

available at www.sciencedirect.comjournal homepage: www.eu-openscience.europeanurology.com

European Association of Urology

Review – Prostate Cancer

Predictive Models for Assessing Patients' Response to Treatment in Metastatic Prostate Cancer: A Systematic Review

Ailbhe Lawlor^{a,*}, Carol Lin^b, Juan Gómez Rivas^c, Laura Ibáñez^c, Pablo Abad López^d, Peter-Paul Willemse^e, Muhammad Imran Omar^f, Sebastiaan Remmers^b, Philip Cornford^g, Pawel Rajwa^h, Rossella Nicoletti^{i,j}, Giorgio Gandaglia^{k,l}, Jeremy Yuen-Chun Teoh^j, Jesús Moreno Sierra^c, Asieh Golozar^{l,m}, Anders Bjartellⁿ, Susan Evans-Axelsson^o, James N'Dow^p, Jihong Zong^q, Maria J. Ribal^p, Monique J. Roobol^b, Mieke Van Hemelrijck^a, Katharina Beyer^b, on behalf of the PIONEER Consortium

^aTranslational Oncology and Urology Research (TOUR), King's College London, London, UK; ^bDepartment of Urology, Erasmus MC Cancer Institute, Erasmus University Medical Centre, Rotterdam, The Netherlands; ^cDepartment of Urology, Health Research Institute, Hospital Clinico San Carlos, Madrid, Spain; ^dDepartment of Urology, Hospital Universitario La Paz, Madrid, Spain; ^eDepartment of Oncological Urology, University Medical Center, Utrecht Cancer Center, Utrecht, The Netherlands; ^fAcademic Urology Unit, University of Aberdeen, Aberdeen, UK; ^gLiverpool University Hospitals NHS Trust, Liverpool, UK; ^hDepartment of Urology, Medical University of Silesia, Zabrze, Poland; ⁱDepartment of Experimental and Clinical Biomedical Science, University of Florence, Florence, Italy; ^jS.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China; ^kDepartment of Urology and Division of Experimental Oncology, Urological Research Institute, IRCCS San Raffaele Hospital, Milan, Italy; ^lOHDSI Center, Northeastern University, Boston, MA, USA; ^mOdyssey Data Services, New York, NY, USA; ⁿDepartment of Translational Medicine, Lund University, Malmö, Sweden; ^oBayer AB, Medical Affairs Oncology, Stockholm, Sweden; ^pEuropean Association of Urology, Guidelines Office, Arnhem, The Netherlands; ^qBayer Healthcare, Global Medical Affairs Oncology, Whippany, NJ, USA

Article info

Article history:

15 January 2024
5 February 2024
Accepted March 20, 2024

Associate Editor:

Roderick van den Bergh

Keywords:

Adverse events
Disease progression
Metastatic prostate cancer
Overall survival
Predictive models
Treatment discontinuation
Treatment selection
Toxicity

Abstract

Background and objective: The treatment landscape of metastatic prostate cancer (mPCa) has evolved significantly over the past two decades. Despite this, the optimal therapy for patients with mPCa has not been determined. This systematic review identifies available predictive models that assess mPCa patients' response to treatment.

Methods: We critically reviewed MEDLINE and CENTRAL in December 2022 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. Only quantitative studies in English were included with no time restrictions. The quality of the included studies was assessed using the PROBAST tool. Data were extracted following the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews criteria.

Key findings and limitations: The search identified 616 citations, of which 15 studies were included in our review. Nine of the included studies were validated internally or externally. Only one study had a low risk of bias and a low risk concerning applicability. Many studies failed to detail model performance adequately, resulting in a

* Corresponding author. Translational Oncology and Urology Research, 3rd Floor, Bermondsey Wing, Guy's Hospital, Great Maze Pond, London SE19RT, UK.
E-mail address: ailbhe.lawlor@kcl.ac.uk (A. Lawlor).

<https://doi.org/10.1016/j.euro.2024.03.012>

2666-1683/© 2024 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



high risk of bias. Where reported, the models indicated good or excellent performance.

Conclusions and clinical implications: Most of the identified predictive models require additional evaluation and validation in properly designed studies before these can be implemented in clinical practice to assist with treatment decision-making for men with mPCa.

Patient summary: In this review, we evaluate studies that predict which treatments will work best for which metastatic prostate cancer patients. We found that existing studies need further improvement before these can be used by health care professionals.

© 2024 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Prostate cancer (PCa) is a major cause of morbidity and mortality amongst men. While localised PCa is characterised by high long-term disease-specific (ie, PCa specific) survival, metastatic PCa (mPCa) is considered incurable despite the availability of novel treatment modalities [1].

The treatment landscape of mPCa has evolved significantly over the past two decades. Androgen deprivation therapy (ADT) has been the standard of care for mPCa treatment for over 50 years [2]. In recent decades, owing to significant advances in the understanding of metastatic disease, new drugs have been developed for patients [3]. ADT is now commonly used in combination with other treatments such as androgen receptor (AR) antagonists (eg, apalutamide, darolutamide, and enzalutamide) and chemotherapies (eg, docetaxel and cabazitaxel), known as ARTA and combination therapy, respectively. Evidence suggests that the addition of other treatments in combination with ADT has resulted in an improvement in overall survival for patients with metastatic hormone-sensitive PCa at almost 5 years after treatment, compared with ADT treatment alone [4–7]. Other available treatments for mPCa include abiraterone acetate, radiopharmaceutical therapy (radium-223), immunotherapy (pembrolizumab), and poly ADP-ribose (PARP) inhibitors (olaparib, rucaparib, talazoparib, and niraparib). The emergence of so-called triplet therapies, consisting of an AR antagonist (darolutamide), docetaxel, and ADT, or abiraterone, docetaxel, and ADT, demonstrates greater overall survival benefit than doublet therapy with docetaxel and ADT, as noted in a recent systematic review and met-analysis by Mandel and colleagues [8,9]. This review also included highly anticipated data from the PEACE-1 and ARASENS randomised controlled trials [10,11].

