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Sequencing impact and prognostic factors in metastatic castration-resistant prostate cancer patients treated with cabazitaxel: A systematic review and meta-analysis

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Abstract

Background: Cabazitaxel is an effective treatment of post-docetaxel metastatic castration-resistant prostate cancer (mCRPC). We aimed to assess the sequencing impact and identify prognostic factors of oncologic outcomes in mCRPC patients treated with cabazitaxel.

Methods: PUBMED, Web of Science, and Scopus databases were searched for articles published before January 2022 according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement. Studies were deemed eligible if they investigated pretreatment clinical or hematological prognostic factors of overall survival (OS) in mCRPC patients with progression after docetaxel treated with available treatments including cabazitaxel.

Results: Overall, 22 studies were eligible for the meta-analysis. In mCRPC patients treated with docetaxel, subsequent treatment with cabazitaxel was associated with better OS compared to that without cabazitaxel (pooled hazard ratio [HR]: 0.70, 95% confidence interval [CI]: 0.56−0.89). Among the patients treated with cabazitaxel, several pretreatment clinical features and hematologic biomarkers were associated with worse OS as follows: poor performance status (PS) (pooled HR: 1.92, 95% CI: 1.33−2.77), presence of visceral metastasis (pooled HR: 2.13, 95% CI: 1.62−2.81), symptomatic disease (pooled HR: 1.47, 95% CI: 1.25−1.73), high PSA (pooled HR: 1.76, 95% CI: 1.27−2.44), high alkaline phosphatase (ALP) (pooled HR: 1.45, 95% CI: 1.28−1.65), high lactate dehydrogenase (LDH) (pooled HR: 1.54, 95% CI: 1.00−2.38), high c-reactive protein (CRP) (pooled HR: 4.40, 95% CI: 1.52−12.72), low albumin (pooled HR:1.09, 95% CI: 1.05 −1.12) and low hemoglobin (pooled HR:1.55, 95% CI: 1.20−1.99).

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Conclusions: Sequential therapy with cabazitaxel significantly improves OS in post-docetaxel mCRPC patients. In mCRPC patients treated with cabazitaxel, patients with poor PS, visceral metastasis, and symptomatic disease were associated with worse OS. Further, pretreatment high PSA, ALP, LDH or CRP as well as low hemoglobin or albumin, were blood-based prognostic factors for OS. These findings might help guide the clinical decision-making for the use of cabazitaxel and prognostication of its OS benefit.

Keywords: Metastatic castration-resistant prostate cancer; Cabazitaxel; Prognostic factor

Abbreviations and Acronyms: ADT, Androgen deprivation therapy; ALP, Alkaline phosphatase; ARSI, Androgen receptor signaling inhibitor; CI, Confidential interval; CRP, c-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; GS, Gleason score; LDH, Lactate dehydrogenase; HR, Hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; OS, Overall survival; PCa, Prostate cancer; PS, Performance status; PSA, Prostate specific antigen; PSMA, Prostate specific membrane antigen; WHO-PS, World Health Organization Performance Status

1. Introduction

The management of metastatic prostate cancer (PCa) has rapidly evolved over the past decades, specifically in the field of metastatic disease [1]. Although the majority of metastatic PCa patients achieve an initial response to regimens based on androgen receptor signaling inhibitors (ARSIs) or docetaxel in combination with androgen deprivation therapy (ADT), most of them eventually experience disease progression to metastatic castration-resistant prostate cancer (mCRPC) [2−4]. With the increase use of upfront ADT plus ARSI, docetaxel is often considered a key agent in patients with mCRPC [5,6]. Moreover, in patients who had progression after docetaxel, cabazitaxel has been widely used for mCRPC since 2010[7]. In 2019, the CARD trial investigated the impact of differential sequencing between cabazitaxel and ARSI in mCRPC patients who progressed after initial treatment with docetaxel. This trial revealed that the administration of cabazitaxel was associated with better overall survival (OS) compared to ARSI [8]. In clinical practice, the number of metastatic PCa patients receiving both docetaxel and cabazitaxel during the course of their disease is limited, which can be attributed to several reasons such as the reluctance of patients or physicians to use chemotherapy and the poor patient condition owing to rapid disease progression [9,10]. Indeed, the data on sequential treatment for mCRPC remains suboptimal. In addition, there is a lack of reliable predictive or prognostic factors that can help identify patients who are likely to benefit from cabazitaxel, thus reducing treatment toxicity associated with chemotherapeutics in those unlikely to achieve benefit. Therefore, we conducted this systematic review and meta-analysis to assess the survival impact of cabazitaxel for mCRPC and identify prognostic factors of oncologic outcomes in mCRPC patients treated with cabazitaxel.

2. Materials and methods

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD 42022306505).

2.1. Search strategy

This systematic review and meta-analysis was conducted based on the guidelines of the Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology Statement (Supplementary Table 1) [11]. In January 2022, a literature search on PUBMED, Web of Science, and Scopus databases was performed to identify studies reporting on the oncologic outcomes of cabazitaxel in mCRPC. The keywords used in our search strategy were as follows: prostate cancer AND metastatic AND (overall survival OR cancer-specific survival OR progression-free survival OR prognostic OR survival) AND cabazitaxel. The detailed database search strategy is shown in the Supplementary Appendix. The primary outcome of interest was OS. Two investigators performed initial screening based on the titles and abstracts to identify eligible studies. Potentially relevant studies were subjected to a full-text review. Additionally, manual search of references lists of relevant articles was also performed to identify additional studies. Disagreements were resolved by consensus with co-authors.

2.2. Inclusion and exclusion criteria

Studies were included if they investigated mCRPC patients who were treated with cabazitaxel (Patients), with abnormal pretreatment clinical and hematologic factors (Interventions), compared to those without abnormal pretreatment clinical and hematologic factors (Comparisons) to assess the independent prognostic value of the clinical and the hematological factors on OS (Outcome) utilizing multivariable Cox regression analysis in nonrandomized observational, randomized, or cohort studies (Study design). Studies were also included if they investigated mCRPC patients (Patients), who were treated with cabazitaxel (Interventions), compared to who were treated with other sequential treatments (Comparisons) to assess the differential effect on OS (Outcome) utilizing multivariable Cox regression analysis in nonrandomized observational, randomized, or cohort studies (Study design).

Studies lacking original patient data, reviews, letters, editorial comments, replies from authors, case reports, and

articles not written in English were excluded. References of all papers included were scanned for the additional studies of interest.

2.3. Data extraction

Data were extracted independently by 2 authors. The first author's name, publication year, recruitment country and periods, number of patients, age, dosage and cycles of cabazitaxel, performance status (PS), Gleason score (GS), prostate-specific antigen (PSA) at the initiation of cabazitaxel, symptomatic disease, metastatic sites, number of prior treatment line and ARSIs, follow-up periods, median OS were extracted. Subsequently, the hazard ratios (HRs) and 95% confidential intervals (CIs) of pretreatment prognostic factors associated with OS were retrieved. All HRs were derived from multivariable analysis using Cox regression models. In cases of duplicate cohorts, the higher quality or the most recent data were extracted. All discrepancies were solved by consensus with co-authors.

2.4. Risk of bias assessment

Assessment of study quality and risk of bias was carried out using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool following the Cochrane Handbook for Systematic Reviews of Interventions. Each bias domain and overall risk of bias were judged as "Low," "Moderate," "Serious" or "Critical" risk of bias. The main confounders were identified as the critical prognostic factors of OS. The presence of confounders was determined by consensus and review of the literature. The ROBINS-I assessment of each study was performed independently by two authors (Supplementary Table 2).

