# Prognostic Value of Lactate Dehydrogenase in Metastatic Prostate Cancer: A Systematic Review and Meta-analysis

Keiichiro Mori,[1,2] Shoji Kimura,[1,2] Mehdi Kardoust Parizi,[1,3] Dmitry V. Enikeev,[10] Petr V. Glybochko,[10] Veronika Seebacher,[1] Harun Fajkovic,[1,8] Hadi Mostafaei,[1,4] Ivan Lysenko,[1] Florian Janisch,[1,5] Shin Egawa,[2] Shahrokh F. Shariat[1,6,7,8,9,10]

## Abstract

The purpose of this study was to assess the prognostic value of lactate dehydrogenase (LDH) in patients with metastatic prostate cancer (PC). A systematic review and meta-analysis was performed in March 2019 according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement. Studies were deemed eligible if they compared patients with PC with high versus low LDH to determine the predictive value of LDH for overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS). We performed a formal meta-analysis for both OS and PFS. A total of 59 articles with 14,851 patients were included in the systematic review and 45 studies with 12,224 patients for the qualitative assessment. High LDH was associated with both worse OS (pooled hazard ratio [HR], 2.07; 95% confidence interval [CI], 1.75-2.44) and PFS (pooled HR, 1.08; 95% CI, 1.01-1.16). In subgroup analyses of both patients with castration-resistant prostate cancer (CRPC) and those with hormone-sensitive prostate cancer (HSPC), LDH was associated with OS (pooled HR, 2.02; 95% CI, 1.69-2.42 and pooled HR, 2.25; 95% CI, 1.78-2.84, respectively). In patients with CRPC, LDH was associated with OS in those treated with docetaxel systemic chemotherapy and androgen receptor–axis-targeting agents (pooled HR, 2.03; 95% CI, 1.37-3.00 and pooled HR, 1.79; 95% CI, 1.25-2.57, respectively). Elevated serum levels of LDH were associated with an increased risk of mortality and progression in patients with metastatic PC. LDH was independently associated with OS in both patients with CRPC and HSPC. LDH could be integrated into prognostic tools that help guide treatment strategy, thereby facilitating the shared decision-making process.

*Clinical Genitourinary Cancer,* Vol. 17, No. 6, 409-18 © 2019 Published by Elsevier Inc.

**Keywords:** Castration-resistant prostate cancer (CRPC), Hormone-sensitive prostate cancer (HSPC), Lactate dehydrogenase (LDH), Meta-analysis, Metastatic prostate cancer

## Introduction

Prostate cancer (PC) is the most common solid cancer and the second most common cause of cancer-related death in men.[1] Systemic therapy based on androgen deprivation is the standard primary treatment strategy in patients with metastatic PC. Despite adequate therapy, the disease eventually progresses to a castration-resistant prostate cancer (CRPC).[2] To improve outcomes, prognostic tools have been developed to help in the daily clinical decision-making and for patient counseling.[3-6] These tools are based on standard clinical features and biomarkers such as prostate-specific antigen, hemoglobin, alkaline phosphatase, albumin, presence of liver metastasis, and performance status.[7] One of the biomarkers

[1]Department of Urology, Medical University of Vienna, Vienna, Austria
[2]Department of Urology, The Jikei University School of Medicine, Tokyo, Japan
[3]Department of Urology, Shariati Hospital, Tehran University of Medical Sciences, Teheran, Iran
[4]Department of Urology, Medical University of Hamburg, Hamburg, Germany
[5]Research Center for Evidence-based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Department of Urology, Weill Cornell Medical College, New York, NY
[7]Department of Urology, University of Texas Southwestern, Dallas, TX
[8]Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria
[9]Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic
[10]Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Submitted: Jun 6, 2019; Revised: Jul 3, 2019; Accepted: Jul 15, 2019; Epub: Jul 19, 2019

Address for correspondence: Shahrokh F. Shariat, MD, Währinger Gürtel 18-20, 1090, Vienna, Austria
E-mail contact: shahrokh.shariat@meduriwien.ac.at

1558-7673/$ - see frontmatter © 2019 Published by Elsevier Inc.
https://doi.org/10.1016/j.clgc.2019.07.009

often used as a reflection of tumor burden in oncology is lactate dehydrogenase (LDH).

LDH is known as a marker for tissue injury, inflammation, hemolysis, and myocardial infarction.[8-10] Many cancers have been found to have elevated LDH levels, and this has been shown to be of prognostic value in various solid and hematologic malignancies.[11-14] In PC, LDH has been reported to be significantly associated with oncologic outcomes, suggesting a possible role for serum LDH as a clinically useful prognostic biomarker. Serum LDH is a simple and inexpensive test that could serve as an objective prognostic parameter to improve daily oncologic clinical practice, plan follow-up, and counsel regarding outcomes to facilitate the shared decision-making process. Unfortunately, to date, the validity and reproducibility of the prognostic impact of LDH in PC remains insufficiently investigated. The aim of the current study was to summarize the available data in order to test the hypothesis that LDH has a strong prognostic value for oncologic outcomes in patients with metastatic PC. To this end, we performed a systematic review and a meta-analysis.

## Patients and Methods

### *Search Strategy*

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[15] We searched the electronic databases PubMed, Web of Science, Cochrane Library, and Scopus on March 2019 investigating the prognostic value of LDH in PC.

After a first screening based on study title and abstract, all papers were assessed based on full text and excluded with reasons when inappropriate; a further check of the appropriateness of the papers based on full-text revision was performed after data extraction. Two investigators (K.M. and S.K.) carried out this process independently. Disagreements were resolved by a consensus meeting with a third investigator (S.F.S.). The following keywords were used in our search strategy: (prostate cancer OR prostate carcinoma OR prostate tumor OR prostatic carcinoma OR prostatic cancer OR prostatic tumor) AND (LDH OR lactate dehydrogenase) AND (overall survival OR OS OR CSS OR cancer-specific survival OR mortality OR survival OR prognostic OR progression-free survival OR PFS OR oncologic outcome OR survival outcome). The primary outcome of interest was overall survival (OS), and the secondary outcomes were cancer-specific survival (CSS) and progression-free survival (PFS).

### *Inclusion and Exclusion Criteria*

Studies were included if they investigated whether patients with high LDH treated for PC (Patients) who had received systemic therapy (Intervention) as compared with those who had low LDH (Comparison) to assess the independent predictive value of LDH on OS, CSS, and PFS (Outcome) utilizing multivariable Cox regression analysis (Study design) in nonrandomized observational, or randomized or cohort studies. We excluded reviews, letters, editorials, meeting abstracts, replies from author, case reports, and articles not published in the English language. In case of duplicate publications, either the higher quality or the most recent publication was selected. References of included manuscripts were scanned for additional studies of interest.

### *Data Extraction*

Two investigators (K.M. and S.K.) independently extracted the information from the included articles. The information contained the following characteristics: first author's name, publication year, recruitment country, period of recruitment, number of patients, age, study design, disease stage, therapy type, oncologic outcome, follow-up duration, conclusion, and LDH cutoff. Subsequently, the hazard ratios (HRs) and 95% confidence intervals (CIs) of LDH associated with each of the outcomes were retrieved. The HRs were extracted from the multivariable analyses. All discrepancies regarding data extraction were resolved by consensus with a third investigator.