Treatment options depend on several factors, including the extent of disease at diagnosis, castration status, and volume or timing of the metastatic disease. Moreover, the efficacy of these treatment options varies according to similar variables, such as whether the patient has metastatic disease at diagnosis as well as the patient's response to treatment.

Despite greater availability of effective treatments, there are no comparative studies to determine the optimal therapy or therapy sequence for the most appropriate patient [12]. This means that treatment selection is currently guided by several other factors: disease characteristics, patient age and fitness, patient comorbidities, potential adverse effects, monetary cost, and availability of the drug [12–14]. Treatment selection should be made jointly by clinicians and patients, based on the clinical evidence and patients' informed preferences [15]. However, efforts are continuing to identify the optimal treatment and treatment sequence for men with mPCa.

One such effort is being undertaken by the PIONEER Consortium, a European network of world leading PCa experts [16]. The consortium aims to establish evidence-based management and clinical practice of PCa across all disease stages by leveraging the power of big data analytics towards an outcome-driven, value-based, and patient-centric health care system. To achieve their objective of identifying the optimal treatment for men with mPCa, it is helpful to examine the existing predictive models that assess these patients' response to distinct treatments. The term predictive model is often misused in the existing literature to refer to diagnostic and/or prognostic models. However, diagnostic models aim to calculate an individual's risk that the disease is present, while prognostic models aim to calculate the risk of a particular health event (eg, survival) occurring in the future [17]. On the contrary, predictive models refer to the prediction of outcomes strictly related to the efficacy and effects of treatment, for example, overall survival, disease progression, treatment discontinuation, toxicity, and adverse events. In mPCa, predictive models can help identify which treatment is most effective for a given patient group in prolonging survival and time to disease progression. Additionally, predictive models can identify which patients are likely to experience adverse events or toxicity from a given treatment based on their clinical characteristics, amongst other factors. This provides useful information for the decision-making process between clinicians and patients when selecting treatment [18].

Therefore, we aimed to identify and evaluate existing predictive models developed for assessing patients'

response to treatment for mPCa. Additionally, we aimed to describe the characteristics of the identified predictive models.

2. Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [19]. A protocol was written a priori (but it was not published). The protocol was shared with some PIONEER Consortium members for their input and was finalised after incorporating their feedback (unpublished work). The protocol is available on request.

2.1. Stage 1: comprehensive literature review

The literature search terms were developed by the members of the core team (A.L., C.L., J.G.R., P.-P.W., S.R., and K. B.), which includes urologists, a bioinformatician, a statistician, and researchers experienced in systematic reviews for urology. We searched for quantitative observational studies that assessed predictive models of mPCa. Relevant studies were identified by conducting searches of Medline (PubMed) and Cochrane (CENTRAL) using the search terms listed below from inception to December 2022. The same search terms were used for both databases:

*prostate cancer and prediction model**

prostate cancer and prediction model filtered by systematic review only*

prostate cancer and prediction model and metas**

Searches were not restricted by publication year or language, and included conference proceedings and abstracts. The complete search strategy is available upon request.

The eligibility of studies was checked independently by two researchers (A.L. and C.L.). Screening of both the abstract and the full text was conducted in duplicate by the same two reviewers. Discrepancies were resolved through discussion, or where the discrepancy could not be resolved through discussion, a third reviewer (K.B.) was consulted to assess the given study.

2.1.1. Eligibility criteria

2.1.1.1. Study design. Only quantitative observational studies were included. Qualitative studies, narrative literature reviews, and commentary pieces were excluded. Studies not published in the English language were excluded.

2.1.1.2. Participants. Participants are adult men (≥ 18 yr of age) diagnosed with mPCa: any T, any N, or M1 a-c. Studies in which local disease (any $\leq T$, any N, and M0) accounted for $>10\%$ of their participants were excluded, unless there were distinct models for metastatic participants. Participants with localised PCa, locally advanced PCa, or non-metastatic castration-resistant PCa (nmCRPC) were excluded.

2.1.1.3. Interventions. Interventions considered for this systematic review were all treatments supported by the

2023 European Association of Urology guidelines for PCa [20].

2.1.1.4. Outcomes. Such studies had to assess the predictive factors (ie, treatment efficacy and effects) of (1) mPCa, (2) risk of progressing mPCa, (3) metachronous PCa, (4) local recurrence of PCa after previously having an mPCa diagnosis, and (5) progression from nmCRPC to metastatic castration-resistant PCa (mCRPC).

Studies that assessed the predictive factors for nmCRPC were also excluded.

2.2. Stage 2: quality evaluation of studies using risk of bias tool

All studies identified through the literature search were assessed using the PROBAST criteria. PROBAST is a tool to assess the risk of bias (RoB) as well as the applicability of studies developing, validating, or updating prediction models [21]. Applicability was judged as low, high, or of unclear concern. Further scoring information is available in Supplementary Table 1.