2.5. Statistical analyses

Forest plots were used to analyze and summarize the multivariable HRs and describe the relationships between pretreatment clinical and hematologic factors and survival outcomes. Heterogeneity among the outcomes of included studies in this meta-analysis was assessed using Cochrane's Q test and the I^2 statistic. When significant heterogeneity (P-value of < 0.05 in the Cochrane Q test and a ratio $>$ 50% in I^2 statistics) was observed, a random-effects model was applied [12,13]. Fixed-effects models for the calculation of pooled HRs for non-heterogeneous results were applied [14]. Funnel plots were used for the assessment of publication bias (Supplementary Figure 1,2). All analyses were conducted using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and the statistical significance level was set at $P < 0.05$.

3. Results

3.1. Study selection and characteristics

Our initial search identified 1,359 records. After removing duplicates, 931 records remained which were screened based on title and abstract (Fig. 1). After screening, a full-text review was performed for 62 articles. According to our inclusion criteria, we finally identified 25 studies eligible for systematic review [15−39] and 19 studies eligible for meta-analysis [15−33]. The demographics of each included study are shown in Tables 1–3, and Supplementary Table 3. Of 19 studies, 3 studies comprising 1,041 patients were eligible for the meta-analysis of survival impact of cabazitaxel and 19 studies comprising 2,412 patients were eligible for the meta-analysis of prognostic factors in mCRPC patients treated with cabazitaxel (Tables 1−3). For the systematic review, 6 studies evaluating the prognostic value of PSA variation were eligible (Supplementary Table 3).

3.2. Meta-analysis of sequential therapy with cabazitaxel compared to other agents

Three studies provided data regarding OS between the sequential therapy with cabazitaxel compared to other agents in mCRPC patients treated with docetaxel. The forest plot (Fig. 2) revealed that sequential therapy with cabazitaxel was significantly associated with better OS compared to other therapies (Pooled HR: 0.70, 95% CI: 0.56−0.89, $P = 0.003$). The Cochrane's Q ($Chi^2 = 2.84$; $P = 0.24$) and I^2 ($I^2 = 30\%$) tests revealed no significant heterogeneity.

3.3. Meta-analysis of prognostic factors for overall survival in mCRPC patients treated with cabazitaxel

3.3.1. Pretreatment clinical features

3.3.1.1. Performance status (PS). Six studies provided data on the association of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) or World Health Organization Performance Status (WHO-PS) with OS in mCRPC patients treated with cabazitaxel. The definition of poor PS differed among included studies; thus, we divided this variable into 3 categories: ECOG PS $\geqq$ 1 vs. 0 or ECOG PS $\geqq$ 2 vs. 0−1, or WHO PS $\geqq$ 1 vs.0. The forest plot (Fig. 3A) revealed that poor PS was associated with worse OS (Pooled HR: 1.92, 95% CI: 1.33 to 2.77, $P < 0.001$). The Cochrane's Q ($Chi^2 = 14.0$; $P = 0.03$) and I^2 ($I^2 = 57\%$) tests revealed significant heterogeneity in overall analysis.

3.3.1.2. Presence of visceral metastasis. Five studies provided data on the association of visceral metastasis with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 3B) revealed that the presence of visceral metastasis was associated with worse OS (Pooled HR: 2.13, 95% CI: 1.62−2.81,

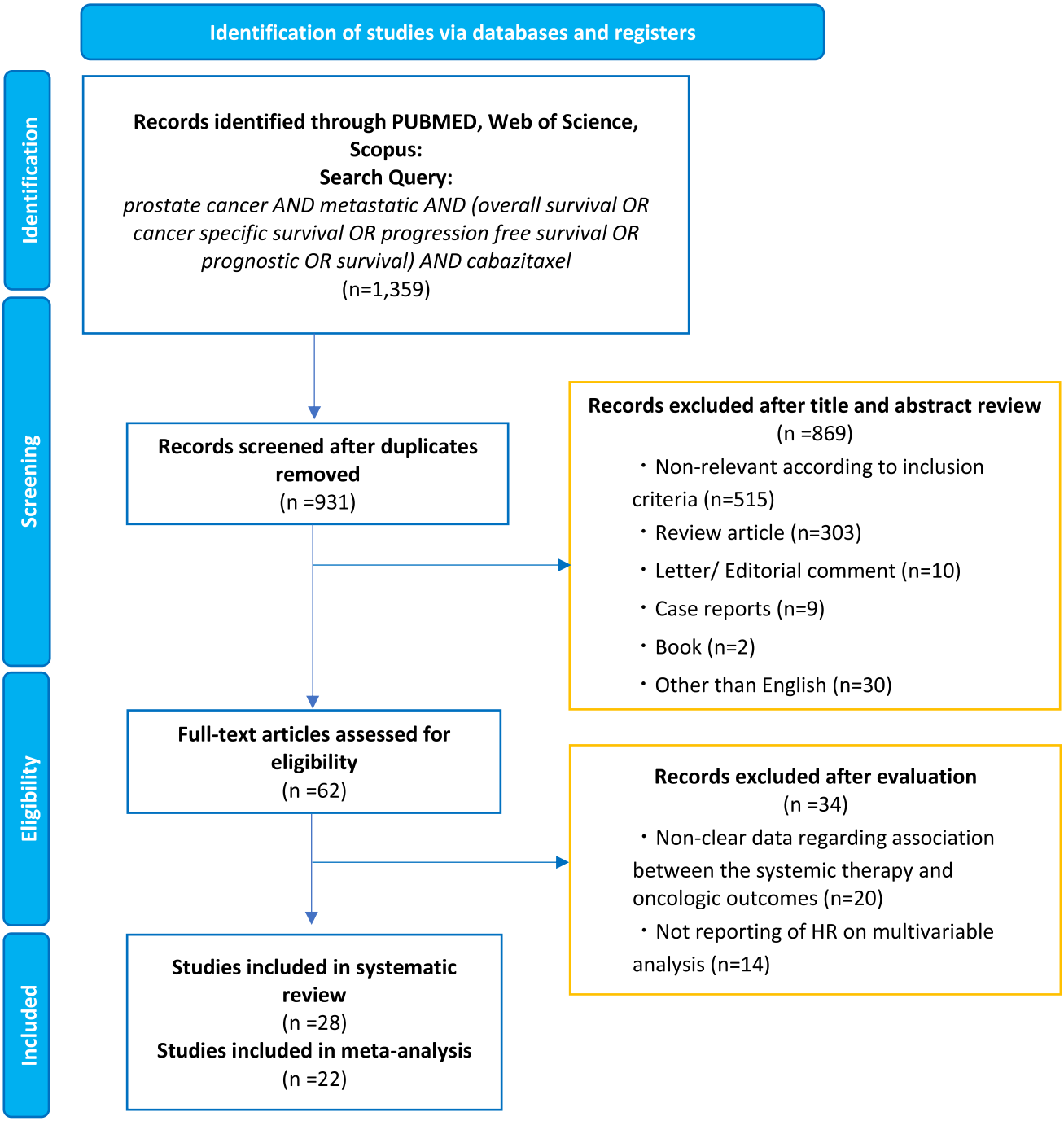


Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart, detailing the article selection process.

$P < 0.001$). The Cochrane's Q ($Chi^2 = 11.1$; $P = 0.05$) and I^2 ($I^2 = 55\%$) tests revealed significant heterogeneity.

3.3.1.3. Symptomatic disease. Four studies provided data on the association of symptomatic disease with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 3C) revealed that symptomatic disease was associated with worse OS (Pooled HR: 1.47, 95% CI: 1.25−1.73, $P < 0.001$). The Cochrane's Q ($Chi^2 = 0.76$; $P = 0.86$) and I^2 ($I^2 = 0\%$) tests revealed no significant heterogeneity.