### *Quality Assessment*

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies according to the Cochrane Handbook for systematic reviews of interventions for included non-randomized studies.[16,17] The NOS focuses on Selection (score, 1-4), Comparability (score, 1-2), and Exposure (score, 1-3), with total scores ranging from 0 (lowest) to 9 (highest). The main confounders were defined as important predictors of OS, CSS, and PFS based on consensus between the investigators and a review of the literature. We defined "high-quality" studies as studies with scores of $> 6$.

### *Statistical Analyses*

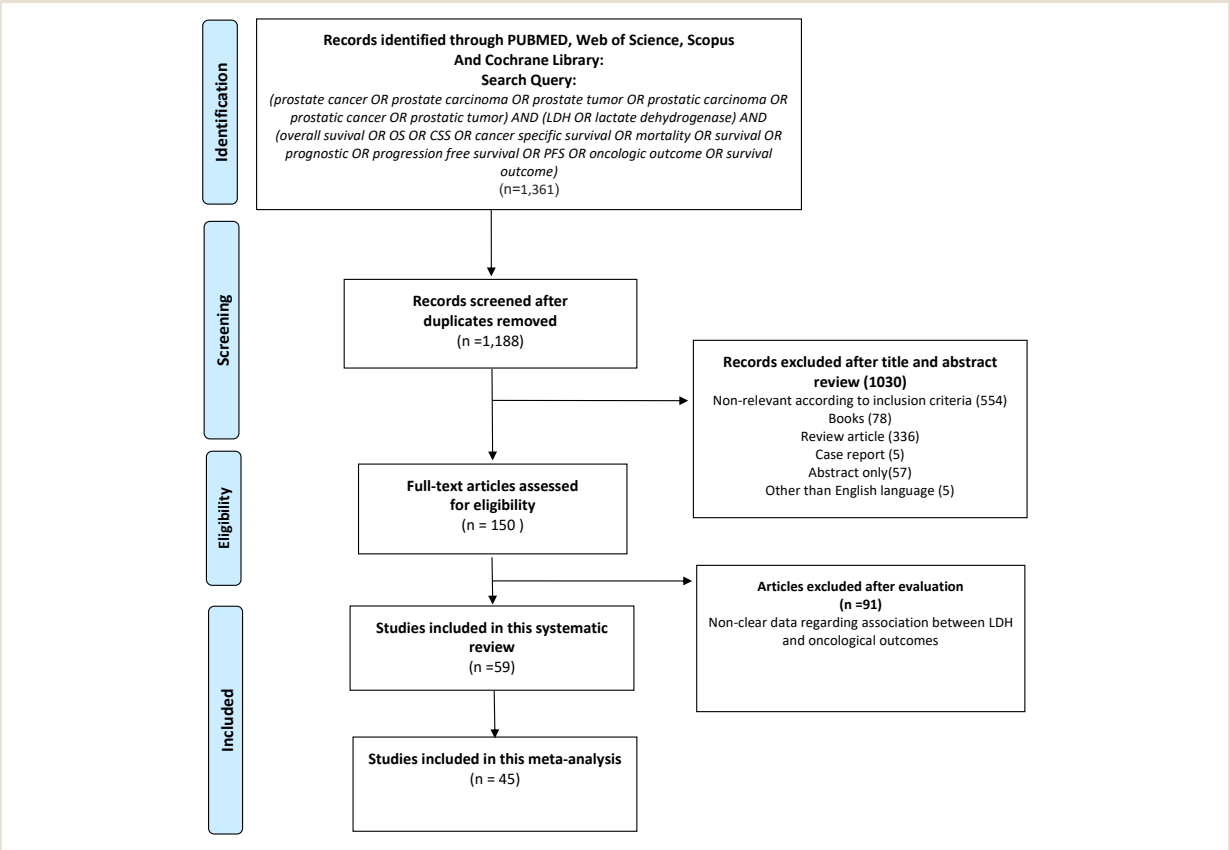
We performed a forest plot to assess HRs from the multivariable analyses of individual studies and obtained a summary HR of the value of LDH on OS and PFS. Studies with Kaplan-Meier log-rank, univariable Cox proportional hazard regression, or general logistic regression analyses were not considered for meta-analysis. We also performed subgroup analyses in patients with CRPC or hormone-sensitive prostate cancer (HSPC). In addition, we performed subgroup analyses in patients with CRPC treated with androgen receptor-axis (AR)-targeting agents (ie, enzalutamide or abiraterone) or docetaxel. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated by using the Cochrane Q test and $I^2$ statistic. Significant heterogeneity was indicated by a $P < .05$ in Cochrane Q tests and a ratio $> 50\%$ in $I^2$ statistics, which led to the use of random-effect models. We used fixed-effects models for calculation of pooled HRs for non-heterogeneous results.[18-20] Publication bias was assessed by funnel plots. Statistical analyses were all performed using Stata/MP 14.2 (Stata Corp, College Station, TX); the statistical significance level was set at $P < .05$.

## Results

### *Study Selection and Characteristics*

Our initial search identified 1361 records. After removal of duplicates, 1188 remained (Figure 1). After screening the titles and abstracts, 1030 articles were excluded. Then, we assessed 158 full texts for further selection. After assessment, the remaining 59 articles with 14,851 patients were included in the systematic review and 45 studies with 12,224 patients for qualitative meta-analysis.[4,21-78] The baseline characteristics of the 59 studies are outlined in Table 1. All included studies were published between 1993 and 2019, with 19 being from Europe, 21 from North America, and 19 from Asia. The median age ranged from 57.3 to 80 years; 47 articles with 12,726 (85.7%) patients

**Figure 1** The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Chart for Article Selection Process to Analyze the Prognostic Value of Lactate Dehydrogenase in Prostate Cancer and Oncologic Outcomes




with CRPC and 12 articles with 2125 (14.3%) patients with HSPC were included. The presence of visceral metastasis ranged from 0% to 47.9%. Studies were heterogeneous regarding the cutoff value for LDH, which ranged from 193 to 546 for OS and from 206 to 546 for PFS; follow-up ranged from 7.2 to 58.3 months.

### *Association of LDH With OS in Metastatic PC*

Forty-three studies including 11,590 patients provided data on the association of LDH with OS in PC. The forest plot (Figure 2A) showed that LDH was significantly associated with OS in PC (pooled HR, 2.07; 95% CI, 1.75-2.44; z = 8.59). The Cochrane Q test ($\chi^2$ = 512.69; $P$ = .000) and $I^2$ test ($I^2$ = 91.8%) showed significant heterogeneity. The funnel plot identified 28 studies over the pseudo 95% CI (Figure 2A).

### *Association of LDH With PFS in Metastatic PC*

Twelve studies including 2587 patients provided data on the association of LDH with PFS in PC. The forest plot (Figure 2B) showed that LDH was significantly associated with PFS in PC (pooled HR, 1.08; 95% CI, 1.01-1.16; z = 2.40). The Cochrane Q test ($\chi^2$ = 63.15; $P$ = .000) and $I^2$ test ($I^2$ = 82.6%) showed significant heterogeneity. The funnel plot identified 6 studies over the pseudo 95% CI (Figure 2B).

### *Association of LDH With OS in HSPC*

Seven studies including 1029 patients provided data on the association of LDH with OS in HSPC. The forest plot (Figure 3A) showed that LDH was significantly associated with OS in HSPC (pooled HR, 2.25; 95% CI, 1.78-2.84; z = 7.33). The Cochrane Q test ($\chi^2$ = 7.07; $P$ = .622) and $I^2$ test ($I^2$ = 0.0%) showed no significant heterogeneity. Funnel plot analysis did not identify any publication bias (Figure 3A).