We conducted pilot screening to prepare the raters for using PROBAST. Both groups received a guidance document to assist with the process [21], and questions were discussed with the groups by a reviewer (K.B.). All raters—one epidemiologist (A.L.), one biostatistician (C.L.), and two urologists (L.I. and P.A.)—were involved in the pilot assessments of two studies from the final study list [22,23]. Any discrepancies were discussed amongst the group.

PROBAST assessments of the remaining studies were then conducted in duplicate by two reviewers for each study. Assessments were conducted independently, and reviewers met to discuss any discrepancies. Where a discrepancy could not be addressed through discussion, a third reviewer was asked to make a judgement.

2.3. Stage 3: data extraction

Data extraction was performed at a study level and guided by the Critical Appraisal and Data Extraction for Systematic Reviews of Predictions Modelling Studies (CHARMS) checklist [24]. Data extraction provides the necessary information for describing and summarising the characteristics of a model. Additionally, it enables an examination of the RoB and applicability concerns of models. As in phase 3, four assessors extracted the data independently. Owing to the anticipated heterogeneity across studies, only a narrative review was planned.

3. Results

3.1. Stage 1: comprehensive literature review

The PRISMA flow chart for study selection is shown in Figure 1.

A multidisciplinary steering committee reviewed the study list, and no recommendations for the exclusion of

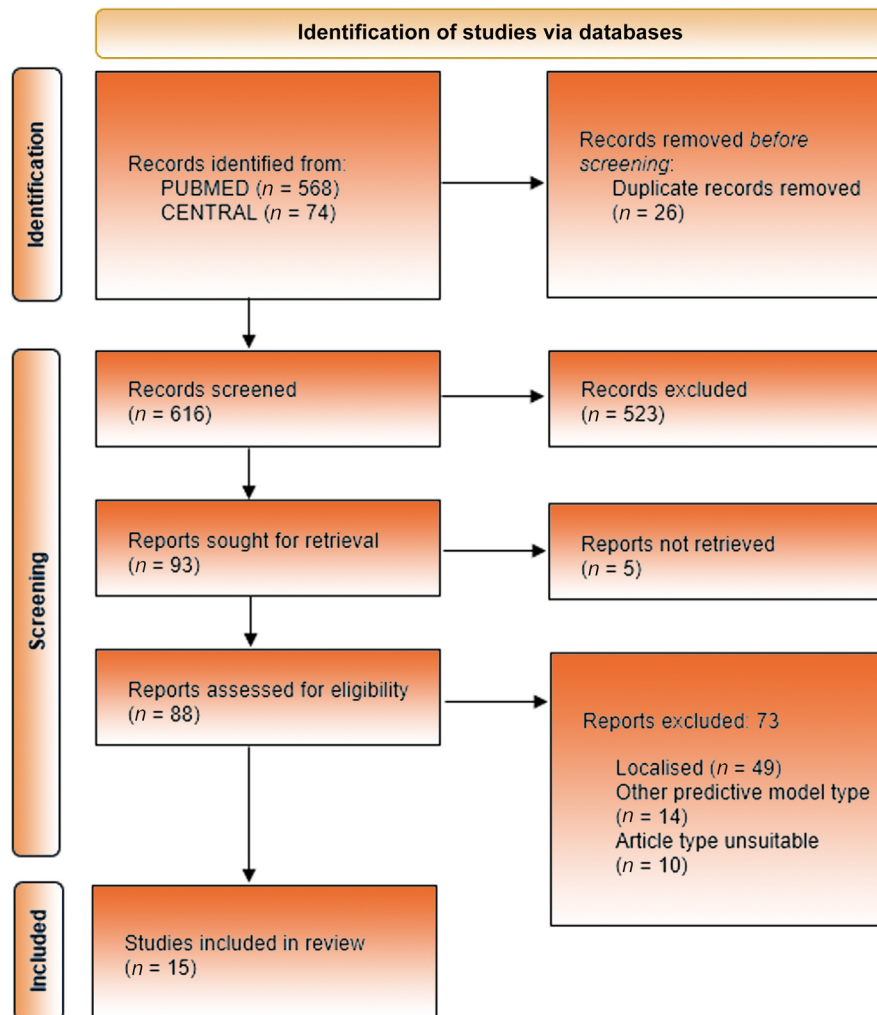


Fig. 1 – PRISMA flow diagram for systematic review of predictive models for mPCa. mPCa = metastatic prostate cancer; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

listed studies or inclusion of additional unlisted studies were received.

3.2. Stage 2: quality evaluation of studies using a RoB tool

We identified 15 studies to be assessed with PROBAST. The RoB was low for one study and high for 13 studies. No study had an unclear RoB. However, it was not possible to assess one study [25] as it was neither a model development nor a validation study. For overall applicability, ten studies were judged to be of low concern and four of high concern. One study was scored to have a low RoB across both domains. Table 1 presents the RoB assessments using PROBAST for all studies, including the overall score and scores for each domain. Supplementary Table 2 presents the full reviewer assessments for all PROBAST signalling questions.

3.3. Stage 3: data extraction

Data extraction was conducted for 14 studies. One study [25] was excluded during stage 3 as it was not a model

development or validation study. Table 2 presents an overview of the key characteristics and performance metrics of the included predictive models extracted during this stage. Tables 3 and 4 describe the treatments and outcomes, respectively, included in the model.