3.3.2. Pretreatment hematologic factors

3.3.2.1. PSA. Eight studies provided data on the association of pretreatment PSA with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 4A) revealed that a high pretreatment PSA level was associated with worse OS (Pooled HR: 1.76, 95% CI: 1.27−2.44, $P < 0.001$). The Cochrane's Q ($Chi^2 = 14.9$; $P = 0.04$) and I^2 ($I^2 = 53\%$) tests revealed significant heterogeneity.

Table 1
Study demographics of included studies assessing sequencing impact of cabazitaxel.

Author	Year	Recruit	Country	Cohort	No. of patients	Dosage	Median age	ECOG-PS	GS	PSA	Symptomatic	Metastatic site, *n* (%)	Duration of prior treatments	Prior ARSI	Follow-ups (months)	OS (months)
de Wit [17]	2021	2015–2018	CARD study	Post docetaxel third line CBZ vs. another ARSI	246 (*255) 123 pts. Each	25mg/m2 every 3 weeks	CBZ: 70 (range: 46– 85) ARSI: 71 (range: 45– 88)	0– 1: CBZ: 123 (95) ARSI: 119 (94)	≧8 CBZ: 73 (57) ARSI: 81 (64)	CBZ: 62.0 (range: 1.1– 15,000) ARSI: 60.5 (range: 1.5 –2868)	CBZ: 86 (67) ARSI: 90 (71)	Visceral: CBZ: 21 (16) ARSI: 25 (20)	1st line ADT (median, range) CBZ: 13.7 (2–114) ARSI: 12.6 (3– 179)	Abiraterone: 43%/ 53% Enzalutamide: 56%/ 47%	9.2	CBZ: 13.6 ARSI: 11.0
Oh [10]	2017	2011–2014	USA	Post docetaxel 2nd line CBZ vs. ARSI	629 CBZ: 123 ARSI: 506	25mg/m2 every 3 weeks	CBZ: 72 ARSI: 73	0– 1: CBZ: 34 (28) ARSI: 143 (28) 404 cases were unknown	NA	CBZ: 126.6 ARSI: 47	CBZ: 53 (43) ARSI: 231 (46)	Bone: CBZ:90(73) ARSI:325 (64) LN: CBZ: 3 (2.4) ARSI:35(6.9 Visceral: CBZ: 10 (8) ARSI: 24 (4.7)	NA	NA	NA	CBZ: 15.1 ARSI: 10.2
Miyake [24]	2021	2014–2019	Japan	Post docetaxel third line CBZ vs. another ARSI *all patients ARSI treated before DOC	166	NA	CBZ: 69.8 (range: 55– 82) Others: 70.4 (range: 53– 88)	0– 1: CBZ: 68 (84) Others: 70 (82)	≧8 CBZ: 66 (82) ARSI: 69 (81)	CBZ: 78.3 (range: 6.4 – 701.3) Others: 79.6 (range: 8.9 – 729.8)	NA	Visceral: CBZ: 15 (19) ARSI: 19 (22)	NA	Abiraterone: 61%/ 57% Enzalutamide: 40%/ 44%	8.2	CBZ: 14.9 Others: 7.1

IQR = interquartile range; ECOG-PS = Eastern Cooperative Oncology Group performance status; GS = Gleason score; PSA = prostate specific antigen; ARSI = androgen receptor signaling inhibitor; OS = overall survival; pts. = patients; CBZ = cabazitaxel; mo. = months; NA = not applicable.

* patient demographics are represented as the original cohort of the CARD trial.

Table 2
Study demographics of included studies assessing prognostic factors of mCRPC patients treated with cabazitaxel.

Author	Year	Recruit	Country	No. of patients	Dosage	Cycles of CBZ	Cycles of DOC	Median age (IQR)	PS	GS	PSA	Symptomatic	Metastatic site, n (%)	No. of prior treatments	No. of prior ARSI	Follow-ups (months)
Belderbos [15]	2017	2011–2015	Netherlands CABARASEC post-hoc	224	25mg/m2 every 3 weeks *maximum 10 cycles	6	NA	68.8±7.2 (mean±SD)	WHO-PS 0–1: 222 (99)	NA	154.1 (59–388)	NA	NA	1: 204(91) ≧2: 20 (9)	NA	NA
Buonerba [16]	2013	2011	Italy	47	25mg/m2 every 3 weeks	NA	NA	66.7±7.0 (mean±SD)	ECOG-PS 0–1: 42 (89)	≦7: 27 (58) ≧8: 20 (43)	120 (range:4 –786)	NA	Visceral: 11 (23)	1: 29 (62) 2:11 (23) 3:7 (15)	ARSI:4 (10)	NA
Delanoy [18]	2021	2011–2013	PROSELICA post-hoc	1,075 (*1,200) ITT population of	PROSELICA	20mg or 25mg/m2 every 3 weeks	C20: 6 (range: 1 –11) C25: 7 (1–11)	NA	C20: 68.2±7.2 C25: 68.4±7.8	ECOG-PS 0–1: C20: 539 (90) C25: 540 (90)	≧7 C20: 468 (78) C25: 482 (80)	C20: 159.5 C25: 170.9	589 (55)	Bone: 1128 (94) LN: 593 (49) Visceral: 373 (31)	1:284 (24) 2: 326 (27) ≧3: 577 (48)	Abiraterone: 291 (24)
			Enzalutamide:32 (2.6)	NA												
Kosaka [21, 22]	2018	2014–2017	Japan	45 47	20mg or 25mg/m2 every 3–4 weeks	5 (range:1–26)	8 (range: 3–43)	71 (range: 46 –85)	ECOG-PS 0:38 (88) 1–2: 7 (12)	NA	124.3 (range: 0.17 –11,660)	NA	Bone: 44 (98) LN:17 (39) Visceral:13 (9.1)	Including DOC: 1–2: 11 (7.3) 3:17 (38) ≧4: 17 (38)	Abiraterone: 22 (49) Enzalutamide: 29 (61)	NA
Ito [19]	2019	2015–2018	Japan	66	20mg/m2 every 3 weeks	3 (range:1–23)	NA	74 (range: 55 –94)	ECOG-PS 0: 19 (29) 1: 29 (44) ≧2: 18 (27)	NA	164.0 (range: 1.7 –4477)	NA	Bone: 52 (79) LN: 34 (52) Visceral: 19 (29)	NA	NA	6 (range: 1–35)
Iwamoto [20]	2021	2014–2020	Japan	30	20mg/m2 every 3 weeks	4 (range: 1–10)	Total dose 770 mg/m2 (range: 120 –2760)	69.5 (48–80)	Sarcopenia: 15 (50)	≧9: 18 (60)	63.75 (range: 0.24 –22141)	NA	M1b: 14 (47) M1c: 14 (47)	Median 6(3–8)	NA	NA
Miyake [23]	2018	2014–2017	Japan	74	NA	5 (range:1–12)	NA	Group1:67.4 (range:55 –74) Group2: 72.1 (range:59 –82)	ECOG-PS 0–1: 62 (84)	≧8: 61 (82)	Group1: 72.3 (range: 6.4 –450.3) Group2: 83.6 (range: 8.7 –701.2)	10 (14)	Bone: 52 (70) LN:32 (43) Visceral:13 (18)	NA	ARSI:59 (80)	14 (range: 2 –29)
Rouyer [25]	2019	2013–2015	France	401	Every 3 weeks: 91% 25mg/m2: 51% <25mg/m2: 44%	5 (3.4 months) Discontinuation rate at 18 months: 95%	NA	70 (65–77)	ECOG-PS 0–1: 101 (62)	≧8: 188 (47)	112.5 (38–380)	NA	Visceral: 79 (20) >5 bone metastases: 269 (67)	1: 72 (18) 2: 155 (39) ≧3: 174(43)	Abiraterone: 307 (77)	
			Enzalutamide:134 (33)	18 months												
Shiota [26]	2020	2014–2017	Japan	74	20mg or 25mg/m2 every 3–4 weeks	NA	8	72 (67–76)	ECOG-PS 0: 43 (65) 1: 15 (23) ≧2: 8 (12)	8: 12 (17) ≧9: 47 (66)	48.3 (19.4 –376.8)	37 (50)	Bone: 66 (89) LN: 43 (58) Visceral:20 (27)	NA	ARSI: 62 (84)	7.2 (4.8–13.2)
Uemura [27, 28]	2017/2018	2014–2016	Japan	47 48	20mg/m2 every 3 weeks	4(1–15)	9 (1–55)	71.2 (52.5 –82.9)	NA	NA	152.1 (1.6 –3564)	NA	Bone: 47 (100) LN: 31 (66) Visceral: 22 (47)	NA	Abiraterone: 26 (54) Enzalutamide: 35 (73)	7.2 (0.6–25)
Soest [29]	2015	2011-2014	Netherlands CABARASEC post-hoc	114	25mg/m2 every 3 weeks ※maximum 10 cycles	NA	NA	ARSI: 69 (53 –83) No ARSI: 68 (49–82)	WHO-PS 0: 43 (38) 1: 69 (61)	NA	ARSI:210 (range: 15 –5000) No ARSI:154 (range: 12.5 –4,172)	NA	NA	NA	ARSI:44 (35) No ARSI:70 (65)	NA
Westgeest [30]	2019	2010–2018	Netherlands	173	25mg/m2 every 3 weeks	4 (3–6)	SOC: 7 (5–10) Trial: 10 (7 –10)	SOC: 68(64 –72) Trial: 67(64 –72)	ECOG-PS 0: 39 (23) 1: 105 (61) ≧2: 12 (7)	≦7: 67(39) ≧8: 118(68)	SOC: 200 (65 –567) Trial: 209 (79-500)	150 (87)	Visceral: 30 (17) ※96 patients were missing data	NA	Abiraterone: 12 (7) Enzalutamide: 12 (7)	SOC: 9.2 (4.2 –14.9) Trial: 13.6 (6.0 –22.2)

