Prognostic value of serum alkaline phosphatase in the survival of prostate cancer: evidence from a meta-analysis

Dongyang Li¹, *, Hang Lv², *, Xuanyu Hao³, Bin Hu², Yongsheng Song¹
¹Department of Urology, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, P.R. China; ²Department of Urology, Liaoning Cancer Hospital & Institute, Cancer Hospital of China Medical University, Shenyang, Liaoning 110042, P.R. China; ³Department of Rheumatology and Immunology, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110022, P.R. China
*These authors contributed equally to this work

Background: Many studies have evaluated the relationship between alkaline phosphatase (ALP) and the prognosis for prostate cancer (PCa). But they have not reached a widespread consensus yet. Therefore, we completed a meta-analysis to ascertain the significance of ALP and the prognosis for PCa.

Methods: A literature search was performed in the PubMed, Embase, and Web of Science databases. HRs concerning overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS) were extracted to evaluate the impacts of ALP on the prognosis for PCa. Subgroup analyses were conducted on different study types, regions, sample sizes, and cutoff values. Sensitivity analysis was performed by removing one study in sequence.

Results: A total of 63 studies from 54 articles with 16,135 patients were included in this meta-analysis. The pooled results indicated that high baseline ALP was associated with obviously poor OS (HR=1.74, 95% CI: 1.47–2.06) and PFS (HR=1.60, 95% CI: 1.13–2.26) in patients with PCa. The pooled HR for bone-specific ALP and OS was 1.76 (95% CI: 1.45–2.15). However, no association between ALP and CSS (HR=1.002, 95% CI: 0.998–1.005) was found for PCa. The results of subgroup analyses were all in accordance with the main findings. Sensitivity analysis suggested that no single study could affect the stability of the results.

Conclusion: High serum ALP is significantly associated with poor OS and PFS except for CSS in PCa. ALP is an efficient and convenient biomarker for PCa prognosis.

Keywords: prostate cancer, alkaline phosphatase, prognosis, survival, meta-analysis

Introduction
Prostate cancer (PCa) is the most common malignancy in western males.¹ It is estimated that 164,690 new PCa cases and 29,430 PCa-related deaths will occur in 2018 in USA.¹ So far, prostate-specific antigen (PSA) has been mostly used for early detection and recurrence evaluation as a biomarker. Gleason score is a classical prognostic factor but not sufficient to portray the complexity of clinical prognosis.² The heterogeneous genomic property of PCa can lead to the difficulty in survival prognosis and therapy monitoring. Therefore, there is an urgent need for novel effective parameters to predict outcomes for treatment decision. Recently, a number of biomarkers about PCa have been investigated and established in patient cohort studies.³–⁶ In comparison with cancer tissues, serum is an ideal source of biomarkers because of the convenience in routine clinical measurement.⁷ Scientists have been trying for decades to seek the biomarkers among the different kinds of molecules such as proteins, noncoding RNAs, and chemical compounds.⁸ Interestingly, we notice that alkaline phosphatase (ALP), a classical parameter, also has a great potential in the prognosis of PCa.
The enzyme ALP can physiologically dephosphorylate compounds under alkaline pH environment. Serum ALP level is a widely used parameter for liver disease, bone disease burden, and treatment effects. It is acknowledged that the elevation in ALP level is positively related to the rise of bone activity like osteosarcoma. Therefore, we speculate that bone metastatic cancer may also lead to the rising of serum ALP, given that bone is the most common metastatic site of PCa. Over 85% patients died from bone metastasis among PCa-related deaths. So, can we identify the relationship between ALP and different survival outcomes in patients with PCa?

Up to now, the prognostic performance of ALP in patients with PCa has been discussed in many studies; however, these studies have yielded some conflicting conclusions. The aim of this study was to quantitatively and comprehensively derive a more precise prognostic estimation of ALP in patients with PCa by a meta-analysis.