3.4. Characteristics of low RoB models

We identified one model with an overall low RoB [26]. The internally validated machine-learning model aimed to predict skeletal-related events following denosumab treatment discontinuation in 421 men diagnosed with PCa and bone metastases between January 1, 2007 and September 1, 2019. Patient data were extracted from the Optum PanTher Electronic Health Record repository. A c-statistic of 0.82 (95% confidence interval: not available) was achieved by the model, which indicates good model discrimination (c-statistic >0.75) [26]. Precision was reported as 0.62 or 60%, which is below the minimum value required for the model to be considered useful [27].

Table 1 – Predictive models for examining mPCa patient's response to treatment assessed for risk of bias using PROBAST

Study ID	Year	RoB				Applicability			Overall	
		Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	RoB	Applicability
1	2016	Low	Low	High	High	Low	Low	High	High	High
2	2019	Low	Low	Low	Unclear	Low	Low	Low	High	Low
3	2021	Low	Low	Low	High	Low	Low	Low	High	Low
4	2020	Low	Low	Low	High	Low	Low	Low	High	Low
5	2021	High	Low	Low	High	Low	Low	Low	High	Low
6	2018	Low	Low	Low	High	Low	Low	Low	High	Low
7	2022	Low	Low	Low	Low	Low	Low	Low	Low	Low
8	2014	Low	Low	High	High	Low	Low	Low	High	Low
9	2016	Low	Low	Low	High	Low	Low	Low	High	Low
10	2020	High	Low	Low	High	High	Low	High	High	High
11	2018	Low	High	High	High	Low	Low	Low	High	Low
12	2021	High	Low	Low	High	Low	Low	Low	High	High
13	2017	Low	Low	Low	High	Low	Low	Low	High	High
14	2013	Low	Low	Low	High	Low	Low	Low	High	Low

mPCa = metastatic prostate cancer; RoB = risk of bias.

3.5. Characteristics of high RoB models

3.5.1. Validation

The remaining 13 studies were identified with an overall high RoB [18,22,23,28–37]. Eight of these studies were validated internally or externally. Patient data were extracted from registries, cohort studies, and phase 3 clinical trials. Most of the high overall RoB judgements were made based on high RoB within the analysis domain (Table 1). Many studies failed to detail model performance evaluation adequately, as demonstrated in Table 2.

3.5.2. Treatment discontinuation

Treatment discontinuation or treatment completion was predicted by three models [22,23,36]. Two models predicted treatment completion of docetaxel for mCRPC patients as part of the Prostate Cancer DREAM (Dialogue for Reverse Engineering Assessment and Methodology) challenge. The challenge aimed to determine whether baseline clinical characteristics could be used to predict which patients will discontinue their docetaxel treatment due to adverse events and involved 34 teams worldwide. The challenge compiled data from 2070 patients across four phase 3 clinical trials for docetaxel chemotherapy [22,36]. Model performance (eg, discrimination and calibration) was described by only one model that reported poor discrimination (c-statistic: 0.6) [22], where a c-statistic of 0.5 indicates no predictive ability [38]. The third model predicted completion of six cycles of radium-223 in patients with bone mCRPC. Model performance was not reported.

3.5.3. Disease progression

Disease progression was predicted by four studies [28,30,33,37]. Two studies aimed to predict progression to castration-resistant disease in patients treated with ADT alone [28,33], and one study predicted progression in those treated with ADT, docetaxel and abiraterone acetate [37]. The fourth study retrospectively predicted disease progression to metastases in mPCa patients who received radical prostatectomy [30]. Discrimination was reported by all models and ranged from 0.72 to 0.91 (Table 2). Calibration

plots were reported by two models (Supplementary Fig. 1-B-G), and indicated reasonable agreement between the predicted and observed values. Zhao and colleagues [33] also conducted a Hosmer-Lemeshow test, yielding a *p* value of 0.54.

3.5.4. Survival

Survival was predicted by four models, two of which were reported in the same study [35]. Three models aimed to predict overall survival after mCRPC patients were treated with enzalutamide [31], abiraterone acetate alone, or abiraterone combined with prednisone [35]. One model aimed to predict death from castration-resistant PCa in patients who received docetaxel [29]. Model discrimination was reported in all studies, ranging from 0.73 to 0.78, indicating good discrimination. Only one study included a calibration plot (Supplementary Fig. 1A) and indicated reasonable agreement between the predicted and observed probabilities of survival [35].

3.5.5. Treatment efficacy

Two models examined the efficacy of ADT and alternative nonsteroidal antiandrogen therapy, in terms of biochemical recurrence and prostate-specific antigen (PSA) decrease for PCa patients, respectively. The biochemical recurrence prediction model demonstrated excellent discrimination (0.95) [32], while the PSA decrease model reported good discrimination (0.73) [18]. Neither model reported calibration.

The final model predicted tumour, node, metastasis staging, extracapsular extension, seminal vesicle involvement, and lymph node metastasis for PCa patients who received radical prostatectomy [34]. Model performance is not described.