(*continued on next page*)

Table 2 (*Continued*)

Author	Year	Recruit	Country	No. of patients	Dosage	Cycles of CBZ	Cycles of DOC	Median age (IQR)	PS	GS	PSA	Symptomatic	Metastatic site, n (%)	No. of prior treatments	No. of prior ARSI	Follow-ups (months)
Yasuoka [31]	2019	2011−2019	Japan	44	20mg or 25mg/m2 every 3-4 weeks	NA	≧10: 24 (55) <10: 20 (45)	70 (41-83)	ECOG-PS 0: 41 (93) 1: 3 (7)	7: 4 (9) 8: 5 (11) ≧9: 35 (80)	19.2 (range: 0 −4262)	12 (27)	Bone: 35 (80) LN: 17 (39) Visceral:4 (9)	1:8 (18) 2: 15 (34) 3:21 (48)	Abiraterone: 25 (57) Enzalutamide: 32 (73)	NA
Yokom [32]	2018	NA	Canada	45	25mg/m2 every 3 weeks	6 (1−27)	6 (1−27)	65 (47−81)	ECOG-PS 0: 15 (33) 1: 26(58) ≧2: 4 (9)	median 8 (range:6−10)	249.7 (13.6-4428)	31 (69)	Bone-only: 26 (58) Visceral: 10 (22)	NA	Abiraterone: 15 (33)	NA

IQR = interquartile range; PS = performance status; ECOG-PS = Eastern Cooperative Oncology Group performance status; WHO-PS = World Health Organization Performance Status; GS = Gleason score; PSA = prostate specific antigen; ARSI = androgen receptor signaling inhibitor; OS = overall survival; pts. = patients; DOC = docetaxel; C/CBZ = cabazitaxel; mo. = months; SOC = standard of care; ITT = intention to treat; NA = not applicable.

Continuous variables are represented as mean±SD or median (IQR) or percent unless noted otherwise.

3.3.2.2. ALP. Five studies provided data on the association of pretreatment alkaline phosphatase (ALP) with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 4B) revealed that a high pretreatment ALP level was associated with worse OS (Pooled HR: 1.45, 95% CI: 1.28−1.65, $P < 0.001$). The Cochrane's Q ($Chi^2 = 4.42$; $P = 0.35$) and I^2 ($I^2 = 10\%$) tests revealed no significant heterogeneity.

3.3.2.3. LDH. Six studies provided data on the association of pretreatment lactate dehydrogenase (LDH) with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 4C) revealed that a high pretreatment LDH level was not associated with worse OS (Pooled HR: 1.54, 95% CI: 1.00−2.38, $P = 0.05$). However, confidence intervals included clinically meaningful differences. The Cochrane's Q ($Chi^2 = 12.9$; $P = 0.02$) and I^2 ($I^2 = 61\%$) tests revealed significant heterogeneity.

3.3.2.4. CRP. Two studies provided data on the association of pretreatment c-reactive protein (CRP) with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 4D) revealed that a high pretreatment CRP level was associated with worse OS (Pooled HR: 4.40, 95% CI: 1.52−12.72, $P = 0.006$). The Cochrane's Q ($Chi^2 = 0$; $P = 1$) and I^2 ($I^2 = 0\%$) tests revealed no significant heterogeneity.

3.3.2.5. NLR. Two studies provided data on the association of pretreatment neutrophil-lymphocyte ratio (NLR) with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 4E) revealed that a high pretreatment NLR was not associated with worse OS (Pooled HR: 1.15, 95% CI: 0.73−1.79, $P = 0.55$). The Cochrane's Q ($Chi^2 = 4.06$; $P = 0.04$) and I^2 ($I^2 = 75\%$) tests revealed significant heterogeneity.

3.3.2.6. Albumin. Three studies provided data on the association of pretreatment serum albumin with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 4F) revealed that a low pretreatment albumin level was associated with worse OS (Pooled HR: 1.09, 95% CI: 1.05−1.12, $P < 0.001$). The Cochrane's Q ($Chi^2 = 2.60$; $P = 0.27$) and I^2 ($I^2 = 23\%$) tests revealed no significant heterogeneity.

3.3.2.7. Hemoglobin. Six studies provided data on the association of pretreatment hemoglobin with OS in mCRPC patients treated with cabazitaxel. The forest plot (Fig. 4G) revealed that a low pretreatment hemoglobin level was associated with worse OS (Pooled HR: 1.55, 95% CI: 1.20−1.99, $P < 0.001$). The Cochrane's Q ($Chi^2 = 13.1$; $P = 0.01$) and I^2 ($I^2 = 69\%$) tests revealed significant heterogeneity.

3.4. PSA kinetics

Six studies investigated the oncologic impact of PSA variation, such as PSA flare and PSA response, on OS. Halabi et al. showed that more than 30% decrease in PSA

Table 3
Oncologic outcomes and prognostic factors of included studies of mCRPC treated with cabazitaxel.