Methods

Search strategy

This meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive literature search in the PubMed, Embase, and Web of Science was conducted from the databases onset to February 5, 2018. The key words were as follows: (“prostate neoplasms” OR “prostate cancer”) AND “alkaline phosphatase” or “ALP” AND (“prognosis” OR “survival”). The language of studies was not restricted. Additional relevant publications were also manually searched based on the reference lists.

Study selection

Inclusion and exclusion criteria

Studies were included only if they met the following criteria: 1) clinical cohort/trial evaluated the prognostic ability of ALP in PCa; 2) studies compared ALP with other prognostic models and reported survival outcomes such as overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS); 3) reported original HR with 95% CI or the HR could be calculated from sufficient data; 4) articles with the most complete information if there were several studies among overlapping cohorts or time periods.

The exclusion criteria were 1) duplicate publications; 2) studies based on less than 20 patients; 3) laboratory studies, animal studies, letters, or review articles.

Assessment of study quality

Two investigators (DL and XH) independently reviewed all the relevant articles, then evaluated the methodological quality of observational studies using Newcastle–Ottawa Quality Assessment Scale (NOS) assessment tool, including selection, comparability, and outcomes. The Jadad composite scale was utilized to assess randomized controlled trials (RCTs). The NOS score ≥7 or Jadad score ≥4 indicated high quality. Disagreements in data collection and quality assessment were resolved through consensus by involving a third author (HL).

Data extraction

The baseline and outcome data were obtained from each study: first author’s surname, year of publication, study design, country, sample size, age, PSA level, cutoff value, follow-up time, outcomes, and HRs with 95% CI. If the HRs of both univariate and multivariate analysis were available, only the latter was used.

Statistical analysis

HRs with 95% CI from all eligible studies were pooled via a meta-analysis to access the strength of ALP to survival endpoints. The Cochran Q test was used to determine the heterogeneity among studies. A P value <0.10 indicated heterogeneity. The inconsistency (I²) was also calculated to evaluate heterogeneity. An I² value >50% indicated the presence of statistical heterogeneity. The random-effect model (DerSimonian and Laird method) was used to calculate pooled results when there was heterogeneity among included studies; otherwise, the fixed-effect model was used. To seek deeper relationship between ALP and OS, we conducted subgroup analyses on study type, cutoff value, sample size, and region of study. Furthermore, to test the reliability of the results, sensitivity analysis was conducted by removing each single study in turn. Begg’s test with funnel plots was used to measure publication bias. The P value >0.05 indicated no potential publication bias. The Stata 12.0 software (StataCorp, College Station, TX, USA) was used to perform all the statistical analyses. A two-sided P value <0.05 was considered as statistically significant.

Results

Studies selection and evaluation

The flowchart of articles searching process is shown in Figure 1. A total of 1,107 relevant citations were initially retrieved by the search strategy as described above in
PubMed, Embase, and Web of Science. Seven hundred forty duplicate articles were removed. Among the remaining 367 articles, 286 were further excluded for unrelated information and not clinical research articles. Eighty-one potential articles were screened carefully, 27 articles were ruled out because of lack of essential data of survival outcome or overlapping cohorts. If there were multiple outcomes in the same article, we considered them as different studies. Finally, 63 studies from 54 articles published between 1995 and 2017 encompassing 16,135 patients were included in the meta-analysis, with the sample size ranging from 30 to 1,183 patients (Table 1). The characteristics of the included studies are summarized in Table 1. The median length of follow-up varied from 8.3 to 63.4 months. Prognostic outcomes were quantitatively synthesized, including OS, CSS, and PFS. A total of 36 observational studies and five RCTs had available data for the OS analysis, while seven studies reported HRs for CSS, and nine studies reported HRs for PFS. The quality assessment results of the 54 eligible articles shown in Table S1 revealing the NOS score were equal or greater than 6 in all 48 observational studies and the Jadad score was over 4 in all six RCTs.