4. Discussion

Predictive models can aid in treatment selection by identifying which treatments a patient is likely to respond well to. We aimed to identify existing predictive models assessing mPCa patient's response to treatment. Our review found

Table 2 – Characteristics and performance metrics of the predictive models for assessing patients' response to treatment

Study ID	Authors	Year	Data source	Population	Sample size		Treatment	Significant predictors	Outcome(s)	Discrimination		Calibration
					Total	Outcome				AUC	Confidence interval	
<i>Development</i>												
1	Anand et al [31]	2016	Registry	mCRPC	62	40	Enzalutamide	Automated BSI, PSA	Overall survival	0.77	0.71-0.81	NR
2	Choi et al [28]	2019	Registry	Locally advanced PCa, mPCa	602	272	ADT	PSA, regional lymph node metastasis, non-lymph node metastasis, bone metastasis, visceral metastasis	Progression to CRPC	0.72	NR	NR
3	Martini et al [36]	2021	Phase 3 clinical trials	mCRPC	1600	238	Docetaxel chemotherapy	Age, ECOG performance status, AST, bilirubin, use of analgesics, presence of diabetes, chronic kidney disease	Toxicity-related treatment discontinuation	NR	NR	NR
4	Mei et al [32]	2020	Cohort	PCa—all stages	145	43	ADT	Lymph node metastasis, GS, pretreatment PSA, treatment method, TIC indicators (PI and TTP)	Biochemical recurrence	0.95	0.91-0.98	NR
5	Miyoshi et al [23]	2021	Hospital records	Bone mCRPC	122	83	Ra-223	ALP, HB, baseline pain	Completion of 6 cycles of Ra-223	NR	NR	NR
6	Yang et al [35]	2018	Cohort	mCRPC	110	43	Abiraterone acetate & prednisone	Liver metastases, HB, time interval from ADT to initiation of abiraterone therapy	Overall survival	0.76	0.68-0.84	NR ^a
<i>Development and internal validation</i>												
7	Jacobson et al [26]	2022	Electronic health records	mPCa	1414	490	Denosumab	Denosumab duration, cumulative number of SREs, unique anticancer drugs	Skeletal-related events	0.82	NR	0.62
8	Kamiya et al [18]	2014	Cohort	PCa—all stages	161	75	Alternative nonsteroidal antiandrogen therapy	Initial diagnosis PSA, PSA nadir to first-line hormone therapy, initial diagnosis HB, C-reactive protein, GS	PSA decrease	0.73	NR	NR
9	Mahmoudian et al [29]	2016	Phase 3 clinical trials	mCRPC	1600	585	Docetaxel chemotherapy	ALP, HB, AST, PSA, lesions	Death	0.78	NR	NR
10	Rho et al [34]	2020	Registry	PCa—all stages	7128	NA	RP	Age at diagnosis, BMI, marital status, education, smoking, alcohol, family history of PCa, PSA, GS, maximum positive core, total cores, HGPIN, core ratio	TNM, ECE, SVI, lymph node metastasis	NR	NR	NR
11	Zhao et al [37]	2018	Cohort	De novo mPCa	449	286	ADT, docetaxel chemotherapy, abiraterone acetate	Biopsy GS, IDC-P status, ECOG score, baseline ALP, haemoglobin, PSA	Incidence of CRPC	0.76	NR	NR ^a
12	Zhao et al [33]	2021	Cohort	Locally advanced PCa, mPCa	183	124	ADT	T stage, distant metastasis, GS, AUC, PSA nadir, time to PSA nadir	Time to CRPC	0.91	0.85-0.96	0.54
<i>Development and external validation</i>												
13	Seyednasrollah et al [22]	2017	Phase 3 clinical trials	mCRPC	1600	197	Docetaxel chemotherapy	Albumin, HB, lactate dehydrogenase, PSA, sodium, RBC, ALP, calcium, AST, creatinine clearance, total protein	Treatment discontinuation	0.60	NR	NR
<i>External validation</i>												
14	Karnes et al [30]	2013	Cohort	mPCa	256	73	RP	GS	Metastatic disease	0.79	0.68-0.87	NR
6	Yang et al [35]	2018	Cohort	mCRPC	110	43	Abiraterone acetate	ECOG PS, liver metastases, albumin, ALP, time interval from ADT to initiation of abiraterone therapy	Overall survival	0.73	0.64-0.81	NR

ADT = androgen deprivation therapy; ALP = alkaline phosphatase; AST = aspartate aminotransferase; AUC = area under the curve; BMI = body mass index; BSI = bone scan index; CRPC = castration-resistant prostate cancer; ECE = extracapsular extension; ECOG = Eastern Cooperative Oncology Group; GS = Gleason's score; HB = haemoglobin; HGPIN = high-grade prostatic intraepithelial neoplasia; IDC-P = intraductal carcinoma of the prostate; mCRPC = metastatic castration-resistant prostate cancer; mPCa = metastatic prostate cancer; NA = not available; NR = not reported; PCa = prostate cancer; PI = peak intensity; PS = prostate specific antigen; RBC = red blood count; RP = radical prostatectomy; SRE = skeletal-related events; SVI = seminal vesicle involvement; TIC = time-intensity curve; TNM = tumour, node, metastasis; TTP = time to peak.

Note: Given the high number of predictors included in some models, we elected to include only significant predictors in this table.

^a Calibration plot is provided, but no p value is specified.

