Clinical implication of prognostic and predictive biomarkers for castration-resistant prostate cancer: a systematic review

Shengri Tian†, Zhen Lei†, Zuo Gong, Zhonghai Sun, Dongyuan Xu*† and Minhu Piao*†

Abstract

Background: Diagnosis of metastatic castrate resistant prostate cancer (mCRPC) with current biomarkers is difficult and often results in unnecessary invasive procedures as well as over-diagnosis and over-treatment. There are a number of prognostic biomarkers for CRPC, but there are no validated predictive biomarkers to guide in clinical decision-making. Specific biomarkers are needed that enable to understand the natural history and complex biology of this heterogeneous malignancy, identify early response to treatment outcomes and to identify the population of men most likely to benefit from the treatment. In this systematic review, we discuss the existing literature for the role of biomarkers in CRPC and how they aid in the prognosis, treatment selection and survival outcomes.

Methods: We performed a literature search on PubMed and EMBASE databases from January 2015 through February 2020 in accordance to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. Articles were assessed to identify relevant observational studies and randomized controlled trials regarding biomarkers which aid in identifying progression to mCRPC as well as predictive biomarkers which help in treatment selection.

Results: We identified 3640 number of hits of which 58 articles were found to be relevant. Here we addressed biomarkers in the context of prognosis, prediction and patient selection of therapy. These biomarkers were found to be effective as prognostic or predictive factors under variety of conditions. The higher levels for all these biomarkers were associated with shorter median OS and sometimes PFS. Lower amounts of biomarkers in serum or urine were associated with prolonged survival outcomes, longer time to CRPC development or CRPC progression and longer median follow-up irrespective of any therapy.

Conclusion: We observed that the biomarkers included in our study predicted clinically relevant survival outcomes and treatment exposure. Though the current biomarkers are prognostic when measured prior to initiating treatment, not all are validated as predictive markers in post treatment setting. A greater understanding of biomarkers in CRPC is need of the hour for development of more personalized approach to maximize benefit and minimize harm in men with CRPC.

Keywords: Prostate cancer, Metastatic cancer, Biomarker, Prognostic, Predictive
recent treatment guidelines for CRPC trials and consequently have been recommended in the efficacy in terms of survival outcomes in phase 3 clinical therapeutic (cabazitaxel) drugs. These drugs have shown efficacy in terms of survival outcomes in phase 3 clinical trials and consequently have been recommended in the recent treatment guidelines for CRPC [6]. Therefore, it is becoming essential to understand the optimal and rational combination and sequences of these treatments in clinical practice so as to identify patients most likely to benefit from a specific treatment. Minimizing harms and costs of ineffective therapies is another equally important goal [7].

CRPC is characterized by a heterogeneous natural history and despite the availability of these treatment options, CRPC remains a lethal disease [8]. The variable response observed in the targeted therapies could be due to the biologic heterogeneity of CRPC, including both AR-mediated or AR-independent pathways [9]. Over recent decades, the development of molecular biomarker assays and genetic assays has provided an avenue for PCa biomarker development [10]. Prognosis of patients can be estimated by prognostic models and nomograms; however, response to the therapies are not predictable. Emerging biomarkers utilize serum, urinary, or tissue samples as a test substrate [10]. In clinical practice, the utility of these biomarkers is variable and may be used at different time points throughout the care of a patient with suspected or diagnosed PCa. Specifically, these biomarkers assist in diagnosis, guiding definitive treatment options, determine the risk of ongoing monitoring versus intervention, or provide risk stratification in the setting of negative initial biopsy [10].

Prostate-specific antigen (PSA) is a widely used marker of diagnosis and prognosis; however, there is evidence of disconnection between PSA level changes and survival outcomes. Sipuleucel-T treatment extends overall survival (OS) in metastatic CRPC patients; however, it has little effect on the PSA level [11]. Whereas, bevacizumab with docetaxel did not significantly improve survival but greatly reduced PSA levels [12]. Additionally, radium-223 chloride demonstrated an OS benefit in patients with metastatic CRPC but had no clear effect on PSA levels [13]. Clinicians thus need predictive biomarkers to select treatment choices for individual patients. Similarly, prognostic biomarkers provide information about a patient's disease outcome independent of therapy [14]. New biomarkers have been discovered owing to the recent advances in the metabolomic, genomic, and transcriptomic analysis, which can be utilized in the prediction of PCa outcome and response to therapy [15]. This systematic review was conducted to evaluate the available evidence on the prognostic and the potential predictive biomarkers in CRPC and to discuss the clinical implications of these markers on the patients.

The following questions were evaluated in completing this overall objective.

- What are the currently available prognostic biomarkers that aid in predicting clinical outcomes for progression to CRPC?
- What is the role of the predictive biomarkers in the treatment selection for CRPC patients and are they helpful in clinical decision making?

**Methods**

A review protocol was developed and registered on Prospero with registration number CRD42020181860.

**Evidence acquisition**

**Search strategy**

A systematic review of the literature was conducted from January 2015 to February 2020 by searching National Center for Biotechnology Center (NCBI), PubMed and EMBASE database. The following search string was used for screening of relevant literature in PubMed and EMBASE databases with minor changes in Boolean signs to suit the database: (“prostate cancer” OR “cancer of the prostate” OR “prostatic cancer” OR “castration-resistant prostate cancer” OR “non-metastatic prostate cancer” OR “hormone sensitive prostate cancer”) AND (“tumor marker” OR “biomarker” or “biologic markers” OR “serum markers” OR “surrogate marker” OR clinical marker” OR “tumor marker” OR “urine biomarkers”) AND (“survival” OR “progression free survival” OR overall survival” OR “prognostic factor/s” OR “predictive factor/s” OR “clinical outcomes”).