**Overall analysis**

**Meta-analysis on OS**

There were 33 observational studies presenting the data of ALP and OS. The random effects model was used to analyze the relationship between them. The pooled HR was 1.74 (95% CI: 1.47–2.06, Figure 2A) with significant heterogeneity between studies ($I^2=96.1\%, P<0.001$), which demonstrated
### Table 1 Baseline characteristics of included studies

| Study ID          | Country     | Duration       | Type     | Sample size | Median age (years) | Median serum PSA (ng/mL) |
|-------------------|-------------|----------------|----------|-------------|-------------------|-------------------------|
| Halabi et al 2013 | USA         | 2007–2008      | RCT      | 488         | 70 (63–75)        | 118 (40.3–370.2)         |
| Goldkorn et al 2014 | USA       | NR             | RCT      | 470         | 69 (63–76)        | 68 (13–355)             |
| Scheihammer et al 2013 | USA | 2003–2009       | RCT      | 512         | 71               | 50.1                    |
| Humphrey et al 2006 | USA        | 1996–1998      | RCT      | 390         | 70 (64–75)        | 129 (50–339)            |
| Halabi et al 2014  | USA         | NR             | RCT      | 705         | 69               | 79                      |
| Qu et al 2013     | China       | 2005–2011      | Re       | 115         | 68 (51–82)        | 90.5 (0.1–4,066)        |
| Mikah et al 2016  | Germany     | 2009–2014      | Re       | 84          | 69 (62.3–76)      | 174 (55–500)            |
| Klaff et al 2016  | Sweden      | 1992–1997      | Pro      | 319         | 69               | 233                     |
| Miyamoto et al 2012 | Japan    | 1992–2002      | Pro      | 94          | 72.5 (47–90)      | 1,015.6 (8.5–18,948)    |
| Kita et al 2013   | Japan       | 2005–2008      | Re       | 57          | 71 (57–80)        | 51.3 (0.03–1,450)       |
| Bilen et al 2017  | USA         | 2010–2012      | Re       | 48          | 67 (51–84)        | 8.9 (2–477)             |
| Omlin et al 2013  | UK          | 2003–2011      | Re       | 183         | 62 (41.8–77.3)    | 120 (0.97–11,343)       |
| Nakashima et al 2004 | Japan  | NR             | Pro      | 114         | 73               | NR                      |
| Templeton et al 2014 | UK         | 2001–2011      | Re       | 357         | 71 (44–90)        | 162 (56–496)            |
| van Soest et al 2015 | the Netherlands | 2011–2014   | Re       | 114         | 68 (49–83)        | 182 (12.5–5,000)        |
| Sonpavde et al 2014 | USA       | 2008–2010      | Pro      | 873         | 68 (39–90)        | 130 (0.1–5,927)         |
| Halabi et al 2003  | USA         | 1992–1998      | Pro      | 760         | 71               | 126                     |
| Shiota et al 2014 | Japan       | 2008–2013      | Re       | 97          | 71 (51–85)        | 136.9 (3.1–10,860)      |
| Oh et al 2017     | USA         | 2011–2014      | Re       | 629         | 72               | 310                     |
| Brasso et al 2006 | Denmark     | 1993–1996      | Re       | 153         | 72 (54–89)        | 270 (10–7,730)          |
| Chi et al 2016    | Canada      | 2008–2009      | Pro      | 762         | 69 (42–95)        | 128.8 (0.4–9,253.0)     |
| Nozawa et al 2015 | Japan       | 2008–2010      | Pro      | 52          | 72 (55–86)        | 249.4                   |
| Penta et al 1997  | USA         | 1993–1996      | Pro      | 62          | 67 (47–80)        | 378 (0.7–2,007)         |
| Reynard et al 1995 | UK         | 1986–1993      | Pro      | 85          | 71 (47–89)        | NR                      |
| Thatai et al 2004 | USA         | 1991–2001      | Pro      | 145         | 70 (52–82)        | NR                      |
| Vesalainen et al 1995 | Finland  | 1971–1992      | Pro      | 188         | 71.5 (39.9–92)    | NR                      |
| Etchebehere et al 2016 | USA     | 2013–2015      | Pro      | 110         | 70 (43–89)        | 37 (0.4–2,433)          |
| George et al 2003 | USA         | 1996–1998      | Pro      | 197         | 68 (62–75)        | 150 (48–418)            |
| Butticelli et al 2017 | Italy    | 2004–2016      | Re       | 71          | 68 (48–85)        | 47 (0.2–3.310)          |
| Shigeta et al 2016 | Japan       | 2007–2014      | Re       | 106         | 73 (52–95)        | 31.7 (0.3–751.45)       |
| Wyatt et al 2004  | USA         | 1988–1995      | Re       | 380         | 65.1             | NR                      |
| Ramankulov et al 2007 | Germany   | NR             | Pro      | 90          | 64               | 25.4                    |
| Sonpavde et al 2012 | Canada  | 2000–2002      | Pro      | 601         | 68 (36–92)        | 144 (0.06–4,740)        |
| Halabi et al 2004  | USA         | 1992–2002      | Pro      | 1,183       | 71 (65–76)        | 106 (37–310)            |
| Oh et al 2011    | USA         | 1998–2006      | Pro      | 302         | 62               | 22.6 (5.2–95.1)         |