### *Association of LDH With OS in CRPC*

Thirty-six studies including 10,561 patients provided data on the association of LDH with OS in CRPC. The forest plot (Figure 3B) showed that LDH was significantly associated with OS in CRPC (pooled HR, 2.02; 95% CI, 1.69-2.42; z = 7.76). The Cochrane Q test ($\chi^2$ = 473.37; $P$ = .000) and $I^2$ test ($I^2$ = 92.6%) showed significant heterogeneity. The funnel plot identified 25 studies over the pseudo 95% CI (Figure 3B).

### *Association of LDH With PFS in CRPC*

Eleven studies including 2248 patients provided data on the association of LDH with PFS in CRPC. The forest plot (Figure 3C) showed that LDH was not significantly associated with PFS in CRPC (pooled HR, 1.06; 95% CI, 0.99-1.78; z = 1.76). The Cochrane Q test ($\chi^2$ = 53.65; $P$ = .000) and $I^2$ test ($I^2$ = 81.4%)

**Table 1** Baseline Characteristics of the 59 Studies in the Systematic Review

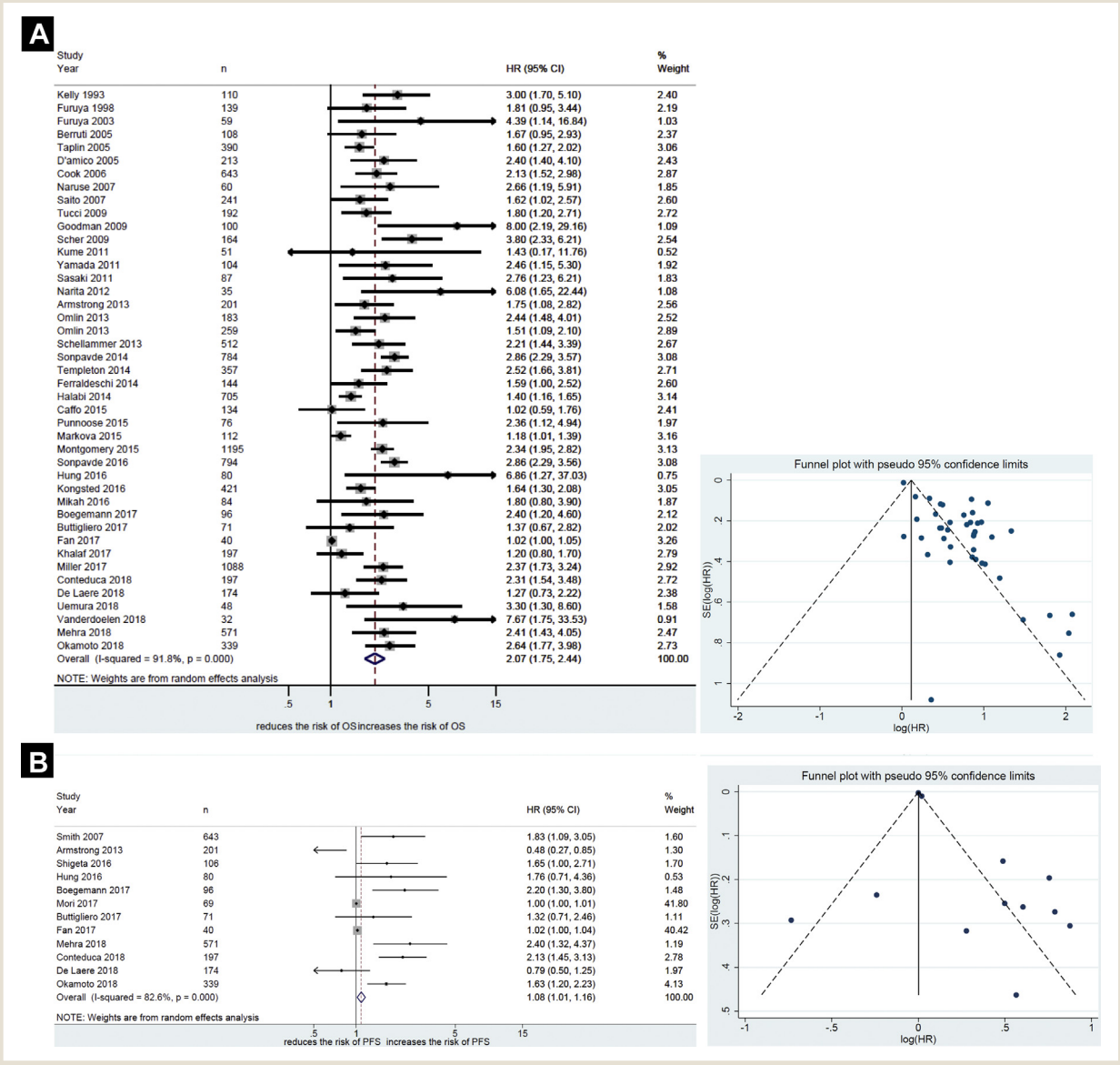
| Author | Year | Country | Recruitment Period | Design | N | Outcome | Age, y | Metastasis | Visceral Metastasis, % | Treatment | Follow-up, mos | Conclusion | Cut off (U/L) | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CPRC** | | | | | | | | | | | | | | |
| Kelly | 1993 | USA | 1987-1991 | R | 110 | OS | C | M1 | 24.6 | C | 18 | P | 230 | 5 |
| Pienta | 1997 | USA | 1993-1996 | P | 62 | OS | 67 | M1 | 4.8 | C | NR | N | NR | 5 |
| Berruti | 2005 | Italy | 1998-2003 | P | 108 | OS | 74 | M1 | 10.2 | E | NR | N | 398 | 6 |
| D'amico | 2005 | USA | 1996-2001 | P | 213 | OS | 72 | M1 | NR | C, E | 15 | P | Continuous | 6 |
| Taplin | 2005 | USA | 1996-1998 | P | 390 | OS | 70 | M1 | 13.0 | E | NR | P | 208.5 | 6 |
| Cook | 2006 | Canada | 1998-2001 | R | 643 | OS | 71.7 | M1 | NR | B | 24 | P | 454 | 6 |
| Smith | 2007 | USA | 1998-2001 | R | 643 | PFS | 72 | M1 | NR | B | 24 | P | 454 | 6 |
| Goodman | 2009 | USA | 2007-2008 | P | 100 | OS | 71 | M1 | NR | C | 26 | P | NR | 6 |
| Scher | 2009 | USA | 2004-2006 | P | 164 | OS | 70 | M1 | 37.8 | C | NR | P | NR | 6 |
| Tucci | 2009 | Italy | 1990-2003 | R | 192 | OS | 73 | M1 | 10.4 | C, E | 38 | P | NR | 7 |
| Kume | 2011 | Japan | 2004-2010 | R | 51 | OS | NR | M1 | NR | C | NR | N | Upper normal limit | 6 |
| Narita | 2012 | Japan | 2003-2009 | P | 35 | OS | 68 | M1 | 17.1 | C | NR | P | 193 | 5 |
| Aparicio | 2013 | USA | 2006-2010 | P | 114 | OS, PFS | 64 | M1 | 16.7 | C | 39.1 | P | 546 | 6 |
| Armstrong | 2013 | USA | 2007-2009 | P | 201 | OS, PFS | 72 | M1 | NR | I | 37 | P | 204 | 7 |
| Kamiya | 2013 | Japan | 2005-2011 | R | 145 | CSS | 69.7 | M0, M1 | NR | C | NR | N | 211 | 6 |
| Omlin | 2013 | UK | 2003-2011 | R | 183 | OS | 62 | M1 | 9.3 | C | NR | P | NR | 6 |
| Omlin | 2013 | UK | 2003-2011 | R | 259 | OS | 62.1 | M1 | 4.2 | E | NR | P | NR | 6 |
| Schellammer | 2013 | USA | 2003-2007 | R | 512 | OS | 71 | M1 | 0.0 | I | 34.1 | P | NR | 7 |
| Halabi | 2014 | USA | 2005-2007 | R | 705 | OS | 69 | M1 | 16.7 | C | NR | P | Upper normal limit | 6 |
| Sonpavde | 2014 | USA | 2008-2010 | R | 784 | OS | 68 | M1 | 29.7 | M | NR | P | Upper normal limit | 6 |
| Templeton | 2014 | Canada | 2001-2011 | R | 357 | OS | 71 | M1 | 19.0 | C | NR | P | Upper normal limit × 1.2 | 6 |
| Caffo | 2015 | Italy | 2002-2013 | R | 134 | OS | 57 | M1 | 23.1 | C | 19 | N | 382 | 6 |
| Ferraldeschi | 2015 | UK | 2006-2013 | R | 144 | OS | 68 | M1 | 17.4 | E | 16 | P | Upper normal limit | 6 |
| Markova | 2015 | Russia | 2005-2014 | R | 112 | OS | 66.1 | M1 | 10.7 | C, E | NR | P | 450 | 6 |
| Montgomery | 2015 | USA | 2008-2009 | R | 1195 | OS | 69 | M1 | 9.9 | E | NR | P | Upper normal limit | 6 |
| Punnoose | 2015 | UK | 2012-2013 | P | 76 | OS | 68.9 | M1 | 15.8 | E | NR | P | Upper normal limit | 6 |
| Hung | 2016 | USA | NR | R | 80 | OS, PFS | 64.6 | M1 | 8.8 | E | NR | P | NR | 6 |
| Kongsted | 2016 | Denmark | 2007-2013 | R | 421 | OS | 70 | M1 | NR | C | 52.2 | P | Upper normal limit | 7 |
| Mikah | 2016 | Germany | 2009-2014 | R | 84 | OS | 69 | M1 | 20.2 | E | 14 | N | Upper normal limit | 6 |
| Shigeta | 2016 | Japan | 2007-2014 | R | 106 | PFS | 73 | M1 | 27.4 | C | NR | P | 206 | 6 |
| Sonpavde | 2016 | USA | 2008-2012 | R | 610 | OS | NR | M1 | 27.0 | E | NR | P | Upper normal limit | 6 |
| Boegemann | 2017 | Germany | 2009-2015 | R | 96 | OS, PFS | 70 | M1 | 28.1 | E | 20 | P | Upper normal limit | 6 |