**Study eligibility**

Studies were selected for review based on the following criteria: (1) patients progressing from hormone sensitive prostate cancer (HSPC) or non-metastatic prostate cancer to CRPC or with mCRPC, (2) randomized clinical
trials (RCTs), (3) observational studies, (4) English language, (5) Studies reporting outcomes based on prognostic and/or predictive biomarkers, (6) Patients on any therapy. Studies were excluded if they fell under the following criteria: (1) non-English language, (2) non-RCTs, (3) duplicate publications, (4) conference abstracts, (5) meta-analyses and systematic reviews, (6) not reporting appropriate outcomes. This review was performed in accordance to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Initially, titles were reviewed to assess whether they met the inclusion criteria. These studies were categorized into three categories: excluded, included and possibly relevant. Included and possibly relevant studies were rescreened to confirm eligibility.

Evidence synthesis

Only articles that clearly defined the intended study population, with or without interventions, and clinical endpoints including progression-free survival (PFS) and overall survival (OS) (biomarker-associated, clinical or radiographic), time to follow-up, significant cutoff for being a predictive or prognostic biomarker, time to CRPC progression, time to CRPC development, were included in this review.

Data extraction and quality assessment

Data from included studies regarding author, year of publication, title, study design, demographics of the study population and outcomes of interest was extracted by two independent reviewers into standardized MS Office Excel. The methodological quality of eligible RCTs was determined using the JADAD scale [16] and Newcastle–Ottawa scale [17] was used for observational studies.

Results

The literature search identified in total 3640 articles. After initial title screening and manual reduplication, 712 studies were excluded (not relevant to the topic or not original research) and 2928 references remained for abstract review. Full-text evaluation for the remaining 710 citations identified by abstract review or by a manual search of the references list was done (Fig. 1). A total of 58 articles that investigated as prognostic and predictive biomarkers in development of CRPC or its progression were finally included in the study. The summary of included studies characteristics along with quality assessment is described in Table 1.

Prognostic biomarkers

Androgen receptor (AR) splice variants in CTC

Six studies were observed for the presence of ARVs in CTC. The presence of AR-V9-positive CTCs at baseline in mCRPC was associated with poor survival outcome to cabazitaxel treatment [18], while another study reported no association of AR-V7 with OS on treatment with cabazitaxel [19]. ARV7+ was associated with shorter OS on treatment with androgen-receptor signaling inhibitors (ARSi) [20]. Further, after transurethral resection of prostate, AR-V7 expression was found to be a significant prognosticator for the development of CRPC (HR 2.627, 95% CI 1.480–4.663, p = 0.001) [21]. Similarly, ARV7+ patients had worst outcomes on OS on treatment with abiraterone acetate and enzalutamide [22, 23] (Table 2).

Number of circulating tumor cell count (CTC)

Four studies were associated with CTC as biomarker. Patients with baseline CTC counts ≥ 5 cells/7.5 ml showed decreased OS and lower adherence to radium-223 therapy in a study [24]. Patients with < 5 CTCs prior to start of cabazitaxel therapy was prognostic indicator of better PFS and OS as compared to patients with ≥ 5 CTCs at baseline (both p < 0.001) [25]. Low CTC count was associated with longer OS than high CTC count [16.6 months (95% CI 11.7, 20.9) and 8.9 months (95% CI 6.3, 11.2)] on treatment with abiraterone or enzalutamide [26]. Similarly, CTC-positive patients were associated with shorter PFS [HR: 7.2 (95% CI 1.7–31.0; p < 0.01)]. Also, CTC-positivity (p < 0.001; HR 5.02; 95% CI 2.13–11.9) at 3 months after the start of ADT were negative prognostic markers of early progression [27] (Table 2).

Predictive biomarkers

Bone turnover markers

Most of the prostate cancer patients develop significant bone pain when progressed to CRPC [28]. Seven articles assessed the predictive role of bone biomarkers in the treatment selection for CRPC. Early changes in serum/urine biomarkers (N-telopeptide-NTx and bone alkaline phosphatase-BAP) did not predict clinical benefit in mCRPC patients with cabozantinib therapy or docetaxel with/without atrasentan [29, 30]. Patients with good bone scan index response had better performance status and achieved OS prolongation when treated with radium-223 [31]. Further, normal total alkaline phosphatase (tALP) was associated with longer OS than with elevated tALP (p = 0.01) in patients treated with 223Ra-Dichloride [32]. Automated bone scan index (aBSI) as a predictive marker showed no significant difference in OS from baseline to 16 weeks of treatment with cabazitaxel (p = 0.72) [33]. Patients with fast alkaline phosphatase velocity (APV) values (≥ 5.42 U/l/y) and faster PSA doubling time (PSADT) (p = 0.0289) had significantly shorter median post-CRPC BAP values (p ≤ 0.0001) with androgen deprivation therapy (ADT) [34]. The combined predictive model of percent PSA change and change in automated
BSI (C-index 0.77) was significantly higher than that of percent PSA change alone (C-index 0.73), \( p = 0.041 \) in enzalutamide treated patients \([35]\) (Table 3).

**Neutrophil lymphocyte ratio**

Six studies were analysed for the role of NLR as biomarker. High-NLR (\( \geq 3.1 \)) patients predicted worse OS and PFS in patients treated with abiraterone acetate than low NLR patients \([36, 37]\). Similar observations were noted in another two studies in patients with NLR low and on docetaxel when NLR cut-off was 2.59 and 2.14 \([38, 39]\). Treatment of cabazitaxel over mitoxantrone was favored due to demonstration of higher median OS [15.9 vs 12.6 months, HR 1.55 (95% CI 1.3–1.84), \( p < 0.001 \)], PSA progression-free survival [3 vs 3.1 months; HR 1.35 (95% CI 1.12–1.62); \( p = 0.002 \)] and radiographic progression-free survival [9.3 vs 5.7 months; HR 1.42 (95% CI 1.15–1.76); \( p = 0.001 \)] in patients with NLR cut-off < 3 than with NLR \( \geq 3 \) \([40]\). Further another study reported that NLR \( \geq 2.5 \) was an independent predictor of a lower risk for CSS in patients treated with docetaxel \([41]\) (Table 3).