| Izumi et al 2012 | Japanese    | 2006–2010      | Pro      | 30          | 65.5 (46–83)      | 200 (6–4,370)           |
| Hammerich et al 2017 | USA       | 1989–2010      | Re       | 89          | 62.4 (6.7)        | 6.7 (0.8–53.2)          |
| Cook et al 2006  | USA         | 1998–2001      | RCT      | 278         | 71.7 (7.9)        | 282 (839)               |
| Park et al 2012  | Korea       | 2003–2009      | Re       | 55          | 72.5±7.6         | 209.2±424.5             |
| Yamada et al 2010 | Japan       | 1998–2006      | Re       | 454         | 74               | 268.7                   |
| Kamiya et al 2010 | Japan       | 2002–2008      | Re       | 58          | 69.8±2.7         | 1,402±2,055.3           |
| Mohammed et al 2015 | Saudi Arabia | 2011–2015     | Re       | 71          | 72±8.7           | 54 (0.1–16,430)         |
| Akimoto et al 1997 | Japan      | 1979–1992      | Re       | 56          | 71.8             | NR                      |
| Koo et al 2015    | Korea       | 2002–2012      | Re       | 248         | NR               | NR                      |
| Kato et al 2016   | Japan       | 2002–2012      | Re       | 181         | 73               | 328                     |
| Treatment                                    | Median follow-up (months) | Cutoff value (U/L) | HR | 95% CI          | Outcome | Multivariate analysis | Study quality (NOS score) |
|---------------------------------------------|---------------------------|-------------------|----|-----------------|---------|-----------------------|--------------------------|
| Docetaxel                                   | 15                        | NR                | 1.02 | 0.96–1.07       | OS      | Yes                   | 7 (Jadad)                |
| Docetaxel                                   | 24                        | NR                | 1.06 | 0.88–1.27       | OS      | Yes                   | 8 (Jadad)                |
| Sipuleucel-T                                | 51.7                      | 131               | 1.25 | 1.03–1.510      | OS      | Yes                   | 7 (Jadad)                |
| Suramin                                     | 35                        | 170               | 1.713 | 1.204–2.437     | OS      | Yes                   | 8 (Jadad)                |
| Docetaxel                                   | 24                        | NR                | 1.16 | 1.00–1.30       | OS      | Yes                   | 8 (Jadad)                |
| Docetaxel                                   | 40                        | 110               | 1.934 | 1.112–3.363     | OS      | Yes                   | 7                        |
| Abiraterone                                 | 14                        | NR                | 1.4  | 0.8–2.5         | OS      | No                    | 6                        |
| Hormonal therapy                            | 75.6                      | NR                | 1.16 | 0.76–1.75       | OS      | Yes                   | 7                        |
| Hormonal therapy                            | 38.8                      | 440               | 2.16 | 1.01–4.62       | OS      | Yes                   | 7                        |
| Docetaxel                                   | 20.5                      | 260               | 2.39 | 1.12–5.10       | OS      | Yes                   | 7                        |
| Sipuleucel-T                                | 28                        | 90                | 8.7  | 1.7–46          | OS      | Yes                   | 7                        |
| Postchemotherapy                            | 40                        | NR                | 1.29 | 1.02–1.64       | OS      | Yes                   | 7                        |
| Hormonal therapy                            | 40                        | 620               | 1.28 | 0.608–2.695     | OS      | Yes                   | 6                        |
| Docetaxel                                   | 18                        | 300               | 1.58 | 1.01–2.45       | OS      | Yes                   | 7                        |
| Cabazitaxel                                 | 24                        | 125               | 1.65 | 1.06–2.57       | OS      | Yes                   | 7                        |
| Sunitinib                                   | 15                        | NR                | 1.13 | 0.99–1.28       | OS      | Yes                   | 7                        |
| Mitoxantrone                                | 37                        | 172               | 1.23 | 1.12–1.36       | OS      | Yes                   | 7                        |
| Docetaxel                                   | 25                        | 360               | 10.26 | 2.04–39.74     | OS      | Yes                   | 7                        |