Author	Year	No. of patients	Dosage	Cycles of CBZ	OS (months)	Significant prognostic factors (cut off value)
Belderbos [15]	2017	224	25mg/m2 every 3 weeks *maximum 10 cycles	6	13.3 (IQR: 7.0−22.3)	WHO-PS (0 vs.1) Hb, ALP, Alb (continuous)
Buonerba [16]	2013	47	25mg/m2 every 3 weeks	NA	14.0 (95% CI: 11−16)	Visceral metastasis ECOG-PS (0 vs.1) Time to docetaxel progression
Delanoy [18]	2021	1,075 (*1,200) ITT population of PROSELICA	20mg or 25mg/m2 every 3 weeks	C20: 6 (range: 1−11) C25: 7 (1−11)	C20: 13.4 (95% CI: 12.2−14.9) C25: 14.5 (95% CI: 13.5−15.3)	ECOG-PS (0−1 vs. 2) Symptomatic Neutrophil, PSA, Hb, ALP, Alb (median) PSA doubling time (median)
Kosaka [21, 22]	2018	45 47	20mg or 25mg/m2 every 3−4 weeks	5 (range:1−26)	16.1 (95% CI: 6.8-25.5)	Visceral metastasis ECOG-PS (0 vs. ≧1) monocyte, PSA (100)
Ito [19]	2019	66	20mg/m2 every 3 weeks	3 (range:1−23)	9	PSA (median)
Iwamoto [20]	2021	30	20mg/m2 every 3 weeks	4 (range: 1−10)	Sarcopenia: 5.45 No sarcopenia: 16.82	Visceral metastasis Sarcopenia
Miyake [23]	2018	74	NA	5 (range:1-12)	Group1: 13.9 Group2: 16.1	ECOG-PS (0−1 vs. 2) LDH (290) De Ritis ratio (1.35)
Rouyer [25]	2019	401	Every 3 weeks: 91% 25mg/m2: 51% < 25mg/m2: 44%	5 (3.4 months) Discontinuation rate at 18 months: 95%	11.9 (95% CI: 10.1−12.9)	Progression during DOC Within 3 months after DOC Visceral metastasis Bone metastasis more than 5 lesions Adverse events (CTCAE ≧3) PSA (135)
Shiota [26]	2020	74	20mg or 25mg/m2 every 3−4 weeks	NA	NA	ECOG-PS (0 vs.2) LDH (continuous)
Uemura [27, 28]	2017/2018	47 48	20mg/m2 every 3 weeks	4(1−15)	10.0 (95% CI: 7.8−12.2)	Age (72) NLR (3.83), LDH (262) BSI (1%)
Soest [29]	2015	114	25mg/m2 every 3 weeks	NA	NA	WHO-PS (0 vs.1) ALP, Alb (continuous)
Westgeest [30]	2019	173	25mg/m2 every 3 weeks	4 (3−6)	SOC: 9.6 (7.8−11.4) Trial: 13.6 (9.4−17.7)	Duration of first line ADT PSA, LDH (continuous)
Yasuoka [31]	2019	44	20mg or 25mg/m2 every 3−4 weeks	NA	20.7	Cycles of DOC Hb (10), PSA (100)
Yokom [32]	2018	45	25mg/m2 every 3 weeks	6 (1−27)	11.3	Hb (per decrease in 10 units)

IQR = interquartile range; PS = performance status; ECOG-PS = Eastern Cooperative Oncology Group performance status; WHO-PS = World Health Organization Performance Status; GS = Gleason score; PSA = prostate specific antigen; ARSI = androgen receptor signaling inhibitor; OS = overall survival; pts. = patients; DOC = docetaxel; CBZ = cabazitaxel; PSA = prostate specific antigen; NLR = neutrophil-lymphocyte ratio; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; Hb = hemoglobin; Alb = Albumin; BSI = bone scan index; NA = not applicable.

Continuous variables are represented as median (IQR) or percent unless noted otherwise.

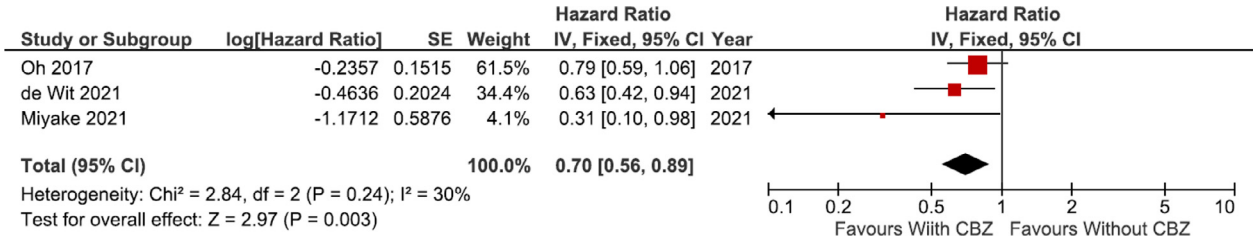


Fig. 2. Forest plots; association of sequencing impact of cabazitaxel on overall survival (OS) in mCRPC patients previously treated with docetaxel. CBZ: Cabazitaxel.

within 3 months was a predictor of better OS in 755 mCRPC patients treated with cabazitaxel or mitoxantrone as second-line chemotherapy (HR: 0.52, 95% CI: 0.43 −0.64) [36]. However, PSA decline was reported not to be a surrogate for OS [36]. For mCRPC patients treated with cabazitaxel, Hammerer et al. showed that patients with a PSA response after 4 cycles had a better median PFS compared to non-responders (15.7 vs. 5.5 months at 50% cut-off; 15.7 vs. 5.3 months at 30% cut-off; both $P < 0.001$). [37]. Furthermore, Fujiwara et al. demonstrated that more than 30% decrease of PSA after 3 cycles was associated with a better OS (HR 2.58, 95% CI: 1.19−6.06) [35].

Angelergues et al. reported that PSA flare after cabazitaxel, defined as any rise in PSA followed by 30% or 50% decrease within 3 months, had no statistically significant association with PFS or OS [34].

4. Discussion

In this systematic review and meta-analysis, we found that sequential therapy with cabazitaxel was associated with an improved OS compared to that with other agents in post-docetaxel mCRPC patients. We further found that several pretreatment clinical features and hematologic biomarkers could impact OS in post-docetaxel mCRPC patients treated with cabazitaxel.