**ERG**

Only two articles were available for screening of ERG as biomarker. ERG positivity correlated with a lower PSA-PFS (3.2 months vs 7.4 months, \( p < 0.001 \)), C/R-PFS (3.8 mos vs 9.0 mos, \( p < 0.001 \)) and OS (10.8 mos vs 21.4 mos,
| Article                        | Year | No of patients | Study type  | Quality assessment |
|-------------------------------|------|----------------|-------------|--------------------|
| Yasouka et al. [48]           | 2019 | 44             | Observational | 4                  |
| Lin et al. [53]               | 2018 | 216            | Observational | 6                  |
| Kosaka et al. [49]            | 2018 | 45             | Observational | 3                  |
| Pei et al. [51]               | 2019 | 170            | Observational | 4                  |
| Satheke et al. [60]           | 2019 | 73             | Observational | 2                  |
| Alvim et al. [63]             | 2019 | 124            | Observational | 6                  |
| Armstrong et al. [70]         | 2018 | 872            | Observational | 4                  |
| Hamano et al. [57]            | 2019 | 321            | Observational | 6                  |
| Yang et al. [52]              | 2015 | 39             | Observational | 4                  |
| Houede et al. [65]            | 2015 | 306            | Observational | 4                  |
| Kuo et al. [56]               | 2015 | 62             | Observational | 5                  |
| Schiff et al. [64]            | 2019 | 110            | Observational | 3                  |
| Rahbar et al. [61]            | 2017 | 104            | Observational | 4                  |
| Ahmadzadehfar et al. [62]     | 2017 | 100            | Observational | 4                  |
| Ji et al. [54]                | 2017 | 185            | Observational | 4                  |
| He et al. [55]                | 2017 | 92             | Observational | 4                  |
| Belderbos et al. [50]         | 2019 | 224            | Observational | 4                  |
| Chang et al. [66]             | 2019 | 77             | Observational | 5                  |
| Fan et al. [67]               | 2018 | 60             | Observational | 7                  |
| Fukuoka et al. [58]           | 2019 | 63             | Observational | 4                  |
| Kodama et al. [87]            | 2019 | 575            | Observational | 6                  |
| Papazoglou et al. [69]        | 2016 | 44             | Observational | 4                  |
| Miyake et al. [68]            | 2017 | 297            | Observational | 4                  |
| Vaishampayan et al. [29]      | 2019 | 20             | Observational | 4                  |
| Dizdarevic et al. [32]        | 2018 | 57             | Observational | 4                  |
| Naito et al. [31]             | 2019 | 20             | Observational | 3                  |
| Miyoishi et al. [33]          | 2019 | 32             | Observational | 4                  |
| Lara et al. [30]              | 2018 | 750            | RCT          | 4                  |
| Hammerrich et al. [34]        | 2017 | 89             | Observational | 5                  |
| Anand et al. [35]             | 2016 | 62             | Observational | 5                  |
| Onal et al. [36]              | 2019 | 102            | Observational | 6                  |
| Loubersac et al. [37]         | 2019 | 1082           | RCT          | 3                  |
| Tatenuma et al. [38]          | 2018 | 73             | Observational | 4                  |
| Kumano et al. [39]            | 2019 | 106            | Observational | 4                  |
| Lorente et al. [40]           | 2015 | 755            | RCT          | 2                  |
| Koo et al. [41]               | 2019 | 303            | Observational | 6                  |
| Ando et al. [44]              | 2019 | 164            | Observational | 5                  |
| Hashimoto et al. [45]         | 2019 | 115            | Observational | 6                  |
| Shiota et al. [46]            | 2018 | 106            | Observational | 4                  |
| Wang et al. [47]              | 2017 | 206            | Observational | 6                  |
| Sieuwerts et al. [18]         | 209  | 124            | Observational | 4                  |
| Belderbos et al. [19]         | 2019 | 127            | Observational | 4                  |
| Cattrini et al. [20]          | 2019 | 39             | Observational | 4                  |
| Qu et al. [21]                | 2014 | 250            | Observational | 6                  |
| Antonarakis et al. [22]       | 2017 | 202            | Observational | 5                  |
| Qu et al. [23]                | 2017 | 171            | Observational | 6                  |
| Carles et al. [24]            | 2018 | 45             | Observational | 5                  |
| De Kruithiff et al. [25]      | 2019 | 114            | Observational | 4                  |
| Bitting et al. [26]           | 2015 | 89             | Observational | 4                  |
Table 1 (continued)

| Article             | Year | No of patients | Study type | Quality assessment |
|---------------------|------|----------------|------------|--------------------|
| Josefsson et al. [27] | 2017 | 53             | Observational | 5                  |
| Kobayashi et al. [71] | 2019 | 104            | Observational | 6                  |
| Hiew et al. [72]    | 2018 | 270            | Observational | 3                  |
| Gravis et al. [73]  | 2015 | 385            | Observational | 4                  |
| Mori et al. [74]    | 2017 | 69             | Observational | 4                  |
| Miyoshi et al. [75] | 2018 | 45             | Observational | 4                  |
| Ohtaka et al. [76]  | 2017 | 49             | Observational | 4                  |
| Song et al. [42]    | 2016 | 71             | Observational | 5                  |
| Berg et al. [43]    | 2015 | 194            | Observational | 5                  |

* Quality assessment of the RCTs were done using Jadad scale and non-RCTs was done using Newcastle–Ottawa scale