Table 3 – Overview of the treatment per study in prediction models for assessing patients, response to treatment

Authors	ADT	ARTA	AA	Chemotherapy	RP	Ra-223	Denosumab	Prednisone	Alternative nonsteroidal antiandrogen therapy
Seyednasrollah et al [22]				X					
Miyoshi et al [23]						X			
Mei et al [32]	X								
Rho et al [34]					X				
Yang et al [35]			X						
			X					X	
Zhao et al [33]	X								
Jacobson et al [26]							X		
Choi et al [28]	X								
Karnes et al [30]					X				
Anand et al [31]		X							
Kamiya et al [18]									X
Mahmoudian et al [29]				X					
Zhao et al [37]	X		X	X					
Martini et al [36]				X					

AA = abiraterone acetate; ADT = androgen deprivation therapy; ARTA = androgen receptor-targeted agents; RP = radical prostatectomy; Ra-223 = radiotherapy.

Table 4 – Overview of the outcomes per study included by prediction models for assessing patients' response to treatment

Authors	Treatment discontinuation	Disease progression	Survival	Treatment efficacy	Adverse events	Other
Seyednasrollah et al [22]	X					
Miyoshi et al [23]	X					
Mei et al [32]				X		
Rho et al [34]						X
Yang et al [35]			X			
Zhao et al [33]		X				
Jacobson et al [26]					X	
Choi et al [28]		X				
Karnes et al [30]		X				
Anand et al [31]			X			
Kamiya et al [18]				X		
Mahmoudian et al [29]			X			
Zhao et al [37]		X				
Martini et al [36]	X					

that almost all identified studies had a high RoB primarily due to poor design, conduct, and/or reporting. Common issues included failing to describe missing data and a lack of model development testing. We identified one study rated to have a low RoB, which reported adequate model development. This study was the only study reviewed, which extracted data from an electronic health record. However, the model has yet to be validated externally. Repeated external validation is required before a predictive model can be deemed suitable for clinical use. We identified three externally validated models predicting disease progression [30], treatment discontinuation [22], and survival [35], none of which had reported complete model development. As such, we did not identify any models suitable for immediate use in clinical practice.

Similar issues with RoB were also observed in Beyer et al's [39] review of diagnostic and prognostic models, with most studies identified as having a high RoB. The authors concluded that additional evaluation and validation in well-designed studies are required before the diagnostic and prognostic factors included in their review can be recommended for use in clinical practice. A high RoB for studies was also observed in systematic reviews of predictive models for other cancer types, such as breast cancer [40]. Lin et al [40] reported that all 17 studies identified in their review were assessed as having a high RoB using PROBAST.

Furthermore, only one model that we identified externally validated the model they developed. An additional two studies validated existing predictive models externally. External validation is critical to ensuring model generalisability and is an important step before model application in clinical settings [41]. The lack of external validation may be in part due to the novelty of predictive models in cancer research. All studies identified in our review were published in the past decade, with many of the studies emphasising the need for external validation of their model in future research.

However, other issues remain, in addition to the lack of external validation. At a data level, challenges with obtaining high-quality, complete, and representative data may hinder the development of low RoB predictive models. For example, phase 3 clinical trial data are likely to be of high quality and complete, but unlikely to be representative of the general population given the strict inclusion criteria for clinical trial participation. Notably, the sole study evaluated as having a low RoB in our review extracted data from an electronic health record. This indicates a role for high-quality real-world evidence, reflective of the population, in developing predictive models suitable for clinical practice.

Moreover, in some of the identified studies, the predictor variables were also used to calculate the outcome and/or

there were not a sufficient number of participants for the number of predictors due to small sample sizes. Such sample sizes could impact study outcomes, decrease statistical power, and highlight a need for additional research on much larger sample sizes. Additionally, missing data, and handling of missing data, were reported rarely. This was also observed in other systematic reviews of predictive models [41,42]. Finally, there was some heterogeneity across the predictors used in the identified models, even where the models aimed to predict the same outcome [29,31,35]. Core outcome sets offer a potential solution to this problem and should be implemented in future model development studies [43].

Relatedly, there is a need for concrete definitions of predictive, diagnostic, and prognostic models. There is substantial confusion in the literature about the differences between these model types. We observed countless studies developing or validating diagnostic and prognostic models that appeared in our literature search described as predictive models, and it is possible that predictive models were missed during our review if these did not use the appropriate term. This issue extends beyond mPCa and covers all fields in which these types of models are used. Not only does this pose an issue for evidence synthesis, but it also may lead to models being missed by researchers who seek to perform external validation of existing models. While definitions of the differing model types exist [17], these are not used across the research landscape, resulting in much confusion. Concrete definitions of the model types and their widespread implementation should be a key focus in future research. This could be achieved by using a study-a-thon approach, a method previously used by PIONEER, which brings together a multidisciplinary team of academics, clinicians, data scientists, epidemiologists, and patient representatives to conduct an observational study focusing on a clinical or research question over 5 days. By using a study-a-thon approach, developed definitions would be suitable for both clinical and nonclinical research, allowing for universal use.

4.1. Strengths and limitations

The strengths of this review include the systematic methodology used to identify eligible studies. All eligibility screening and the PROBAST assessments were conducted in duplicate by both researchers and clinicians working in the (metastatic) PCa field. Moreover, to our knowledge, this is the first systematic review of predictive models for mPCa. This study has identified the limitations of existing predictive models and highlighted areas for improvement that should be addressed in future research.

Our study has several potential limitations. Firstly, our search strategy was limited to English literature only. There is also substantial confusion in the literature surrounding the definitions of predictive, diagnostic, and prognostic models. Thus, it is possible that predictive models relevant to our review were missed in the literature search if these were classified incorrectly. However, by keeping our search strategy relatively broad and acting under the guidance of a multidisciplinary steering committee, we tried to minimise

this risk. Additionally, despite our best efforts to minimise bias during screening and RoB assessments, there is a potential for subjectivity.