**Table 1** Continued

| Author | Year | Country | Recruitment Period | Design | N | Outcome | Age, y | Metastasis | Visceral Metastasis, % | Treatment | Follow-up, mos | Conclusion | Cut off (U/L) | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Buttigliero | 2017 | Italy | 2004-2016 | R | 71 | OS, PFS | 68 | M1 | 15.6 | C | 31.7 | N | Upper normal limit | 7 |
| Fan | 2017 | China | 2013-2016 | R | 40 | OS, PFS | 72 | M1 | NR | E | 20.2 | P | Continuous | 6 |
| Khalaf | 2017 | Canada | 2009-2014 | R | 197 | OS | 80 | M1 | 2.5 | E | NR | N | Upper normal limit | 6 |
| Miller | 2017 | Germany | 2009-2010 | R | 1088 | OS | 70 | M1 | NR | E | 49.2 | P | Continuous | 7 |
| Mori | 2017 | Japan | 2014-2016 | R | 69 | PFS | 75 | M0, M1 | 15.9 | E | 14 | P | Continuous | 6 |
| Rahbar | 2017 | Germany | 2014-2016 | R | 104 | OS | 70 | M1 | 34.6 | R | NR | N | 225 | 5 |
| Sartor | 2017 | USA | 2008-2011 | R | 473 | OS | NR | M1 | NR | R | NR | P | NR | 6 |
| Conteduca | 2018 | Italy | 2013-2015 | R | 197 | OS, PFS | 73 | M1 | 17.4 | E | 32.4 | P | 225 | 6 |
| De Laere | 2018 | Belgium | 2013-2017 | P | 174 | OS, PFS | 74 | M1 | 17.8 | E | NR | N | Continuous | 6 |
| Heck | 2018 | Germany | 2014-2017 | R | 100 | OS, PFS | 72 | M1 | 35.0 | R | NR | P | 50 U/L change | 6 |
| Mehra | 2018 | UK | 2011-2013 | P | 571 | OS, PFS | NR | M1 | 25.0 | C | NR | P | NR | 6 |
| Miyake | 2018 | Japan | 2014-2017 | R | 74 | OS | NR | M1 | 16.2 | C | 14 | P | 290 | 6 |
| Mori | 2018 | Japan | 2014-2017 | R | 114 | OS | 77 | M0, M1 | 6.1 | E | 23 | N | Continuous | 5 |
| Oh | 2018 | USA | 2011-2014 | R | 345 | OS | NR | M1 | NR | C, E | NR | P | Upper normal limit | 5 |
| Uemura | 2018 | Japan | 2014-2016 | R | 48 | OS | 71.2 | M1 | 47.9 | C | 7.2 | P | 262 | 6 |
| Vanderdoelen | 2018 | Netherland | 2013-2016 | R | 32 | OS | 71 | M1 | 8.9 | R | NR | P | 250 | 6 |
| **HSPC** | | | | | | | | | | | | | | |
| Furuya | 1998 | Japan | 1986-1993 | R | 139 | OS | 73.6 | M1 | NR | E | 36.9 | N | Upper normal limit | 7 |
| Nakashima | 2000 | Japan | NR | R | 74 | OS | 73.3 | M1 | NR | E | NR | N | 200 | 6 |
| Furuya | 2003 | Japan | 1990-1999 | R | 59 | OS | 72.9 | M1 | NR | E | 25.3 | P | Upper normal limit | 6 |
| Naruse | 2007 | Japan | 1998-2003 | R | 60 | OS | 72 | M1 | NR | E | 36 | P | Upper normal limit | 6 |
| Saito | 2007 | Japan | 1992-2004 | R | 241 | OS | 72.3 | M1 | 7.4 | E | 31 | P | 400 | 7 |
| Goodman | 2011 | USA | 2007-2009 | P | 33 | PFS | 70 | M1 | NR | E | NR | N | NR | 6 |
| Sasaki | 2011 | Japan | 2000-2009 | R | 87 | OS | 75 | M1 | NR | E | 37.8 | P | 250 | 7 |
| Yamada | 2011 | Japan | 1998-2006 | R | 104 | OS | 74 | M1 | NR | E | 43 | P | Upper normal limit | 7 |
| Gravis | 2015 | France | 2004-2008 | R | 385 | OS | 63 | M1 | 13.2 | C,E | 58.3 | P | Upper normal limit | 6 |
| Okamoto | 2018 | Japan | 2005-2017 | R | 339 | OS, CSS, PFS | 72 | M1 | 12.6 | E | 26 | P | 222 | 6 |
| Miyake | 2019 | Japan | 2010-2017 | R | 437 | OS | NR | M1 | 3.4 | E | 46.5 | N | 300 | 7 |
| Shimodaira | 2019 | Japan | 1999-2012 | R | 167 | PFS | 74.8 | M1 | NR | E | 54.3 | P | 240 | 6 |