| Cabazitaxel                                 | 18                        | 300               | 1.58 | 1.01–2.45       | OS      | Yes                   | 7                        |
| Hormonal therapy                            | 58                        | 275/BAP           | 1.7  | 1.4–2.1         | OS      | No                    | 6                        |
| Abiraterone                                 | 30                        | 160               | 2.02 | 1.69–2.41       | OS      | No                    | 7                        |
| Bicalutamide or hormonal therapy             | 26                        | 300               | 12.7 | 8.6–15.4        | OS      | No                    | 6                        |
| Estramustine                                | 13                        | 115               | 0.878 | 0.62–1.280     | OS      | No                    | 6                        |
| Acetate                                     | 30                        | NR                | 3.1  | 1.2–8.2         | OS      | Yes                   | 6                        |
| Chemotherapy                                | 10.5                      | 185               | 1    | 0.6–1.4         | PFS     | No                    | 6                        |
| Hormonal therapy                            | 36                        | 275               | 1.008 | 1.002–1.011    | OS      | Yes                   | 6                        |
| Radium 233                                  | 8.3                       | 146               | 2.02 | 1.31–3.12       | PFS     | No                    | 7                        |
| Chemotherapy                                | 14                        | 170               | 1.6  | 1.05–2.14       | OS      | Yes                   | 7                        |
| Docetaxel                                   | 31.7                      | 113               | 0.71 | 0.37–1.39       | PFS     | Yes                   | 7                        |
| Docetaxel                                   | 36                        | 284               | 1.651 | 1.04–2.621     | PFS     | Yes                   | 7                        |
| Chemotherapy                                | 13.9                      | NR                | 1.11 | 0.95–1.34       | OS      | Yes                   | 7                        |
| Hormonal therapy                            | 40                        | 205/BAP           | 2.54 | 0.42–15.3       | OS      | Yes                   | 7                        |
| Docetaxel                                   | 36                        | 120               | 1.64 | 1.28–2.10       | OS      | No                    | 6                        |
| Androgen deprivation therapy and antiandrogen withdrawal | 14                        | NR                | 1.29 | 1.18–1.40       | OS      | Yes                   | 7                        |
| Orchietectomy                               | 79.2                      | 102               | 1.72 | 1.17–2.52       | OS      | Yes                   | 7                        |
| Zoledronic acid                             | 17 (4–49)                 | 47/BAP            | 6.391 | 0.660–61.89     | OS      | Yes                   | 7                        |
| Androgen deprivation therapy                | 63.4                      | NR                | 4.47 | 1.56–12.76      | OS      | Yes                   | 7                        |
| Prior cytotoxic chemotherapy, radiation therapy | 24                        | 267.5/BAP         | 1.49 | 1.17–1.90       | OS      | Yes                   | 8 (Jadad)                |
| Docetaxel                                   | 32.2±18.3                 | NR                | 14.112 | 4.235–75.045   | CSS     | Yes                   | 7                        |
| Endocrine therapy                           | 43                        | NR                | 1.829 | 0.881–3.798     | CSS     | Yes                   | 7                        |
| NR                                         | 35.0±24.6                 | 683.4             | 5.55 | 0.919–33.513    | CSS     | Yes                   | 6                        |
| NR                                         | 14.4                      | (0.1–44.1)        | 1.001 | 1.000–1.002    | CSS     | Yes                   | 6                        |
| Endocrine therapy                           | NR                        | 206               | 1.533 | 0.747–3.144    | CSS     | Yes                   | 7                        |
| NR                                         | 39.9                      | 200               | 1.002 | 1.001–1.003    | CSS     | Yes                   | 6                        |
| Androgen deprivation therapy                | 38                        | 398               | 1.42 | 0.88–2.30       | CSS     | Yes                   | 6                        |

