Five studies investigated ABI and/or ENZ, one study investigated chemotherapy (including docetaxel, paclitaxel, chlorambucil, and melphalan) and ARTs (including ABI and ENZ), one study investigated ^{223}Ra, one study investigated sipuleucel-T, and one study did not report the specific treatments received by patients. These treatments were mostly applied in the first-line or second-line setting. However, accurate data regarding the treatment timeline were not explicitly specified in the original studies. Eight studies reported OS and three studies reported PFS.

A quality assessment of all the studies included is shown in Table 2. Publication bias did not appear to be present for studies included in the OS (Supplementary Fig. 1) or PFS (Supplementary Fig. 2) analyses. The p value for the Egger test for funnel plot symmetry was 0.14 for OS and 0.013 for PFS.

3.3. OS and PFS

Eight studies compared OS between Black and White patients with mCRPC receiving systemic therapies. Our meta-analysis revealed significantly better OS for Black men in comparison to White men (HR 0.75, 95% CI 0.70–0.80; $p < 0.0001$). In the ART subgroup, pooled estimates also indicated a statistically significant clinical OS benefit for Black patients in comparison to White patients (HR 0.72, 95% CI 0.66–0.78; $p < 0.0001$). In the subgroup receiving other treatments, there was also a significant OS benefit for Black men (HR 0.79, 95%CI 0.71–0.88; $p < 0.0001$; Fig. 2).

Of the nine studies included, only three reported PFS as a study endpoint, all of which assessed the efficacy of ARTs between Black and White patients with mCRPC. Our meta-analysis revealed significantly better PFS for Black men in comparison to White men (HR 0.84, 95%CI 0.71–0.99; $p = 0.0373$; Fig. 3).

3.4. Discussion

This study was performed to assess survival disparities by race between Black and White men with mCRPC regardless of systemic therapeutic agent (ARTs such as ABI and ENZ, chemotherapies such as docetaxel and paclitaxel, and other agents). Our results demonstrate significantly better OS and PFS for Black men than for White men. To the best of our knowledge, this is the first study summarizing evidence on racial disparity in mCRPC survival outcomes between Black and White patients. Moreover, according to our analyses, the systemic therapeutic agent received did not appear to influence the survival outcomes, and favorable survival outcomes for Black men across all our subgroup analyses. Our meta-analysis provides the latest reliable evidence on this issue and could facilitate a deeper understanding of the molecular mechanisms underlying racial disparities in mCRPC.

The survival disparities between Black and White patients with mCRPC are multifactorial and potential causes can be divided into biological and nonbiological factors. Genetic differences are the primary biological factor contributing to the racial disparities observed [3], and key genes could partly explain these disparities. *HSD3B1* gene variation [31] is related to earlier castration resistance and shorter OS in men with low-volume metastatic PCa and is observed more frequently for White than for Black men. *HSD3B1* alterations could contribute to the increases in androgen production and androgen receptor activation that underlie the potential mechanism responsible for poorer prognosis. According to the genetic and epigenetic landscape, different molecular subclasses have been identified in different races [3]. Based on a combination of genetic alterations, gene expression patterns, and methylation profiles, precision targeted therapy might serve as a promising strategy to balance racial disparities in the mCRPC setting [10]. One study showed that TGF-β expression, which differs by race, modulated taxane and docetaxel sensitivity in PCa cells [32]. Moreover, *SPHKAP*/*SPHK1* was identified as a predictor of clinical benefit based on ancestry, and modulated the efficacy of chemotherapy and radiotherapy and influenced the proliferation of tumor cells [18,33,34]. In summary, genetic differences lead to variations in treatment response between Black and White patients, but the extent of these effects and further mechanisms that may cause differences in outcomes remain unclear. Besides racial differences in PCa genetics, the castration response, hormone levels, and drug pharmacokinetics and pharmacodynamics are also worth taking into consideration.

Among nonbiological factors, socioeconomic status, educational attainment, residential neighbourhood, environment, and choice of treatment are common confounders [35]. A recent meta-analysis found that societal inequities affect a wide range of health and quality-of-life risks and outcomes [36]. Disparities in social determinants of health (SDOH) may have downstream effects on health outcomes and are associated with survival differences between Black and White men in the USA. Common examples of SDOH include income, diet, accommodation, and transportation, all of which are linked to health outcomes [36]. Not all studies could fully consider the impact of these factors on survival outcomes and eliminate the interference of these nontherapeutic factors in mCRPC clinical trials. Thus, nonbiological factors could also partly explain the difference in prognosis between Black and White men.