Abbreviations: B = bone modifying agent; C = chemotherapy; CRPC = castration-resistant prostate cancer; CSS = cancer-specific survival; E = endocrine therapy; HSPC = hormone-sensitive prostate cancer; I = immunotherapy; M = molecular targeted therapy; N (Conclusion) = negative; NOS = The Newcastle Ottawa Scale; NR = not reported; OS = overall survival; P (Conclusion) = positive; P (Design) = prospective; PFS = progression-free survival; R (Design) = retrospective; R (treatment) = radiotherapy.

**Figure 2** Forest and Funnel Plots Showing the Association of Lactate Dehydrogenase With Oncologic Outcomes in all Prostate Cancer: A, Overall Survival; B, Progression-free Survival




Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

showed significant heterogeneity. The funnel plot identified 3 studies over the pseudo 95% CI (Figure 3C).

### *Association of LDH With OS in Patients Treated With AR-targeting Agents for CRPC*

Ten studies including 3295 patients provided data on the association of LDH with OS in CRPC treated with AR-targeting agents. The forest plot (Figure 3C) showed that LDH was significantly associated with OS in CRPC treated with AR-targeting agents (pooled HR, 1.79; 95% CI, 1.25-2.57; z = 3.20). The Cochrane Q test ($\chi^2$ = 134.48; $P$ = .000) and $I^2$ test ($I^2$ = 93.3%) showed significant heterogeneity. The funnel plot identified 3 studies over the pseudo 95% CI (Figure 4A).

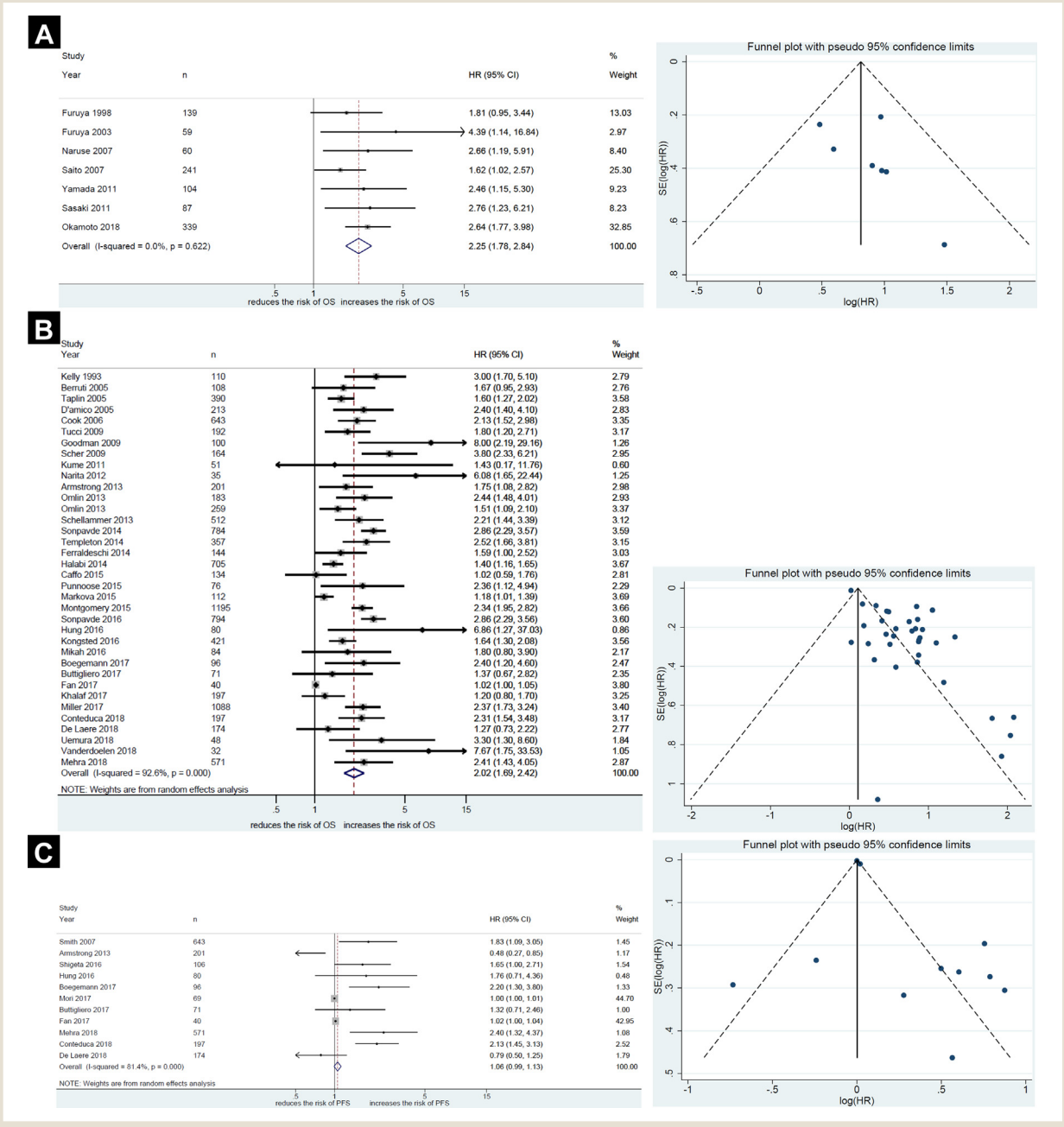
### *Association of LDH With OS in Patients Treated With Cocetaxel for CRPC*

Nine studies including 1852 patients provided data on the association of LDH with OS in CRPC treated with docetaxel. The forest plot (Figure 3C) showed that LDH was significantly associated with OS in CRPC treated with docetaxel (pooled HR, 2.03; 95% CI, 1.37-3.00; z = 3.55). The Cochrane Q test ($\chi^2$ = 19.79; $P$ = .003) and $I^2$ test ($I^2$ = 69.7%) showed significant heterogeneity. The funnel plot identified 2 studies over the pseudo 95% CI (Figure 4B).