Table 2 Summary of included studies for prognostic biomarkers

| Article                      | Year | Biomarker | Intervention   | Significant outcomes                                                                 |
|------------------------------|------|-----------|----------------|--------------------------------------------------------------------------------------|
| Sieuwerts et al. [18]        | 2019 | ARV       | Cabazitaxel    | Median OS: 7.7 months (95% CI 7.0–10.6) Median OS (ARV− vs ARV+): 9 vs 3.7 months   |
| Belderbos et al. [19]        | 2019 | ARV       | Cabazitaxel    | Median OS: HR 1.33, 95% CI 0.81–2.15, *p* = 0.25 Median OS (ARV− vs ARV+): 12.6 vs 12.3 months |
| Cattrini et al. [20]         | 2019 | ARV       | ARAT           | Median OS: 4.7 months (95% CI 0.6–8.9)                                               |
| Qu et al. [21]               | 2014 | ARV       | TURP           | Time to CRPC: 9.0 months                                      Median follow-up: 25 months |
| Antonarakis et al. [22]      | 2017 | ARV       | Abiraterone or enzalutamide | Median follow-up (CTC−, CTC+/AR-V7− and CTC+/AR-V7+): 15.0, 21.7, and 14.6 months |
| De Kruijf et al. [25]        | 2019 | CTC       | Cabazitaxel    | Median follow-up (< 5 CTC at baseline vs < 5 CTC after treatment): 9 vs 3.7 months |
| De Kruijf et al. [25]        | 2019 | CTC       | Cabazitaxel    | Median PFS for CTC < 5 CTC at baseline vs < 5 CTC after treatment: 8.7 months        |
| Carles et al. [24]           | 2018 | CTC       | Radium-223     | Median OS: 16 months                                                      Median OS (> SCTX): 16 months |
| Bitting et al. [26]          | 2015 | CTC       | Abiraterone, enzalutamide | Mean follow-up: 9 ± 6 months              |
| Bitting et al. [26]          | 2015 | CTC       | Abiraterone, enzalutamide | Median OS: 11.2 months                                                      Median PFS: 4.4 months |
| Bitting et al. [26]          | 2015 | CTC       | Abiraterone, enzalutamide | Median OS (< 5 CTC vs > 5 CTC): 16.6 vs 8.9 months                      |
| Josefsen et al. [27]         | 2017 | CTC       | ADT            | Median PFS (CTC− vs CTC+): 8.5 months                                                      Median follow-up: 11.1 months |

**PFS** progression free survival, **OS** overall survival, **ADT** Androgen deprivation therapy
| Article                      | Year | Biomarker | Intervention       | Significant outcomes |
|------------------------------|------|-----------|--------------------|----------------------|
| Vaishampayan et al. [29]     | 2019 | Bone biomarker | Cabozantinib     | Median PFS: 4.1 months |
|                              |      |           |                    | Median OS: 11.2 months |
|                              |      |           |                    | Median change (BSAP) pre and post therapy: 21.3% |
|                              |      |           |                    | Median change in serum Ntx pre and post therapy: — 13% |
|                              |      |           |                    | Median change in urine Ntx pre and post therapy: — 41.7% |
| Dizdarevic et al. [32]       | 2018 | Bone biomarker | ^{223}Ra-Dichloride | Median follow-up: 266 days |
|                              |      |           |                    | ALP OS: 298 days |
|                              |      |           |                    | Median OS (Normal ALP vs elevated ALP): 401 vs 222 days |
|                              |      |           |                    | Median OS (ALP ≥ 30% reduction vs ALP non-responders): 363 vs 115 days |
|                              |      |           |                    | Median OS (ALP ≥ 10% reduction vs ALP non-responders): 256 vs 137 days |
| Naito et al. [31]            | 2019 | Bone biomarker | ^{223}Ra-Dichloride | Median OS: HR, 0.21; 95% CI 0.045–0.95 |
| Miyoshi et al. [33]          | 2019 | Bone biomarker | Cabazitaxel        | Median OS: 16.2 months |
|                              |      |           |                    | Median BSI level: 4.4% (range 0.1–12.9%) |
| Lara et al. [30]             | 2018 | Bone biomarker | Docetaxel + prednisone + atrasentan | Median OS (CICP: ≤ 6.8): 31.6 months |
|                              |      |           |                    | Median OS (BAP < 90.9): 27.1 months |
| Hammerrich et al. [34]       | 2017 | Bone biomarker | ADT                | APV ≥ 5.42 U/l/y vs APV < 5.42 U/l/y: 24.7% vs 75.3% |
|                              |      |           |                    | Follow-up time (fast APV vs slow APV): 63.4 months |
| Anand et al. [35]            | 2016 | Bone biomarker | Enzalutamide       | Median OS: 83 weeks |
|                              |      |           |                    | C-index of aBSI: 0.72 |
|                              |      |           |                    | △BSI: median = 0.05, IQR: [− 0.28–1.43] |
|                              |      |           |                    | C-index of % of PSA change and aBSI: 0.77 |
|                              |      |           |                    | Median follow-up: 56 weeks |
| Onal et al. [36]             | 2019 | NLR       | Abiraterone either pre- or post-chemotherapy | Median follow-up: 24 months |
|                              |      |           |                    | Median OS: 20.8 months (IQR: 17.3–24.4 months) |
|                              |      |           |                    | Median OS (NLR < 3.1 vs ≥ 3.1): 10.5 vs 6.5 months |
|                              |      |           |                    | HR: 3.13; 95% CI 1.67–5.88; p < 0.001 |
|                              |      |           |                    | HR: 3.30; 95% CI 1.33–8.19; p = 0.01 |
|                              |      |           |                    | NLR PFS: HR: 2.25; 95% CI 1.44–3.51; p < 0.001 |
| Loubersac et al. [37]        | 2019 | NLR       | Abiraterone + prednisone or prednisone | Median OS (NLRlow vs NLR high): HR, 0.66; 95% CI 0.50–0.86, vs HR, 0.84; 95% CI 0.67–1.04 p = 0.002 |
| Tatenuma et al. [38]         | 2018 | NLR       | Docetaxel          | Median OS: 21.0 months |
|                              |      |           |                    | Median OS (NLR > 2.59 vs NLR < 2.59): 12.0 vs 31.6 months |
| Kumanoe et al. [39]          | 2019 | NLR       | Enzalutamide       | Median OS (NLR): HR = 4.57; 95% CI 1.31–15.96; p = 0.01 |
|                              |      |           |                    | Median OS (NLR > 14 vs < 14): 17.9 months vs 22.0 months |
| Lorente et al. [40]          | 2015 | NLR       | cabazitaxel versus mitoxantrone | Median OS: 14 months (95% CI 13.2–14.8) |
|                              |      |           |                    | BLNLR > 3 vs < 3 on PSA response: 40.1% vs 59.9% |
|                              |      |           |                    | Median follow-up: 12.8 months |
| Koo et al. [41]              | 2019 | NLR       |                    | Median follow-up: 18.5 months |
|                              |      |           |                    | Median RFS: 3.7 (2.3–8.3) |
| Miyoshi et al. [75]          | 2018 | ERG       | ADT                | Median time to CRPC: 40.2 months |
|                              |      |           |                    | Median time to CRPC with PTP (high vs low): 14.8 months vs 86.3 months |
| Ohtake et al. [76]           | 2017 | ERG       | ADT                | Median overall OS high PTP: Not reached |
|                              |      |           |                    | Median overall OS low PTP: 23.8 months |