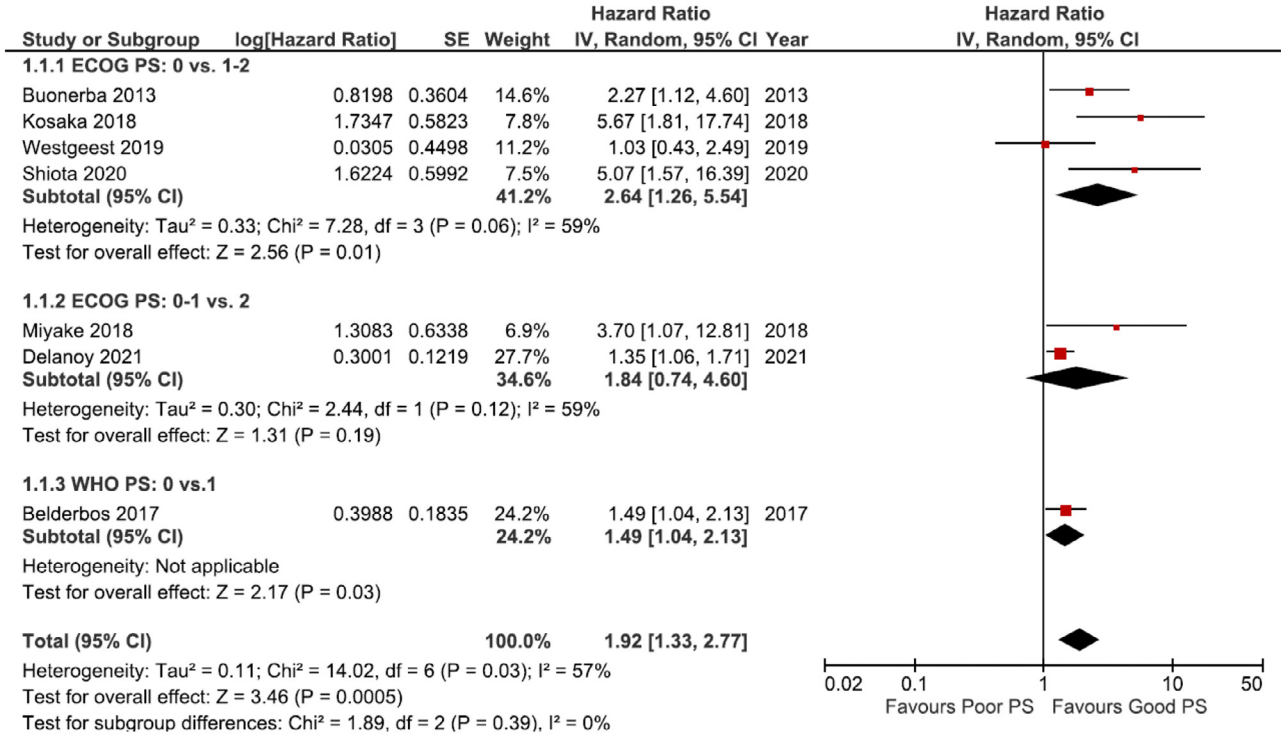
The recently published CARD trial investigated the survival impact of cabazitaxel in mCRPC patients previously treated with docetaxel and found that cabazitaxel was associated with a better OS compared to abiraterone or enzalutamide (HR:0.64, 95% CI: 0.46−0.89) [8]. A retrospective study comprising 629 patients, conducted by Oh et al., compared the oncologic outcomes of cabazitaxel with ARSIs after docetaxel as first line treatment for mCRPC; they reported a favorable trend for cabazitaxel but failed to detect a statistically significant difference in OS on multivariable analysis [25]. Furthermore, a retrospective study conducted by Miyake et al., which assessed the sequential impact of third line cabazitaxel after ARSI followed by docetaxel in mCRPC patients, demonstrated that cabazitaxel significantly improved OS compared to other agents [24]. Taken together, in this meta-analysis, we confirm that the sequential therapy with cabazitaxel leads to significantly better OS compared to other agents in mCRPC patients who were previously treated with docetaxel.

Cabazitaxel has been used since 2010 in mCRPC patients previously treated with docetaxel and had progression [7]. Although established as a standard, only a limited number of patients eventually receive this therapy [25]. This is partly due to the significant adverse events of cabazitaxel such as the hematologic toxicity, including severe neutropenia. However, the positive impact of cabazitaxel on health-related QOL together with the decreasing pain has been reported in the literature [40,41]. In addition, the CABADOC trial demonstrated that patients prefer cabazitaxel over docetaxel [42]. Nevertheless, in real-world practice, approximately 27% to 39% of patients received docetaxel and only 5.4% to 11% of patients received cabazitaxel among mCRPC patients treated with at least one regimen of life-prolonging therapy [9,10]. These findings could suggest the importance of ensuring an effective sequential treatment plan by assessing the OS benefit of cabazitaxel over other more widely used strategies. In addition to its OS benefit, the increased adoption of cabazitaxel in the treatment strategy of mCRPC could help identify patients who are most likely to receive true benefit from it.

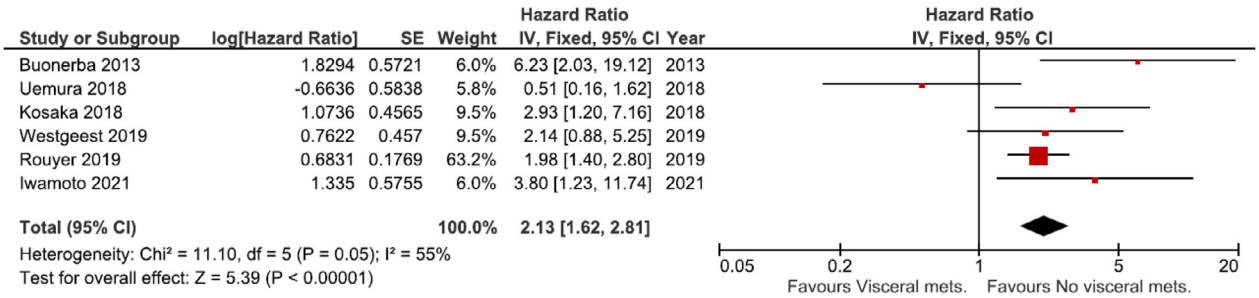
In this study, we further demonstrated the value of several clinical features such as poor PS, visceral metastasis and symptomatic disease in prognosticating OS in patients treated with cabazitaxel. In general, patients with poor PS are less likely to benefit from systemic treatment. However, when symptoms related to the disease progression are causing the poor PS, administration of an active, potentially life-prolonging agent can improve PS by decreasing tumor burden and alleviating sequalae [43]. In addition, symptomatic progression of disease is often an indicator for change of treatment [43]. We found, however, a negative survival impact for poor PS and symptomatic disease in post-docetaxel mCRPC patients on OS despite cabazitaxel initiation. Thus, a shared decision-making process is necessary for the patients with poor PS or symptomatic disease to decide whether cabazitaxel is a good choice for the individual patient.

We found that several hematologic markers such as pretreatment high PSA, ALP, LDH, and/or CRP, as well as the low hemoglobin and/or albumin were associated with worse OS in post-docetaxel mCRPC patients treated with cabazitaxel. Most of these biomarkers have been previously found to prognosticate oncologic outcomes in patients at all stages of PCa [44,45]. In addition, there has been increasing