## Discussion

In this systematic review and meta-analysis, we investigated the prognostic value of LDH in metastatic PC by assessing its impact on

**Figure 3** Forest and Funnel Plots Showing the Association of Lactate Dehydrogenase With Oncologic Outcomes: A, OS in Hormone-sensitive Prostate Cancer; B, OS in Castration-resistant Prostate Cancer; C, PFS in Castration-resistant Prostate Cancer

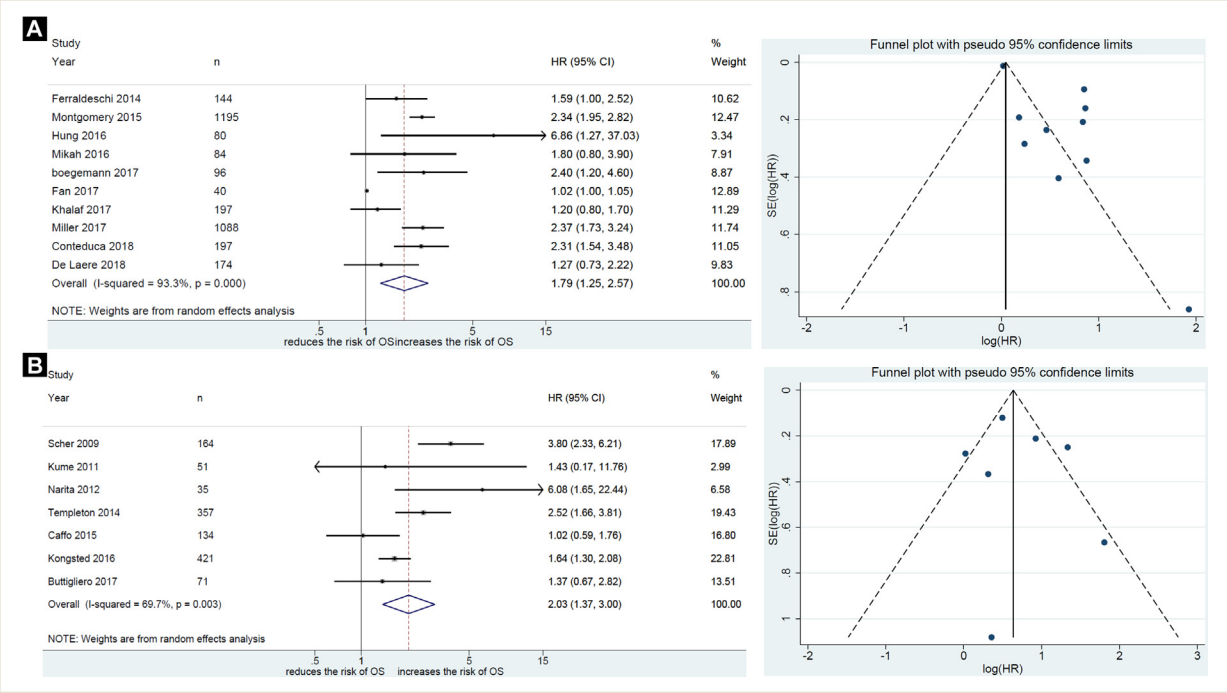



Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

PFS, CSS, and OS. We found that metastatic PC patients with elevated LDH have significantly worse OS and PFS compared with their counterparts with normal LDH levels.

The prognostic value of LDH has been shown in various solid and hematologic malignancies.[11-14] There is a strong biological rationale underlying this association; however, the exact mechanism remains poorly understood. One potential explanation could be the association between LDH and the well-established phenomenon of oncogenic anaerobic glycolysis (ie, the Warburg effect).[79,80] This metabolic reprogramming is regulated by hypoxia-inducible factor-1α, as well as MYC, through the transcriptional activation of key genes encoding metabolic enzymes; these include LDH, which converts pyruvate to lactate.[81-83] This process is closely associated with an increased risk of tumor growth, invasion, metastasis, and patient death. As a result, elevated LDH levels are observed in patients with cancer, and the prognostic value of LDH has been

**Figure 4** Forest and Funnel Plots Showing the Association of Lactate Dehydrogenase With Oncologic Outcomes: A, OS in Castration-resistant Prostate Cancer Treated With Androgen Receptor-axis-targeting Agents; B, OS in Castration-resistant Prostate Cancer Treated With Docetaxel




Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival.

shown in various aggressive malignancies. In the current literature, LDH is already included in several prognostic tools used for prognosticating PC outcomes.[3-7]

Interestingly, LDH was significantly associated with worse OS in patients with metastatic HSPC. In other words, pre-treatment LDH values may be a useful biomarker in the choice of treatment even in early metastatic PC, suggesting that LDH is an indirect measure of tumor burden and not a direct measure of biological potential of the individual cell. Although few studies have assessed this patient subgroup, LDH could be used to select patients who may benefit more from intensive therapy such as upfront docetaxel or abiraterone in addition to androgen deprivation therapy. In addition, LDH could be used as a response/monitoring marker.

Subgroup analysis also revealed that elevated LDH is associated with worse OS in patients with metastatic CRPC. Interestingly, it was associated with worse OS in both patients treated with docetaxel and AR-targeting agents, limiting its use in the evaluation of therapy options in these patients. Intensive therapy such as combination therapy may be needed in patients with CRPC with elevated LDH levels as a biomarker of early treatment failure; it could help select patients most likely to benefit from combination therapy.

Despite showing a strong association of LDH with mortality and progression in patients with metastatic PC, this systematic review and meta-analysis has some limitations. There is a reporting bias as some studies with negative results may not have been published. Further, many included studies were retrospective, resulting in a bias in patient selection. In addition, we only included studies reporting HRs from the multivariable analyses, whereas some studies with Kaplan-Meier log-rank, univariable Cox proportional hazard regression, or general logistic regression analyses were not considered for meta-analysis, possibly introducing bias. Second, unknown pretreatment conditions (ie, infective symptoms, physical conditions, comorbidities, heart failure, anemia, hypothyroidism, and hepatitis, medication, and life-style habits) could have altered LDH values, leading to a systematic bias. Third, heterogeneity was detected for OS and PFS in overall and subgroup analyses, limiting the value of these results. Although the random effect model takes into account the heterogeneity among studies, the conclusions should be interpreted with caution. Fourth, there is no established cutoff value for LDH among the included studies; most investigators chose the cutoff based on statistical methods assessing for the highest sensitivity and specificity, using upper normal limit, or using literature-predefined LDH cutoffs. Only 6 studies investigated LDH as a continuous variable. Regardless of these limitations, LDH is a fast and easily available biomarker that is accessible. Well-designed prospective studies with longer follow-up are needed to validate the prognostic value of LDH and its potential value in risk stratification of patients with metastatic PC using clinical decision-analytical tools.

## Conclusions

In this meta-analysis, high serum LDH was associated with an increased risk of overall mortality and disease progression in patients with metastatic PC. Furthermore, LDH was an independent factor for OS in patients with both metastatic CRPC and HSPC. LDH was also an independent factor for OS in patients with metastatic CRPC treated with both AR-targeting agents and docetaxel. LDH could help in clinical decision-making regarding treatment selection and patient counseling.

## Disclosure

The authors have stated that they have no conflicts of interest.