5. Conclusions

To our knowledge, 15 studies have developed and/or validated predictive models in mPCa to date. Existing predictive models are not suitable for use in clinical practice due to a lack of model performance evaluation and external validation. The models may be improved by conducting additional evaluation and validation, but the need for further high-quality, externally validated predictive models remains. Future research developing predictive models for mPCa should ensure sufficient patient numbers for their planned analysis, adequate handling of missing data, appropriate model evaluation, and extensive reporting of all steps taken throughout the model development process. This review supports PIONEER in their work to identify the best treatments for men diagnosed with PCa, across all disease stages.

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

Study concept and design: Lawlor, Beyer, Lin, Rivas, Remmers, Willemse, Van Hemelrijck.

Acquisition of data: Lawlor, Lin, Ibáñez, López, Rivas, Van Hemelrijck.

Analysis and interpretation of data: Lawlor, Lin, Ibáñez, López, Rivas, N'Dow, Van Hemelrijck.

Drafting of the manuscript: Lawlor, Omar, Lin, Ibáñez, López, Rivas, Van Hemelrijck.

Critical revision of the manuscript for important intellectual content: Lawlor, Beyer, Omar, Willemse, Remmers, Cornford, Rajwa, Nicoletti, Gandaglia, Teoh, Sierra, Golozar, Bjartell, Evans-Axelsson, N'Dow, Zong, Ribal, Roobol, Van Hemelrijck.

Statistical analysis: None.

Obtaining funding: Van Hemelrijck.

Administrative, technical, or material support: None.

Supervision: Van Hemelrijck.

Other: None.

Financial disclosures: Ailbhe Lawlor certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Susan Evans-Axelsson and Jihong Zong are employees of Bayer, which makes products used to treat PCa. The other authors declare no conflict of interest.

Funding/Support and role of the sponsor: This research is part of PIONEER—an international Big Data Consortium led by the European Association of Urology to answer key questions for men with PCa, funded through the IMI2 Joint Undertaking under grant agreement no.777492. IMI2 receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Acknowledgements: This project was conducted by a multidisciplinary group as part of the PIONEER Consortium. PIONEER brings together 36 key stakeholders from academic institutions, patient organisations, pharmaceutical companies, and world-leading clinical epidemiologists, urologists, data scientists, and health economists. Patients, their family members, and patient advocates are involved and actively participate in all research conducted by the PIONEER Consortium as an integral part of their goal to improve patient care in PCa.

Ethics statement: This study does not involve any human participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euro.2024.03.012>.