(A) Performance status



(B) Presence of visceral metastasis



(C) Symptomatic disease

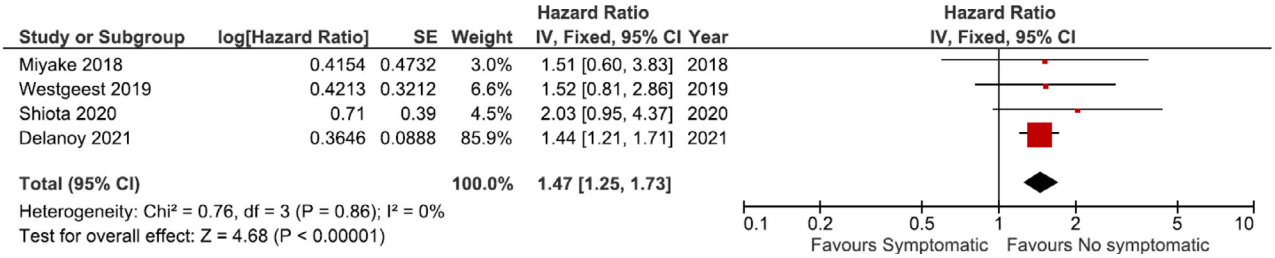
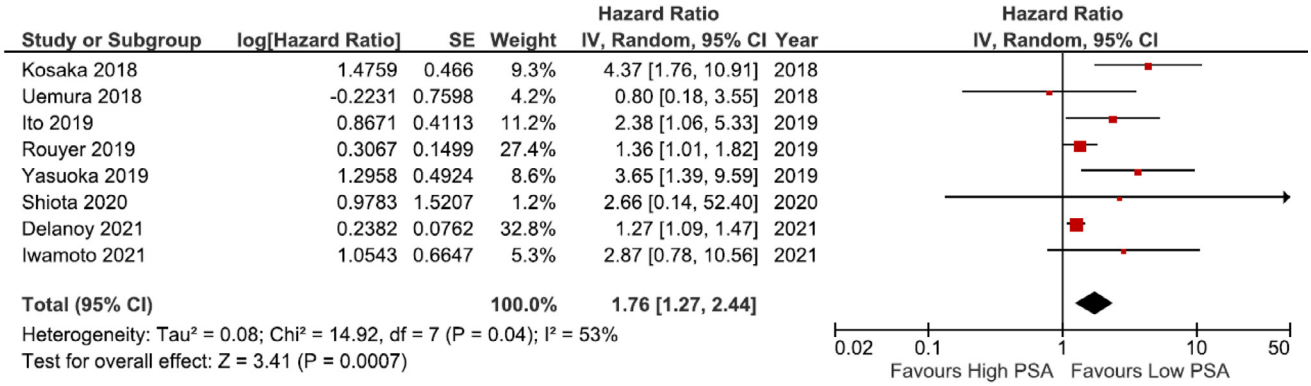
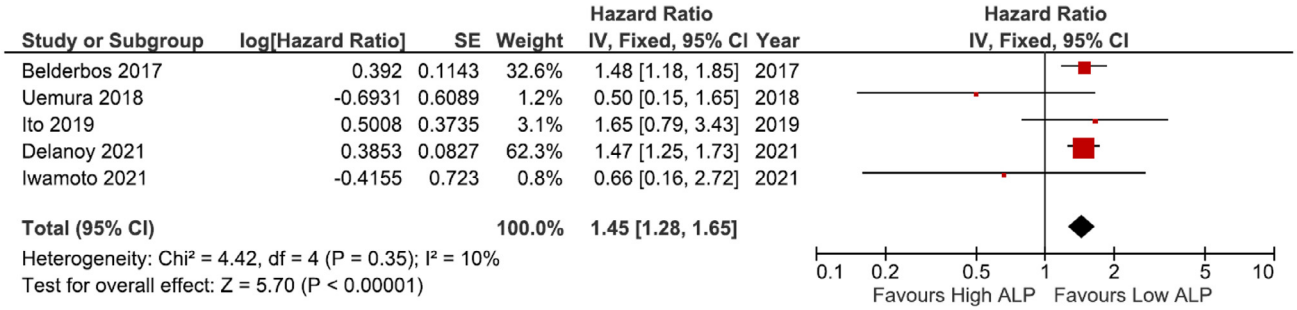


Fig. 3. Forest plots; association of clinical features with overall survival in mCRPC patients treated with cabazitaxel; (A) Performance status, (B) Presence of visceral metastasis, (C) Symptomatic disease. PS: Performance status.

(A) PSA



(B) ALP



(C) LDH

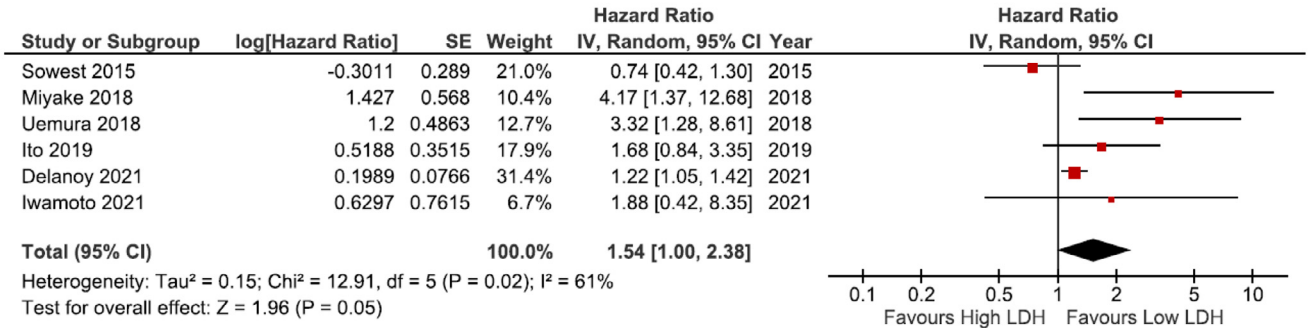
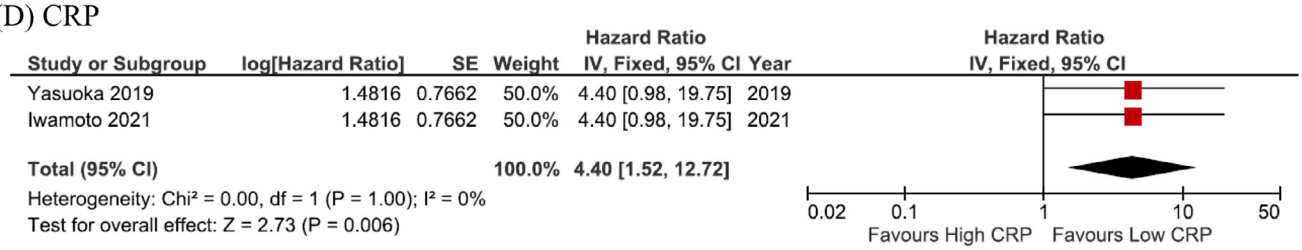


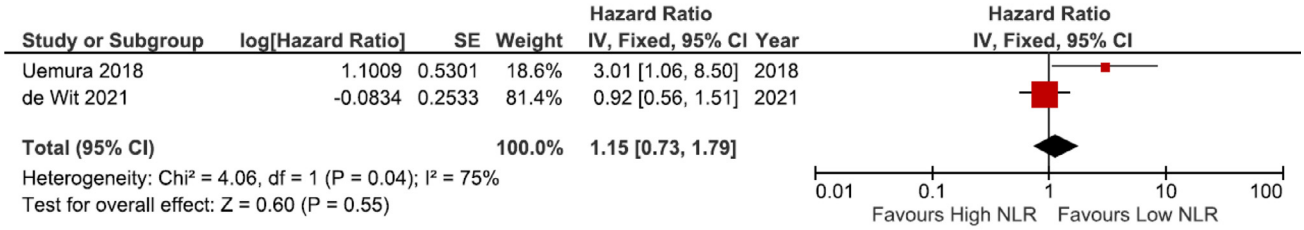
Fig. 4. Forest plots; association of hematologic biomarkers with overall survival in mCRPC patients treated with cabazitaxel; (A) PSA, (B) ALP, (C) LDH, (D) CRP, (E) NLR, (F) Albumin, and (G) Hemoglobin. PSA: Prostate specific antigen, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, CRP: c-reactive protein, NLR: Neutrophil-lymphocyte ratio.

evidence supporting the value of inflammation biomarkers, such as NLR, platelet-lymphocyte ratio (PLR), and CRP in reflecting the tumor microenvironment across several metastatic urological malignancies [46,47]. In mCRPC, NLR and PLR have been found to be effective hematologic prognosticators in patients treated with docetaxel or ARSIs [48−50]. In mCRPC patients treated with cabazitaxel, Uemura et al. reported that NLR has a prognostic value for OS in a small cohort of 48 mCRPC patients receiving cabazitaxel [28]. However, de Wit et al. found no value to NLR as a prognosticator of OS in a post-hoc analysis of the CARD trial comprising 246 patients (HR 0.92, 95% CI: 0.56−1.51) [17]. On the other hand, we found that pretreatment CRP was a prognostic marker for OS in mCRPC patients treated with cabazitaxel. Taking together, the utility of these inflammation biomarkers in mCRPC planned