## References


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; 68: 7-30.
2. Kluth LA, Shariat SF, Kratzik C, et al. The hypothalamic-pituitary-gonadal axis and prostate cancer: implications for androgen deprivation therapy. *World J Urol* 2014; 32:669-76.
3. Chi KN, Kheoh T, Ryan CJ, et al. A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. *Ann Oncol* 2016; 27:454-60.
4. Halabi S, Lin C-Y, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2014; 32:671-7.
5. Shariat SF, Kattan MW, Vickers AJ, Karakiewicz PI, Scardino PT. Critical review of prostate cancer predictive tools. *Future Oncol* 2009; 5:1555-84.
6. Armstrong AJ, Garrett-Mayer E, de Wit R, Tannock I, Eisenberger M. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res* 2010; 16:203-11.
7. Shariat SF, Semjonow A, Lilja H, Savage C, Vickers AJ, Bjartell A. Tumor markers in prostate cancer I: blood-based markers. *Acta Oncol* 2011; 50(Suppl 1):61-75.
8. Drent M, Cobben NA, Henderson RF, Wouters EF, van Dieijen-Visser M. Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. *Eur Respir J* 1996; 9:1736-42.
9. Kemp M, Donovan J, Higham H, Hooper J. Biochemical markers of myocardial injury. *Br J Anaesth* 2004; 93:63-73.
10. Kato GJ, McGowan V, Machado RF, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. *Blood* 2006; 107: 2279-85.
11. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999; 17:2530-40.
12. Balch CM, Soong SJ, Atkins MB, et al. An evidence-based staging system for cutaneous melanoma. *CA Cancer J Clin* 2004; 54:131-49, quiz: 182-4.
13. Chibaudel B, Bonnetain F, Tournigand C, et al. Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: a GERCOR study. *Oncologist* 2011; 16: 1228-38.
14. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol* 1997; 15:594-603.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6:e1000100.
16. Deeks JJ, Dinnes J, D'Amico R, et al, International Stroke Trial Collaborative Group, European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; 7, iii-x, 1-173.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603-5.
18. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* 2007; 28:105-14.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7:177-88.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557-60.
21. Kelly WK, Scher HI, Mazumdar M, Vlamis V, Schwartz M, Fossa SD. Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 1993; 11:607-15.
22. Pienta KJ, Redman BG, Bandekar R, et al. A phase II trial of oral estramustine and oral etoposide in hormone refractory prostate cancer. *Urology* 1997; 50:401-6, discussion: 406-7.
23. Berruti A, Mosca A, Tucci M, et al. Independent prognostic role of circulating chromogranin A in prostate cancer patients with hormone-refractory disease. *Endocr Relat Cancer* 2005; 12:109-17.
24. D'Amico AV, Chen MH, Cox MC, Dahut W, Figg WD. Prostate-specific antigen response duration and risk of death for patients with hormone-refractory metastatic prostate cancer. *Urology* 2005; 66:571-6.
25. Taplin ME, George DJ, Halabi S, et al. Prognostic significance of plasma chromogranin a levels in patients with hormone-refractory prostate cancer treated in Cancer and Leukemia Group B 9480 study. *Urology* 2005; 66:386-91.
26. Cook RJ, Coleman R, Brown J, et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin Cancer Res* 2006; 12: 3361-7.
27. Smith MR, Cook RJ, Coleman R, et al. Predictors of skeletal complications in men with hormone-refractory metastatic prostate cancer. *Urology* 2007; 70: 315-9.
28. Goodman OB Jr, Fink LM, Symanowski JT, et al. Circulating tumor cells in patients with castration-resistant prostate cancer baseline values and correlation with prognostic factors. *Cancer Epidemiol Biomarkers Prev* 2009; 18:1904-13.
29. Scher HI, Jia X, de Bono JS, et al. Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. *Lancet Oncol* 2009; 10:233-9.
30. Tucci M, Mosca A, Lamanna G, et al. Prognostic significance of disordered calcium metabolism in hormone-refractory prostate cancer patients with metastatic bone disease. *Prostate Cancer Prostatic Dis* 2009; 12:94-9.
31. Kume H, Suzuki M, Fujimura T, et al. Docetaxel as a vital option for corticosteroid-refractory prostate cancer. *Int Urol Nephrol* 2011; 43:1081-7.
32. Narita S, Tsuchiya N, Yuasa T, et al. Outcome, clinical prognostic factors and genetic predictors of adverse reactions of intermittent combination chemotherapy with docetaxel, estramustine phosphate and carboplatin for castration-resistant prostate cancer. *Int J Clin Oncol* 2012; 17:204-11.
33. Aparicio AM, Harzstark AL, Corn PG, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. *Clin Cancer Res* 2013; 19:3621-30.
34. Armstrong AJ, Häggman M, Stadler WM, et al. Long-term survival and biomarker correlates of tasquinimod efficacy in a multicenter randomized study of men with minimally symptomatic metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2013; 19:6891-901.
35. Kamiya N, Suzuki H, Ueda T, et al. Clinical outcomes by relative docetaxel dose and dose intensity as chemotherapy for Japanese patients with castration-resistant prostate cancer: a retrospective multi-institutional collaborative study. *Int J Clin Oncol* 2014; 19:157-64.
36. Omlin A, Pezaro C, Mukherji D, et al. Improved survival in a cohort of trial participants with metastatic castration-resistant prostate cancer demonstrates the need for updated prognostic nomograms. *Eur Urol* 2013; 64:300-6.
37. Schellhammer PF, Chodak G, Whitmore JB, Sims R, Frohlich MW, Kantoff PW. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology* 2013; 81:1297-302.
38. Sonpavde G, Pond GR, Armstrong AJ, et al. Prognostic impact of the neutrophil-to-lymphocyte ratio in men with metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2014; 12:317-24.
39. Templeton AJ, Pezaro C, Omlin A, et al. Simple prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil-to-lymphocyte ratio. *Cancer* 2014; 120:3346-52.
40. Caffo O, Ortega C, Di Lorenzo G, et al. Clinical outcomes in a contemporary series of "young" patients with castration-resistant prostate cancer who were 60 years and younger. *Urol Oncol* 2015; 33, 265.e15-21.
41. Ferraldeschi R, Nava Rodrigues D, Riisnaes R, et al. PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. *Eur Urol* 2015; 67:795-802.
42. Markova AS, Polikarpova SB, Kamolov BS, et al. Predictors of overall survival in patients with metastatic castration-resistant prostate cancer. *Onkourologiya* 2015; 11:77-84.
43. Montgomery B, Kheoh T, Molina A, et al. Impact of baseline corticosteroids on survival and steroid androgens in metastatic castration-resistant prostate cancer: exploratory analysis from COU-AA-301. *Eur Urol* 2015; 67:866-73.
44. Punnoose EA, Ferraldeschi R, Szafer-Glusman E, et al. PTEN loss in circulating tumour cells correlates with PTEN loss in fresh tumour tissue from castration-resistant prostate cancer patients. *Br J Cancer* 2015; 113:1225-33.
45. Hung J, Taylor AR, Divine GW, Hafron JM, Hwang C. The effect of time to castration resistance on outcomes with abiraterone and enzalutamide in metastatic prostate cancer. *Clin Genitourin Cancer* 2016; 14:381-8.
46. Kongsted P, Svane IM, Lindberg H, Sengelov L. Predictors of chemotherapy-induced toxicity and treatment outcomes in elderly versus younger patients with metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2016; 14: e559-68.
47. Mikah P, Krabbe LM, Eminaga O, et al. Dynamic changes of alkaline phosphatase are strongly associated with PSA-decline and predict best clinical benefit earlier than PSA-changes under therapy with abiraterone acetate in bone metastatic castration resistant prostate cancer. *BMC Cancer* 2016; 16:214.
48. Shigeta K, Kosaka T, Kitano S, et al. High absolute monocyte count predicts poor clinical outcome in patients with castration-resistant prostate cancer treated with docetaxel chemotherapy. *Ann Surg Oncol* 2016; 23:4115-22.
49. Sonpavde G, Pond GR, Templeton AJ, Kwon ED, de Bono JS. Impact of single-agent daily prednisone on outcomes in men with metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis* 2017; 20:67-71.
50. Boegemann M, Schlack K, Thomes S, et al. The role of the neutrophil to lymphocyte ratio for survival outcomes in patients with metastatic castration-resistant prostate cancer treated with abiraterone. *Int J Mol Sci* 2017; 18.