References

- [1] Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. *Genes Dev* 2018;32:1105–40.
- [2] Prostate Cancer Foundation. Hormone therapy for prostate cancer. [https://www.pcf.org/about-prostate-cancer/prostate-cancer-treatment/hormone-therapy-prostate-cancer/#:~:text=Hormone%20therapy%20\(also%20called%20androgen,acting%20on%20prostate%20cancer%20cellshttps://www.pcf.org/about-prostate-cancer/prostate-cancer-treatment/hormone-therapy-prostate-cancer/#:~:text=Hormone%20therapy%20\(also%20called%20androgen,acting%20on%20prostate%20cancer%20cells](https://www.pcf.org/about-prostate-cancer/prostate-cancer-treatment/hormone-therapy-prostate-cancer/#:~:text=Hormone%20therapy%20(also%20called%20androgen,acting%20on%20prostate%20cancer%20cellshttps://www.pcf.org/about-prostate-cancer/prostate-cancer-treatment/hormone-therapy-prostate-cancer/#:~:text=Hormone%20therapy%20(also%20called%20androgen,acting%20on%20prostate%20cancer%20cells).
- [3] Yamada Y, Beltran H. The treatment landscape of metastatic prostate cancer. *Cancer Lett* 2021;519:20–9.
- [4] James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163–77.
- [5] Chi KM, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2019;381:13–24.
- [6] Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* 2019;381:121–31.
- [7] Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737–46.
- [8] Mandel P, Hoeh B, Wenzel M, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer patients: a systematic review and network meta-analysis. *Eur Urol Focus* 2023;9:96–105.
- [9] Gómez Rivas J, Fernández Hernández L, Puente Vázquez J, et al. Where do we stand in the management of oligometastatic prostate cancer? A comprehensive review. *Cancer (Basel)* 2022;14:2017.
- [10] Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med* 2022;386:1132–42.
- [11] Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R, Fléchon A. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet* 2022;399:1695–707.
- [12] Aragon-Ching JB, Dreicer R. Treatment in hormone-sensitive metastatic prostate cancer: factors to consider when personalizing therapy. *Expert Rev Anticancer Ther* 2020;20:4578–86.
- [13] Tsao P, Caran MEV. Factors to guide treatment selection for hormone-sensitive metastatic prostate cancer. *Cancer J* 2020;26:76–82.
- [14] Achard V, Putora PM, Omlin A, Zilli T, Fischer S. Metastatic prostate cancer: treatment options. *Oncology* 2022;100:48–59.
- [15] Maskrey N. Shared decision making: why the slow progress? An essay by Neal Maskrey. *BMJ* 2019;367:l6762.
- [16] Omar MI, Roobol MJ, Ribal MJ, et al. Introducing PIONEER: a project to harness big data in prostate cancer research. *Nat Rev Urol* 2020;17:351–62.
- [17] van Smeden M, Reitsma JB, Riley RD, Collins GS, Moons KG. Clinical prediction models: diagnosis versus prognosis. *J Clin Epidemiol* 2021;132:142–5.
- [18] Kamiya N, Suzuki H, Nishimura K, et al. Development of nomogram to non-steroidal antiandrogen sequential alternation in prostate cancer for predictive model. *Jpn J Clin Oncol* 2014;44:263–9.
- [19] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
- [20] European Association of Urology. Prostate cancer. 2023. <https://uroweb.org/guidelines/prostate-cancer>.
- [21] Moons KGM, Wolff RF, Riley RD, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. *Ann Intern Med* 2019;170:W1–W.
- [22] Seyednasrollah F, Koeslter DC, Wang T, et al. A DREAM challenge to build prediction models for short-term discontinuation of docetaxel in metastatic castration-resistant prostate cancer. *JCO Clin Cancer Inform* 2017;1:1–15.
- [23] Miyoshi Y, Tsutsumi S, Yasui M, et al. A novel prediction model for the completion of six cycles of radium-223 treatment and survival in patients with metastatic castration-resistant prostate cancer. *World J Oncol* 2021;39:3323–8.
- [24] Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014;11:e1001744.
- [25] Cooperberg MR, Hinotsu S, Namiki M, et al. Risk assessment among prostate cancer patients receiving primary androgen deprivation therapy. *J Clin Oncol* 2009;27:4306–13.
- [26] Jacobson D, Cadieux B, Higano CS, et al. Risk factors associated with skeletal-related events following discontinuation of denosumab treatment among patients with bone metastases from solid tumors: a real-world machine learning approach. *J Bone Oncol* 2022;34:100423.
- [27] Flach PA, Kull M. Precision-recall-gain curves: PR analysis done right. In: Cortes CLN, Lee DD, Sugiyama M, Garnett R, editors. *Advances in neural information processing systems* 28. Massachusetts Institute of Technology (MIT) Press; 2015. p. 838–46.
- [28] Choi SY, Ryu J, You D, Hong JH, Ahn H, Kim CS. Simple risk assessment in prostate cancer patients treated with primary androgen deprivation therapy: The Korean Cancer Study of the Prostate Risk Classification. *Int J Urol* 2019;26:62–8.
- [29] Mahmoudian M, Seyednasrollah F, Koivu L, Hirvonen O, Jyrkkö S, Elo LL. A predictive model of overall survival in patients with metastatic castration-resistant prostate cancer. *F1000Res* 2016;16:2674.
- [30] Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. *J Urol* 2013;190:2047–53.
- [31] Anand A, Morris M, Larson SM, et al. Automated Bone Scan Index as a quantitative imaging biomarker in metastatic castration-resistant prostate cancer patients being treated with enzalutamide. *EJNMMI Res* 2016;6:23.
- [32] Mei JJ, Zhao YX, Jiang Y, Wang J, Yu JS. Association between contrast-enhanced ultrasound indicators and prostate cancer biochemical recurrence after treatment. *Cancer Manag Res* 2020;12:4959–68.
- [33] Zhao YX, Yao G, Sun J, et al. Nomogram incorporating contrast-enhanced ultrasonography predicting time to the development of castration-resistant prostate cancer. *Clin Med Insights Oncol* 2021;15:1–10.
- [34] Rho MJ, Park J, Moon HW, et al. Dr. Answer AI for prostate cancer: clinical outcome prediction model and service. *PLoS One* 2020;15:e0236553.
- [35] Yang YJ, Lin GW, Li GX, et al. External validation and newly development of a nomogram to predict overall survival of abiraterone-treated, castration-resistant patients with metastatic prostate cancer. *Asian J Androl* 2018;20:184–8.
- [36] Martini A, Parikh A, Sfakianos JP, et al. Predicting toxicity-related docetaxel discontinuation and overall survival in metastatic castration-resistant prostate cancer: a pooled analysis of open

- phase 3 clinical trial data. *Prostate Cancer Prostatic Dis* 2021;24:743–9.
- [37] Zhao J, Sun G, Liao B, et al. Novel nomograms for castration-resistant prostate cancer and survival outcome in patients with de novo bone metastatic prostate cancer. *BJU Int* 2018;122:994–1002.
- [38] Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem* 2008;54:17–23.
- [39] Beyer K, Moris L, Lardas M, et al. Diagnostic and prognostic factors in patients with prostate cancer: a systematic review. *BMJ Open* 2022;12:e058267.
- [40] Lin Q, Yang T, Yongmei J, Die YM. Prediction models for breast cancer-related lymphedema: a systematic review and critical appraisal. *Syst Rev* 2022;11:217.
- [41] Russo V, Lallo E, Munnia A, et al. Artificial intelligence predictive models of response to cytotoxic chemotherapy alone or combined to targeted therapy for metastatic colorectal cancer patients: a systematic review and meta-analysis. *Cancers (Basel)* 2022;14:4012.
- [42] DeBacker JR, McMillian GP, Martchenko N, et al. Ototoxicity prognostic models in adult and pediatric cancer patients: a rapid review. *J Cancer Surviv* 2023;17:82–100.
- [43] Beyer K, Moris L, Lardas M, et al. Updating and integrating core outcome sets for localised, locally advanced, metastatic, and nonmetastatic castration-resistant prostate cancer: an update from the PIONEER Consortium. *Eur Urol* 2022;81:503–14.