Clinical trials are the foundation for evidence-based medicine and provide a sound, realistic basis for clinical decision-making with due consideration of patient expectations and clinician experience [37]. To be able to apply trial results to specific patients, participant enrolment should reflect and represent the population encountered in clinical practice. However, the lack of inclusion of Black men in clin-

Table 1 – Baseline characteristics of the studies included in the review

Study	Design	Race	Sample size	Therapy for metastatic castration-resistant prostate cancer					Age[c] (yr)	PSA[c] (ng/ml)	Study endpoints
				Therapy	Line	ABI (%)	ENZ (%)	Previous CTx, *n* (%)			
Marar 2022 [17]	RS	Black	323	ABI	1L	100	0	DOC: 154 (9)	74[d]	57	OS
		White	2286	ABI	1L	100	0				
		Black	321	ENZ	1L	0	100	DOC: 213 (10)	72[d]	56	
		White	2218	ENZ	1L	0	100				
George 2022 [24]	RS	Black	787	ABI, ENZ	1L/2L	59.7	40.3	0	71.71[d]	44.6	OS
		White	2123	ABI, ENZ	1L/2L	62.3	37.7	0	74.01[d]	26.7	
Freedland 2022 [25]	RS	Black	214	ENZ	1L	0	100	0	60–79[e]	17.6	PSAR, cPFS
		White	1332	ENZ	1L	0	100	0	60–79[e]	10.5	
Ng 2021 [26]	RS	Black	103	CTx[a], ART[b]	1L/2L	NA	NA	0	73	44	OS
		White	322	CTx[a], ART[b]	1L/2L	NA	NA	0	73	43	
George 2021 [18]	PS	Black	50	ABI	1L	100	0	DOC: 16 (32)	69.05	17.73	OS, rPFS, TTP
		White	50	ABI	1L	100	0	DOC: 22 (44)	67.8	22.35	
Zhao 2020 [27]	RS	Black	87	^{223}Radium	1L/2L	91.8	81.4	DOC: 67 (77)	67	159.9	SRE, OS
		White	226	^{223}Radium	1L/2L			DOX: 124 (55)	70	90.2	
Sartor 2020 [28]	RS	Black	219	Sipuleucel-T	1L	NA	NA	NS: 25 (11)	71	32.9	OS
		White	438	Sipuleucel-T	1L	NA	NA	NS: 97 (22)	72	28.7	
Patel 2020 [29]	RS	Black	232	NS	NA	NA	NA	NA	76	41.7	SRE, OS
		White	605	NS	NA	NA	NA	NA	76	29.2	
Ramalingam 2017 [30]	RS	Black	45	ABI	1L/2L	100	0	DOC: 16 (36)	NA	48.0	PSAR, OS, bPFS
		White	90	ABI	1L/2L	100	0	DOC: 32 (36)	NA	37.2	

RS = retrospective study; PS = prospective study; ABI = abiraterone; ENZ = enzalutamide; CTx = chemotherapy; 1L = first line; 2L = second line; PSA = prostate-specific antigen; ART = androgen receptor–targeted therapy; NA = not available; DOC = docetaxel; NS = not specified; SRE = skeletal-related event; PSAR = PSA response; OS = overall survival; PFS = progression-free survival; cPFS = clinical PFS; rPFS = radiographic PFS; bPFS = biochemical PFS; TTP = time to PSA progression.

[a] Including docetaxel, paclitaxel, chlorambucil, and melphalan.

[b] Including ABI and ENZ.

[c] Median unless otherwise stated.

[d] Mean.

[e] Range.

Table 2 – Risk-of-bias assessment for the studies included in the review

Study	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Marar 2022 [17]	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
George 2022 [24]	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Freedland 2022 [25]	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Ng 2021 [26]	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
George 2021 [18]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Zhao 2020 [27]	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Sartor 2020 [28]	Moderate	Moderate	Moderate	Serious	Moderate	Low	Low	Serious
Patel 2020 [29]	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Moderate	Serious
Ramalingam 2017 [30]	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate

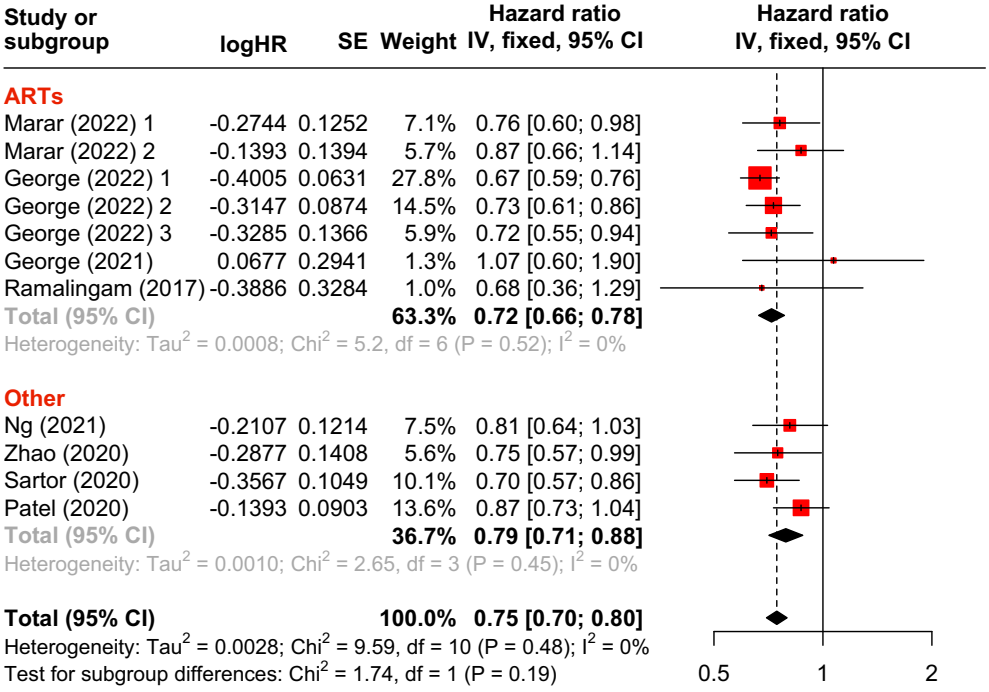


Fig. 2 – Forest plot of overall survival for Black and White patients with metastatic castration-resistant prostate cancer across different therapies. ARTs = androgen receptor–targeted therapies; HR = hazard ratio; SE = standard error; IV = inverse variance; CI = confidence interval; df = degrees of freedom.

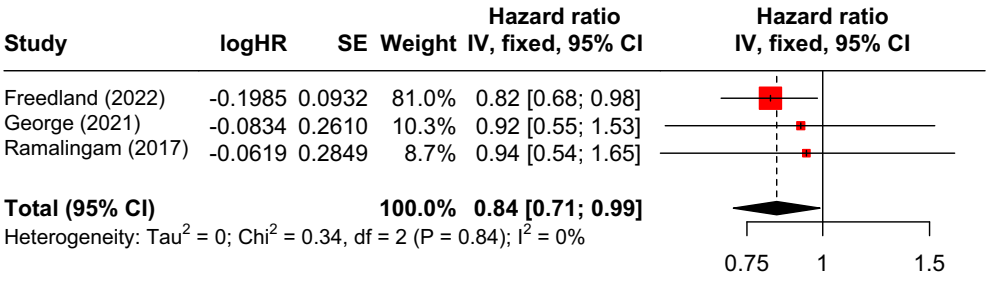


Fig. 3 – Forest plot of progression-free survival for Black and White patients with metastatic castration-resistant prostate cancer receiving androgen receptor–targeted therapies. HR = hazard ratio; SE = standard error; IV = inverse variance; CI = confidence interval; df = degrees of freedom.

ical trials in mCRPC means that limited data and low-power conclusions are available [11,12,38,39], hampering mCRPC management and the elimination of racial disparity in this setting. This pervasive under-representation also impedes the exploration of possible causes of disparate outcomes. The current review included 2058 Black men (22%) and 7404 White men (78%), which represents a greater proportion of Black patients than in typical studies; however, this might still not fully represent Black patients with mCRPC in the real world. Further prospective studies with a sufficient number of Black patients are needed to elucidate differences in survival outcomes by race.

The limitations of our review and meta-analysis must be mentioned. First, only one of nine the studies included was prospective, which is bound to compromise the reliability of the conclusions. The absence of baseline data for parameters such as comorbidities and the location and number of metastatic sites limited the balance between the two races, but for all of the studies included, both races were closely matched across extensive characteristics that are of prognostic significance in mCRPC [40]. Various therapies or combinations of therapies prescribed in each study made it difficult to explain the influence of a single therapy on outcomes. The OS endpoint in our study reflects all-cause mortality rather than PCa-specific mortality (PCSM). Given that most men with mCRPC died from their cancer, the lack of PCSM is unlikely to have influenced the outcomes of our analysis.

4. Conclusions

Our meta-analysis of survival outcomes for patients with mCRPC stratified by race confirmed a significant survival benefit for Black men in comparison to White men, regardless of the systemic therapeutic agent received. Future prospective studies in the mCRPC setting should include a greater proportion of Black men and explore the potential mechanisms behind discrepant outcomes to address the long-standing racial disparity in mCRPC prognosis.

Author contributions: Qiang Wei had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: L. Yang, Wei.
Acquisition of data: Liao, Xu.
Analysis and interpretation of data: J. Yang, Xiong, Zheng.
Drafting of the manuscript: J. Yang, Xiong, Liao, Xu.
Critical revision of the manuscript for important intellectual content: L. Yang, J, Yang, Xiong.
Statistical analysis: J, Yang, Xiong, Zheng.
Obtaining funding: L. Yang, Wei.
Administrative, technical, or material support: Xiong, J. Yang.
Supervision: L. Yang, Wei.
Other: None.

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Data sharing statement: All data used in this work can be found in the article and references.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.01.004.

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