(Continued)
There was a significant relationship between ALP and OS. However, the pooled HR was 1.15 (95% CI: 1.02–1.30, Figure 2B), which demonstrates a significant relationship among five RCTs. There were three studies comparing the decrease in serum ALP level and OS, whose pooled HR was 0.56 (95% CI: 0.42–0.75, Figure 3A). Besides, five studies investigated the relationship between bone-specific ALP (BAP) and OS in patients with PCa. The pooled HR for BAP and OS is 1.65 (95% CI: 1.41–1.92, Figure 3B).

Meta-analysis on CSS

Seven studies provided sufficient data on ALP and CSS outcome. The pooled HR was 1.002 (95% CI: 0.998–1.005) via a random effects model, and the potential heterogeneity among studies was observed ($P<0.001$, Figure 4A).

Meta-analysis on PFS

Nine studies reported the data concerning the association between ALP and PFS. Meta-analysis adopting the random effects model revealed that elevated ALP was significantly associated with shorter PFS (HR=1.60, 95% CI: 1.13–2.26) with potential heterogeneity ($P=82.1\%$, $P<0.001$, Figure 4B).

Subgroup analyses

Moreover, we conducted a subgroup meta-analysis on different study designs. Although the main results were not affected by different study design, heterogeneity still existed in both prospective cohorts (HR=1.76, 95% CI: 1.42–2.19, Figure S1A) and retrospective studies (HR=1.58, 95% CI: 1.24–2.00, Figure S1B). In epidemiological studies, ethnicity difference was usually recognized as a critical source of bias. Notably, we also found the elevated serum ALP was significantly associated with poor OS among the studies in Asia (Figure S1C), Europe (Figure S1D), and North America (Figure S1E). Furthermore, we performed subgroup analysis in different cutoff values (Figure S1F, G) and sample sizes (Figure S1H, I). To sum up, the pooled HRs indicated that higher ALP was significantly associated with poorer OS in all subgroups of patients with PCa (Table 2).

Sensitivity analysis

The sensitivity analysis was performed by the sequential deletion of any individual article to measure the effects of each individual study. The results showed that the overall HRs were not significantly influenced by individual study, as shown in Figure 5, indicating the robustness of the results in our meta-analysis.

Assessment of publication bias

Begg’s test was performed to evaluate the publication bias of the inclusion studies (Figure 6). The $P$-values of Begg’s test for OS (observational studies and RCTs) were 0.747 and 0.086, respectively, indicating that there was no significant publication bias.