PFS progression free survival, OS overall survival, ADT Androgen deprivation therapy
Higher PSA nadir, higher TTN and a shorter time to PSA nadir were significant predictors of an increased risk of progression to CRPC during initial ADT and was associated with shorter PFS in ADT treated patients [53–55]. Correlation of testosterone to PSA levels during treatment with ADT showed median time to PSA rise was 4.5 months and especially after T > 50 ng/dl was a significant prognosticator associated with a 71% reduction in the risk of developing CRPC (p = 0.05) [56]. Similar observations were noted when nPSA cut-off was > 0.64 ng/ml in patients treated with ADT [57].

Time to CRPC (p = 0.007, HR = 4.77), regional lymph node involvement at the diagnosis of CRPC (p = 0.022, HR = 2.42), and PSA-PFS of alternative first generation androgen (FGA) therapy ≤ 6 months were identified as prognostic factors, while nPSA > 1 ng/ml during and time from starting FGA to nPSA ≤ 1 year were predictive factors for worse PSA-PFS in alternative FGA therapy [58]. CRPC-free survival was significantly shorter in the PSA ≥ 100 group than in PSA < 100 group in patients treated with ADT. However, the OS after CRPC diagnosis was significantly shorter in the PSA < 100 group indicating it might be a poor prognostic factor in CRPC patients [59]. PSA decline of > 50% proved significantly associated with better OS (20.1 months vs 10.5) and PFS (17.9 months vs 6.6 months) following treatment with [225]Ac-PSMA-617 over PSA decline ≤ 50% [60]. PSA decline ≥ 20.87% and ≥ 14% was a prognosticating indicator for longer survival, in another two studies [61, 62].

Treatment with abiraterone acetate demonstrated that PSA reduction ≥ 30% or ≥ 50% remained predictive of better PFS and OS [63, 64]. Duration of treatment > 3 months by abiraterone acetate was significantly predictor (p = 0.00025) of treatment [65]. To determine the suitability of treatment approach, PSA response rate at > 50% and > 90% was evaluated which showed no statistically significant difference in patients treated with abiraterone acetate or enzalutamide. However, overall, nPSA (HR = 1.000, 95% CI 1.000–1.001, p = 0.010) was an independent prognostic factor for OS [66]. Time from therapy to castration resistance of ≤ 18 months was a determinant of shorter OS in another study (p = 0.007) [67]. TTPN > 19 weeks was superior to TTPN ≤ 19 weeks in abiraterone acetate group than in enzalutamide group (11.1 months vs 8.4 months) [68]. PSA response of ≥ 50% had significantly longer times to PSA progression, rPFS, and OS in patients treated with enzalutamide [69, 70] (Table 4).

**Lactate dehydrogenase and alkaline phosphatase**

Four studies assessed lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) as biomarker. Serum LDH value was significantly prognostic marker for PFS
Table 4 Summary of included studies for predictive/prognostic biomarkers