51. Buttigliero C, Pisano C, Tucci M, et al. Prognostic impact of pretreatment neutrophil-to-lymphocyte ratio in castration-resistant prostate cancer patients treated with first-line docetaxel. *Acta Oncol* 2017; 56:555-62.
52. Fan L, Wang Y, Chi C, et al. Chromogranin A and neurone-specific enolase variations during the first 3 months of abiraterone therapy predict outcomes in patients with metastatic castration-resistant prostate cancer. *BJU Int* 2017; 120: 226-32.
53. Khalaf DJ, Aviles CM, Azad AA, et al. A prognostic model for stratifying clinical outcomes in chemotherapy-naive metastatic castration-resistant prostate cancer patients treated with abiraterone acetate. *Can Urol Assoc J* 2018; 12:E47-52.
54. Miller K, Carles J, Gschwend JE, Van Poppel H, Diels J, Brookman-May SD. The phase 3 COU-AA-302 study of abiraterone acetate plus prednisone in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: stratified analysis based on pain, prostate-specific antigen, and Gleason score. *Eur Urol* 2018; 74:17-23.
55. Mori K, Kimura T, Onuma H, et al. Lactate dehydrogenase predicts combined progression-free survival after sequential therapy with abiraterone and enzalutamide for patients with castration-resistant prostate cancer. *Prostate* 2017; 77:1144-50.
56. Rahbar K, Boegemann M, Yordanova A, et al. PSMA targeted radioligandtherapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging* 2018; 45:12-9.
57. Sartor O, Coleman RE, Nilsson S, et al. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223. *Ann Oncol* 2017; 28:1090-7.
58. Conteduca V, Scarpi E, Salvi S, et al. Plasma androgen receptor and serum chromogranin A in advanced prostate cancer. *Sci Rep* 2018; 8:15442.
59. De Laere B, Oeyen S, Van Oyen P, et al. Circulating tumor cells and survival in abiraterone- and enzalutamide-treated patients with castration-resistant prostate cancer. *Prostate* 2018; 78:435-45.
60. Heck MM, Tauber R, Schwaiger S, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with (177)Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. *Eur Urol* 2019; 75:920-6.
61. Mehra N, Dolling D, Sumanasuriya S, et al. Plasma cell-free DNA concentration and outcomes from taxane therapy in metastatic castration-resistant prostate cancer from two phase III trials (FIRSTANA and PROSELICA). *Eur Urol* 2018; 74:283-91.
62. Miyake H, Matsushita Y, Watanabe H, et al. Significance of De Ritis (aspartate transaminase/alanine transaminase) ratio as a significant prognostic but not predictive biomarker in Japanese patients with metastatic castration-resistant prostate cancer treated with cabazitaxel. *Anticancer Res* 2018; 38:4179-85.
63. Mori K, Kimura T, Ito K, et al. Earlier use of androgen receptor-axis-targeted drugs may improve overall survival in patients with non-metastatic castration-resistant prostate cancer. *Prostate* 2018; 78:766-72.
64. Oh WK, Miao R, Vekeman F, et al. Real-world characteristics and outcomes of patients with metastatic castration-resistant prostate cancer receiving chemotherapy versus androgen receptor-targeted therapy after failure of first-line androgen receptor-targeted therapy in the community setting. *Clin Genitourin Cancer* 2018; 16:50-7.
65. Uemura K, Miyoshi Y, Kawahara T, et al. Prognostic value of an automated bone scan index for men with metastatic castration-resistant prostate cancer treated with cabazitaxel. *BMC Cancer* 2018; 18:501.
66. Vandekerkhove G, Chi KN, Wyatt AW. Clinical utility of emerging liquid biomarkers in advanced prostate cancer. *Cancer Genet* 2018; 228-9:151-8.
67. Furuya Y, Akimoto S, Akakura K, et al. Response of prostate-specific antigen after androgen withdrawal and prognosis in men with metastatic prostate cancer. *Urol Int* 1998; 60:28-32.
68. Nakashima J, Tachibana M, Horiguchi Y, et al. Serum interleukin 6 as a prognostic factor in patients with prostate cancer. *Clin Cancer Res* 2000; 6:2702-6.
69. Furuya Y, Nagakawa O, Fuse H. Prognostic significance of changes in short-term prostate volume and serum prostate-specific antigen after androgen withdrawal in men with metastatic prostate cancer. *Urol Int* 2003; 70:195-9.
70. Naruse K, Yamada Y, Aoki S, et al. Lactate dehydrogenase is a prognostic indicator for prostate cancer patients with bone metastasis. *Hinyokika Kiyo* 2007; 53:287-92.
71. Saito T, Hara N, Kitamura Y, Komatsubara S. Prostate-specific antigen/prostatic acid phosphatase ratio is significant prognostic factor in patients with stage IV prostate cancer. *Urology* 2007; 70:702-5.
72. Goodman OB Jr, Symanowski JT, Loudyi A, Fink LM, Ward DC, Vogelzang NJ. Circulating tumor cells as a predictive biomarker in patients with hormone-sensitive prostate cancer. *Clin Genitourin Cancer* 2011; 9:31-8.
73. Sasaki T, Onishi T, Hoshina A. Nadir PSA level and time to PSA nadir following primary androgen deprivation therapy are the early survival predictors for prostate cancer patients with bone metastasis. *Prostate Cancer Prostatic Dis* 2011; 14:248-52.
74. Yamada Y, Nakamura K, Aoki S, et al. Lactate dehydrogenase, Gleason score and HER-2 overexpression are significant prognostic factors for M1b prostate cancer. *Oncol Rep* 2011; 25:937-44.
75. Gravis G, Boher JM, Fizazi K, et al. Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the Glass model and development of a novel simplified prognostic model. *Eur Urol* 2015; 68:196-204.
76. Okamoto T, Hatakeyama S, Narita S, et al. Impact of nutritional status on the prognosis of patients with metastatic hormone-naive prostate cancer: a multicenter retrospective cohort study in Japan. *World J Urol* 2018.
77. Miyake H, Matsushita Y, Watanabe H, et al. Prognostic significance of time to castration resistance in patients with metastatic castration-sensitive prostate cancer. *Anticancer Res* 2019; 39:1391-6.
78. Shimodaira K, Nakashima J, Nakagami Y, et al. Prognostic value of platelet counts in patients with metastatic prostate cancer treated with endocrine therapy. *Urol J* 2019.
79. Warburg O. On the origin of cancer cells. *Science* 1956; 123:309-14.
80. Hsu PP, Sabatini DM. Cancer cell metabolism: Warburg and beyond. *Cell* 2008; 134:703-7.
81. Vaupel P, Mayer A. Hypoxia in tumors: pathogenesis-related classification, characterization of hypoxia subtypes, and associated biological and clinical implications. *Adv Exp Med Biol* 2014; 812:19-24.
82. Scartozzi M, Giampieri R, Maccaroni E, et al. Pre-treatment lactate dehydrogenase levels as predictor of efficacy of first-line bevacizumab-based therapy in metastatic colorectal cancer patients. *Br J Cancer* 2012; 106:799-804.
83. Armstrong AJ, George DJ, Halabi S. Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin. *J Clin Oncol* 2012; 30:3402-7.