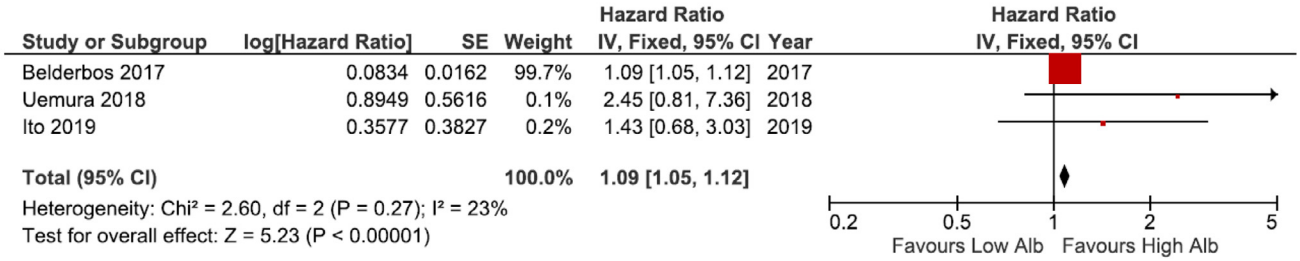
(D) CRP



(E) NLR



(F) Albumin



(G) Hemoglobin

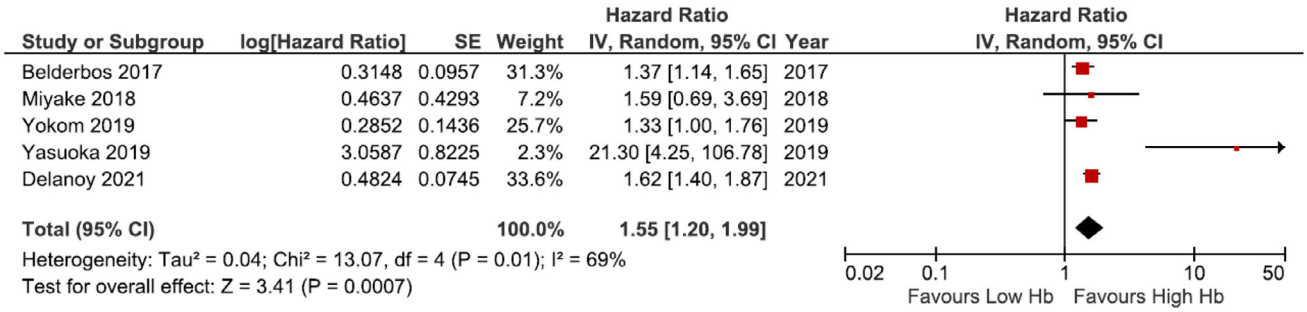


Fig. 4. Continued

for cabazitaxel treatment remains promising, requiring more robust evidence on the integration of these biomarkers in patients' assessment [51,52].

In addition to inflammation biomarkers, the nutritional status has also been recognized as an important parameter affecting survival outcomes in mCRPC [53–55]. The nutritional status might be affected by the cachexia phenomenon associated with cancer progression, resulting in sarcopenia [56]. Recently, a retrospective study showed that sarcopenia is a strong prognostic factor for OS in mCRPC patients treated with cabazitaxel [20]. We found that a low pretreatment albumin level is a prognostic factor in patients with post-docetaxel setting [45]. Due to having more advanced disease, inflammation and nutritional status appear to be important elements in predicting OS in mCRPC patients treated with cabazitaxel. Taken together, pretreatment CRP and albumin may help, along with other hematologic markers, guide clinical decision-making regarding cabazitaxel, as they reflect both tumor biology and patients' condition.

Even in heavily treated mCRPC patients, high pretreatment serum PSA remained associated with worse OS. Moreover, PSA response kinetics after cabazitaxel initiation were even stronger prognostic factors in these patients.

Indeed, the several authors have shown that a PSA decrease of more than 30% after 3 to 4 cycles of cabazitaxel was associated with better OS in mCRPC [35,37]. Thus, the serum PSA remains an important prognostic and monitoring biomarker together with radiographic examinations.

Our study suffers from several limitations. First, most of the included studies were retrospective in design, thus, increasing the risk of selection bias. Second, unknown pretreatment factors (e.g. nutritional deficiencies, comorbidities, medications, and lifestyle factors) may have affected the clinical and hematologic biomarkers, potentially resulting in a systematic bias. Third, there was no established definition of cut-off values for the hematologic biomarkers among the studies evaluated. Most investigators chose the cut-off value based on differential statistical methods or the lower/higher limit of standard predefined biomarker cut-off values in the literature. Fourth, regarding ALP, which is widely used as a surrogate for bone damage, our analysis includes around 35% of patients with visceral metastasis. Therefore, the true value of ALP on prognosticating OS in patients with bone metastasis only is still unproven. Fifth, approximately half of included studies were from Japan; thus, the generalizability of this study to non-pacific Asians needs to be interpreted with care. Sixth, although the random effect model was used to address heterogeneity among the studies evaluated, the conclusions should be interpreted with care.

We revealed several prognosticators of OS; however, in later lines of mCRPC treatment, improvement of QOL is also an important endpoint for patients. Therefore, in addition to OS benefit, an assessment of each patient's QOL derived from disease progression would be important to identify which patients are more likely to achieve true benefit from cabazitaxel. Furthermore, recently, in the TheraP trial, lutetium (Lu)-177-prostate specific membrane antigen (PSMA)-617 showed superiority in PSA decrease compared to cabazitaxel in post-docetaxel mCRPC patients [57]. Further studies are warranted to compare OS benefit between those agents and develop prognostic factors to identify patients who are more likely to benefit from 177Lu-PSMA-617. Finally, in the era of upfront intensification treatment including docetaxel and/or ARSI for mHSPC [58,59], there is no robust data regarding oncologic outcomes of sequential treatment for mCRPC. Further studies on sequencing impact of currently available regimens in this setting are also warranted.

5. Conclusions

We found that sequential therapy with cabazitaxel results in significantly better OS compared to other agents for mCRPC patients previously treated with docetaxel. Patients with poor PS, visceral metastasis, and/or symptomatic disease have a worse survival despite cabazitaxel treatment. Moreover, the high pretreatment PSA, ALP, LDH, and/or CRP as well as low hemoglobin and/or albumin were significant prognostic factors for OS. Despite the limitations regarding the nature of the primary data used in this study, our findings might help to guide the clinical decision-making regarding more optimal usage of cabazitaxel and to design future studies regarding prognostic factors for later lines mCRPC treatment.

Authors' contributions

TY contributed to protocol/project development, data collection and management, data analysis, and manuscript writing/editing. TK (Tatsushi Kawada) and PR contributed to data analysis and manuscript writing/editing. HM, RSM, FQ, EL, FK, MP, BP, PIK and PN contributed to manuscript writing/editing. TK (Takahiro Kimura) and SE contributed to manuscript editing. SFS contributed to supervision, protocol/project development/management and manuscript editing.

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Conflicts of interest

Shin Egawa is a paid consultant/advisor of Takeda, Astellas, AstraZeneca, Sanofi, Janssen, and Pfizer. Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen and Sanofi. Shahrokh F. Shariat received follows: Honoraria: Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Roche, Takeda Consulting or Advisory Role: Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Takeda Speakers Bureau: Astellas, Astra Zeneca, Bayer, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Richard Wolf, Roche, Takeda The other authors declare no conflicts of interest associated with this manuscript.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2022.06.018.

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