| Article            | Year | Biomarker | Intervention                                | Significant outcomes                                                                                                                                 |
|--------------------|------|-----------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ando et al. [44]   | 2019 | Testosterone | Docetaxel                                  | Median OS: 35.8 months<br>Median OS (TST > 13 ng/dl vs < 13 ng/dl): 19.2 vs 76.9 months<br>Median PFS (TST > 13 ng/dl vs < 13 ng/dl): 5.1 vs 7.1 months<br>Median follow-up: 21.6 months |
| Hashimoto et al. [45] | 2019 | Testosterone | Abiraterone or enzalutamide               | Median follow-up: 26 months<br>Median PFS (< 5 ng/dl vs 5 ng/dl): 12.2 vs 4.5 months                                                                                             |
| Shiota et al. [46] | 2018 | Testosterone | Enzalutamide, abiraterone, docetaxel, cabazitaxel | PFS (T < 0.05 vs > 0.05): p = 0.047<br>OS (T < 0.05 vs > 0.05): p = 0.18                                                                                       |
| Wang et al. [47]   | 2017 | Testosterone | ADT                                        | Median time to CRPC (T < 25 ng/dl vs > 25 ng/dl): 19.1 vs 14.6 months<br>Median follow-up: 14 months                                                                 |
| Yasouka et al. [48] | 2019 | PSA        | Cabazitaxel                                | Median follow-up: 13.2 (IQR) = 6.9–21.5 months<br>45.5%<br>Median PFS: 4.3 months<br>Median OS: 14.7 months<br>Median TTN: 8.10 months |
| Lin et al. [53]    | 2018 | PSA        | ADT                                        | nPSA > 0.2 ng/ml: HR, 2.665, 95% CI 1.495–4.750, p < 0.001<br>Median follow-up: HR: 0.262, 95% CI 0.161–0.426<br>Median PFS: 14.0 months<br>Median PSA: 14.7 months<br>Median TTN: 8.10 months |
| Kosaka et al. [49] | 2018 | PSA        | Cabazitaxel                                | Median OS: 16.1 months<br>PSA ≥ 100 ng/ml prior to cabazitaxel: HR = 4.375; 95% CI 1.755–10.91, p = 0.002                                                                 |
| Pei et al. [51]    | 2019 | PSA        | Docetaxel                                  | TTN ≥ 15 weeks: HR 0.093, 95% CI 0.044–0.188, p < 0.001<br>PSA nadir < 4.55 ng/ml: HR 4.002, 95% CI 1.890–8.856, p = 0.001<br>PSA decline > 50%: HR 0.573, 95% CI 0.428–0.756, p < 0.001 |
| Satehekge et al. [60] | 2019 | PSA        | ²²⁵Ac-PSMA-617                             | Median OS: 18 months<br>Median PFS: 15.2 months<br>Median follow-up: 9 months                                                                                                                                 |
| Alvim et al. [63]  | 2019 | PSA        | Abiraterone acetate                        | Median OS (PSA): HR: 0.19, 95% CI 0.10–0.38; p < 0.001<br>Median PFS (PSA): HR: 0.24, 95% CI 0.14–0.41; p < 0.001<br>Median OS (PSA): 11.5 months<br>29.3 vs 9.7<br>17 vs 5.3 |
| Armstrong et al. [70] | 2018 | PSA        | Enzalutamide                               | Median OS: 23.1 months<br>Median time to PSA (no-decline or decline < 30% group): 3.7 month<br>Median time to PSA progression: 13.8 months (95% CI 11.3–14.0) |
| Hamano et al. [57] | 2019 | PSA        | Docetaxel, AA and ENZ                      | PSA nadir > 0.64 ng/ml and TTN < 7 months: HR: 3.34; 95% CI 1.99–5.61; p < 0.001<br>Median OS: (PSA nadir > 0.64 ng/ml and TTN < 7 months): HR: 2.98, 95% CI 1.77–5.02; p < 0.001<br>Median follow-up: 35 months                   |
| Yang et al. [52]   | 2015 | PSA        | Docetaxel                                  | Median OS: 13.51 months<br>Median TTN: 5.14 months                                                                                                          |
| Article                      | Year | Biomarker | Intervention              | Significant outcomes                                                                 |
|-----------------------------|------|-----------|---------------------------|--------------------------------------------------------------------------------------|
| Houede et al. [65]          | 2015 | PSA       | Abiracetone acetate       | PSA response > 3 months: \( p = 0.00025 \)  
Median OS: 14.6 months  
Follow-up: 36.3 months |
| Kuo et al. [56]             | 2015 | PSA       | ADT                       | Median time to PSA rise: 4.5 months  
Median time to PSA rises after first T > 50 ng/dl: 1.0 months  
Median times from primary treatment to CRPC: 9.7 years |
| Schiff et al. [64]          | 2019 | PSA       | Abiraterone              | ≥ 30% PSA at 4, 8, 12 weeks OS: range: 35.2 months to 40.0 months  
≥ 50% PSA at 4, 8, 12 weeks OS: range: 37.3 months to 41.1 months |
| Rahbar et al. [61]          | 2017 | PSA       | 177Lu-PSMA-617            | Median OS: 56.0 weeks  
Median OS (PSA decline > 50% vs < 50%): 66 weeks vs 47 weeks |
| Ahmadzadehfar et al. [62]   | 2017 | PSA       | 177Lu-PSMA-617            | PSA decline ≥ 14 OS vs < 14: 88 weeks vs 29 weeks  
PSA decline ≥ 50% vs < 50%: HR: 70; 95% CI 39.5–100.5 vs HR: 49; 95% CI 30.2–67.8  
Time to CRPC progression: 38 months |
| Ji et al. [54]              | 2017 | PSA       | ADT                       | PSA nadir: HR 1.185, 95% CI 1.080–1.301,  
Velocity of PSA decline > 11 ng/ml/month: HR 2.124, 95% CI 1.195–3.750,  
Time to PSA nadir: 9 months  
Median time to progression to CRPC: 38 months |
| He et al. [55]              | 2017 | PSA       | ADT                       | Mean time to CRPC: 23 months  
Time to reach minimal PSA (> 1-year vs < 1 year): 8.5 months vs 3.9 months |
| Belderbos et al. [50]       | 2019 | PSA       | Cabazitaxel              | Median OS: 13.3 months  
Haemoglobin: OR 1.48, 95% CI 1.05–2.07,  
Lower AP: OR 0.61, 95% CI 0.39–0.96,  
Time from starting PADT to PSA nadir ≤ 1 year: HR 1.85, 95% CI 1.063–3.204,  
Median time to CRPC (AA vs Enza): 31.5 vs 24.9 months |
| Chang et al. [66]           | 2019 | PSA       | Abiraterone, enzalutamide | Median follow-up (AA vs Enza): 18.2 vs 14.5 months  
Median PFS: 7.3 months vs 9.5 months  
PSA nadir: HR 1.000, 95% CI 1.000–1.001,  
Median time to CRPC (AA vs Enza): 31.5 vs 24.9 months |
| Fan et al. [67]             | 2018 | PSA       | Abiraterone + prednisone vs prednisone | Median follow-up: 14 months (range 7.0–18.5 months  
Median PSA PFS:10.3 vs 3.0 months  
Median PSA rPFS: 13.9 vs 3.9 months  
Median OS: 23.3 vs 17.5 months  
Time to castration resistance < 18 months: HR, 12.8, 95% CI 2.0–83.1,  
Median time to CRPC < 18 months: HR 1.185, 95% CI 1.080–1.301,  
Median time to CRPC (AA vs Enza): 31.5 vs 24.9 months |
| Fukuoka et al. [58]         | 2019 | PSA       | FGA therapy              | Time to CRPC p = 0.007  
Median PSA PFS: HR 2.30, p = 0.020  
Median PSA nadir > 1 ng/ml: HR 2.40, p = 0.034  
Time from starting PADT to PSA nadir ≤ 1 year:  
HR 1.85, p = 0.047 |
| Kodama et al. [87]          | 2019 | PSA       | ADT                       | Median follow-up: 31 months  
Median time to CRPC: 13 months  
CRPC survival (PSA < 100 vs > 100): 31 vs 18 months  
Median OS (PSA < 100 vs > 100): 85 vs 78 months,  
p = 0.509 |
(HR = 1.42, 95% CI 1.15–1.74; p = 0.00040) and OS (HR = 1.46, 95% CI 1.13–1.82; p = 0.0014), in addition to alkaline phosphatase levels for OS (HR = 1.04; 95% CI 1.00–1.07; p = 0.015) [71]. Pretreatment serum LDH was a strongest biomarker at the point of initiation of docetaxel therapy with LDH ≥ 450 U/l levels associated with poorer PFS (p < 0.00) and OS (p = 0.011). However, pretreatment serum LDH did not predict a positive response to docetaxel [72]. ALP was a strongest prognostic factor in discriminating patients with good or poor prognosis with median OS in patients with normal and abnormal ALP of 69.1 and 33.6 months treated with ADT with/without docetaxel [73]. Similarly, abiraterone acetate-enzalutamide group showed significantly longer total PSA PFS than enzalutamide–abiraterone acetate group (p = 0.049). Survival analysis showed that combined PFS was significantly longer among patients with LDH < 210 IU/l before the first ARAT than in those with ≥ LDH 210 IU/l [74] (Table 4).

**Tyrosine phosphatase**

Of the two articles included, one study reported that median time to CRPC was significantly shorter in the high tyrosine phosphatase (PTP) group (14.8 months) than that in low PTP group (86.3 months, p < 0.01). Thus, high PTP expression was a significant predictor of time to CRPC treated with ADT. [75] This was similar to another study by Ohtaka 2017, where PTP expression (high vs low; HR = 2.7, 95% CI 1.0–7.2, p = 0.04) was independent prognostic factor for OS [76] (Table 4).

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**Table 4 (continued)**

| Article                  | Year | Biomarker          | Intervention      | Significant outcomes                                                                 |
|--------------------------|------|--------------------|-------------------|-------------------------------------------------------------------------------------|
| Papazoglou et al. [69]   | 2016 | PSA                | Enzalutamide      | Median survival time from diagnosis of CRPC: 41.1 months                              |
|                          |      |                    |                   | Median PFS: 3.0 months                                                               |
|                          |      |                    |                   | Median OS: 6.3 months                                                                |
| Miyake et al. [68]       | 2017 | PSA                | Enzalutamide, abiraterone | Median time to PSA progression (TTN < 19 weeks vs TTN > 19 weeks) in Abiraterone acetate: 8.4 vs 11.1 months |
|                          |      |                    |                   | Median time to PSA progression (< 14 weeks vs > 14 weeks) in Enzalutamide: 11 vs 9.9 weeks |
| Kobayashi et al. [71]    | 2019 | LDH/ALP            | ADT               | Median follow-up: 48.1 months                                                        |
|                          |      |                    |                   | Median PFS: 24 months                                                               |
|                          |      |                    |                   | Median OS: 67.4 months                                                              |
|                          |      |                    |                   | LDH PFS: HR = 1.42; 95% CI 1.15–1.74; p = 0.00040                                   |
|                          |      |                    |                   | LDH OS: HR = 1.46; 95% CI 1.13–1.82; p = 0.0014                                     |
|                          |      |                    |                   | ALP OS: HR = 1.04; 95% CI 1.00–1.07; p = 0.015                                     |
| Hiew et al. [72]         | 2018 | LDH                | Docetaxel         | Serum LDH ≥ 450 IU/l: SD: 0.054; 95% CI 0.650–0.864; p < 0.001                      |
|                          |      |                    |                   | LDH PFS: HR = 1.876; 95% CI 1.289–2.7300; LDH OS: HR = 1.630; 95% CI 1.127–2.357 |
| Gravis et al. [73]       | 2015 | ALP                | ADT               | ALP OS: 62.1% vs 23.2%                                                              |
|                          |      |                    |                   | ALP C-index: 0.64; 95% CI 0.52–0.66                                                  |
|                          |      |                    |                   | Median follow-up: 58.3 months                                                        |
| Mori et al. [74]         | 2017 | LDH                | Abiracetone, enzalutamide | LDH (< 210 IU/l: 17 months) vs LDH ≥ 210 IU/l: 8 months                             |
|                          |      |                    |                   | PFS: HR = 0.39; 95% CI 0.15–1.03; 0.056                                             |
|                          |      |                    |                   | OS: HR = 0.79; 95% CI 0.38–2.02; 0.63                                                |
| Song et al. [42]         | 2016 | Tyrosine Phosphatase | Docetaxel   | PSA response (ERG+ vs ERG−): 15.4% vs 62.1%; p = 0.004                              |
|                          |      |                    |                   | OS (ERG+ vs ERG−): 10.8 months vs 21.4 months; p < 0.001                            |
|                          |      |                    |                   | C/R PFS (ERG+ vs ERG−): 3.8 months vs 9.0 months; p < 0.001                          |
|                          |      |                    |                   | Mean follow-up: 52.9 ± 27.2 months                                                   |
| Berg et al. [43]         | 2015 | Tyrosine Phosphatase | ADT              | Median follow-up: 6.8 years (IQR: 4.9–7.3)                                          |
|                          |      |                    |                   | Median time to CRPC (ERG+ vs ERG−): 3.9 years vs 4.5 years                           |
|                          |      |                    |                   | Median OS: 3.6 months                                                               |

PFS progression free survival, OS overall survival, ADT Androgen deprivation therapy
Discussion

With the growing number of various therapeutic options that can extend survival in mCRPC patients, there is a need for the biomarkers to guide in simultaneous decisions for optimal treatment and predict which patients will benefit the most from the treatment. It is unlikely that a single biomarker will provide all information we need to tell how aggressive a newly diagnosed cancer is. No immunochemical, or genetic marker is currently used to differentiate between various stages of prostate cancers. PSA is the most widely used biomarker till now preferred for screening as well in follow-up after treatment [77]. However, PSA level change is variably dependent on the mechanism of action of different treatments. For example, early declines in PSA may be observed in novel hormonal therapies such as AA or enzalutamide which are highly prognostic in nature and associated with their mechanism of action [78]. A rise in PSA while a patient is receiving androgen deprivation therapy potentially signals a transition from hormone-sensitive prostate cancer to CRPC. However, castration levels of serum testosterone must be demonstrated before castration resistance is confirmed [79]. In the above included studies, it was observed that the PSA > 100 ng/ml, nPSA > 0.2 ng/ml, a velocity of PSA decline > 11 ng/ml per month were associated with shorter OS and PFS in patients with mCRPC while PSA decline > 50% or > 30% was associated with longer survival outcomes irrespective of any therapy. Similarly, TTPN > 6 weeks were a significant prognostic factor for survival. Early PSA response > 30% or > 50% after initiation of treatment is a significant predictor for longer OS. However, PSA levels have several restrictions as a biomarker in monitoring CRPC especially in the context of novel non-cytotoxic treatments that may have little effect on its levels. Further, PSA levels may not provide accurate information regarding the extent of bone metastasis or bone-specific effects of treatment, indicating the need of alternative biomarkers for this purpose. Bone is a common site of metastases affecting more than 90% of mean at autopsy. Even though the impact of these biomarkers is not known, they provide useful information related to the survival and progression of CRPC [80]. The elevated baseline level of BAP may be predictive for survival benefit with radium-223 treatments, and post treatment BAP reductions are highly associated with improvements in survival with radium-223 chloride [13]. In our studies, elevated BAP showed poorer outcomes on survival on treatment with radium-223, while faster APV and shorter PSADT were significant predictors of poorer bone metastasis free survival and OS.

It was noted that higher NLR values (>2.14, >2.5 or >3.1) predicted worse OS and CSS in patients treated with novel hormonal therapies and docetaxel chemotherapy. This was in consistence to the other studies where high NLR was associated with poorer PFS in patients with metastatic CRPC across different treatments including abiraterone, docetaxel [81, 82]. Though the biology behind higher NLR to be significant predictor is unclear, it is presumed that the increased NLR may arise from altered tumor-inflammatory cell reactions, which is an indicator of progressive malignancy [83]. Testosterone as prognostic factor demonstrated that lower TST levels were associated with significant longer time to survival to treatment with docetaxel, ARAT and ADT. The mechanism of TST exhibiting benefits at lower levels may be related to acquired resistance than primary resistance, however this role is still unclear [45]. However, one study reported that high levels (>0.05 ng/ml) was significant predictor of OS on treatment with ARAT, thus though TST is a significant prognostic factor, the role of TST in ARAT is unclear [46].

An increased LDH level after treatment may be predictive for poor treatment response [84]. This was also observed when the LDH level was > 450 U/l in patients initiated with docetaxel [72] and > 210 U/l in patients treated with ARAT and predicted poorer OS [74]. Also serum ALP is a significant biomarker for prediction to longer OS [71, 73]. ARV is an important prognostic factor in the progression from prostate cancer to mCRPC. Higher expression of ARV in CTC and not prostate tissues is poor prognostic factor [85]. Presence of ARV7+ and CTC+ in patients with mCRPC were associated with poorer outcomes on OS along with higher ARV7 values. However, one study reported no significant association with ARV7 [18]. Circulating tumor cells (CTCs) have emerged as a viable solution to the problem whereby patients with a variety of solid tumors, including PC, often do not have recent tumor tissue available for analysis [86]. CTC count <5 has been a good prognostic factor for the PFS and OS in patients initiated with cabazitaxel and radium-223 therapy. Presence of CTC in patients after 3 months of initiation of ADT therapy was associated as a negative marker for early progression to CRPC [27]. Lesser explored biomarkers such as tyrosine phosphatase showed that higher levels predicted poorer OS and CSS in the two included studies [75, 76] while patients with ERG positive values showed poorer outcomes of OS and PFS [42, 43].

Thus, through our review, we have given an insight on how the biomarkers are significant in determining treatment selection. A meaningful observation from our included studies was that higher levels with any of the biomarkers in urine or blood were prognostic indicator for poorer survival outcomes, early development of CRPC and shorter follow-up duration to treatment. Also, the appropriate cut-off levels for biomarker was a
significant predictor for exposure to treatment in the included studies. We thus highlight the need to establish the cut-off level for particular biomarker which will be helpful for the clinicians in diagnosis of CRPC and providing a suitable treatment strategy.

**Conclusion**

Diagnosis of CRPC and its management requires an individualized approach to both patient care and trial design. Although we have given a meaningful insight into the utility of the biomarkers for treatment responses and survival outcome, future research is needed with respect to the prediction of biomarker response in sequential therapy so as to design a series of optimal treatment in patients with CRPC. Currently all biomarkers in clinical use have prognostic implications when measure prior to initiating treatment, however not all are validated as predictive markers in post treatment setting. ARV7 splice variant and CTC also look like promising candidates in development of biomarkers and may benefit a specific group of CRPC population. More prospective studies on CRPC biomarkers are required to identify the surrogate value of these biomarkers on survival which will be helpful in clinical decision making.

**Abbreviations**

ABSII: Automated bone scan index; ADT: Androgen deprivation therapy; ALP: Alkaline phosphatase; APV: Alkaline phosphatase velocity; BAP: Bone alkaline phosphatase; CRPC: Castration-resistant prostate cancer; CTC: Circulating tumor cell count; HSPC: Hormone sensitive prostate cancer; LDH: Lactate dehydrogenase; mCRPC: Metastatic castrate resistant prostate cancer; NCBi: National Center for Biotechnology Center; OS: Overall survival; PCA: Prostate cancer; PFS: Progression-free survival; PSA: Prostate-specific antigen; PSADT: PSA doubling time; PTP: Tyrosine phosphatase; RCTs: Randomized clinical trials; TALP: Total alkaline phosphatase; TST: Testosterone.

**Acknowledgements**

The author would like to acknowledge Anwesha Mandal and Dr. Anuradha Nalli (Indegene Pvt Ltd, India), for their medical writing support.

**Authors’ contributions**

Conceptualization: ST and MP. Data curation: ST and ZS. Investigation: MP. Writing and editing: ST, ZS, and MP. All authors read and approved the final manuscript.

**Funding**

The work was supported by Natural Science Research Foundation of Jilin Province for Sciences and Technology (20200201575JC).

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