Discussion

Serum ALP level is a simple and rapid laboratory test in routine clinical practice. An ideal prognostic biomarker can be used to determine prognosis, monitor response to therapy, and postoperative surveillance. The high ALP level has been...
reported related to the poor survival in colorectal cancer. The elevation of ALP is also an independent risk factor in the bone metastasis of gastric cancer and bladder cancer. However, the underlying mechanisms of ALP in patients with PCa remain unclear. A possible explanation is that when the PCa starts metastasis, ALP reflects bone turnover, osteoblast activity, and the osteoid formation in adjacent bone tissues. Thus, ALP may be an indicator of bone metastatic tumor load.

In this meta-analysis, based on the existing data from 63 included studies, the pooled results indicated that high baseline ALP was associated with obviously poor OS and PFS (HR = 1.60, 95% CI: 1.13–2.26) in patients with PCa. As presented in Table 1, most included studies used multivariate cox model to explore ALP and survival. After being adjusted for other factors such as tumor stage/grade, PSA, Gleason score, hemoglobin, and metastasis, the original results of ALP were objective and reliable. The meta-analysis on both observational studies (HR = 1.74, 95% CI: 1.47–2.06) and RCTs (HR = 1.15, 95% CI: 1.02–1.30) reached the consistent conclusions about ALP and OS. In addition, high serum BAP was also significantly related to poor OS (HR = 1.76, 95% CI: 1.42–2.15). However, our result revealed that there was no association between ALP and CSS in patients with PCa (HR = 1.002, 95% CI: 0.998–1.005). We hypothesize that ALP is more sensitive in reflecting bone metastasis, so, high serum ALP is significantly associated with PFS of PCa. PCa patients with bone metastasis and other underlying diseases may lead to poorer OS. Whereas the seven studies about CSS...
Figure 2 Forest plot of pooled HR and 95% CI of high ALP and OS prognosis.

Notes: (A) Observational cohorts; (B) RCTs.

Abbreviations: ALP, alkaline phosphatase; OS, overall survival; RCT, randomized controlled trial; ES, effect size.
Figure 3 Forest plot of pooled HR of low ALP (A) or bone-specific ALP (B) and OS prognosis.

Abbreviations: ALP, alkane phosphatase; OS, overall survival; ES, effect size.
Figure 4 Forest plot of pooled HR and 95% CI of high ALP and CSS (A) or PFS (B) prognosis.

**Abbreviations:** ALP, alkaline phosphatase; CSS, cancer-specific survival; PFS, progression-free survival; ES, effect size.
Figure 5 Sensitivity analyses of high ALP and OS prognosis.

Notes: (A) Observational cohorts; (B) RCTs.

Abbreviations: ALP, alkaline phosphatase; OS, overall survival; RCT, randomized controlled trial.
(Figure 4A) were all retrospective in the study design. The sample size was also relatively smaller for CSS than OS. Thus, we should carefully interpret the result of ALP and CSS. The results of subgroup analyses on different study types, regions, cutoff values, and sample sizes were all in accordance with the main findings. The sensitivity analysis and publication bias tests’ outcomes also supported our results. Therefore, we may recommend ALP as a valuable prognostic marker for PCa treatment decision and adjustment. Compared with the positron emission tomography-computed tomography, ALP combined with bone scintigraphy may also be useful to assess the metastatic burden and survival possibility of PCa with a remarkably less expensive cost.

To our knowledge, this is the first meta-analysis on ALP and the prognosis of PCa. However, there are still a couple of limitations to be stated. First, although the language was not restricted during the searching process, all the included studies were in English, which might lead to language bias. Second, although sensitivity analysis supported the stability of our results, the findings should be cautiously interpreted. Heterogeneity among studies was found in overall and subgroup analyses. It was probably owing to multivariate factors in some included studies. Third, the data of ALP on other prognostic clinical parameters such as metastasis and all-cause mortality are lacking at present. Meanwhile, the retrospective design in 23 included studies (Table 1) may cause potential recall bias. Thus, more large-scale prospective studies are warranted to testify the prognostic ability of ALP in PCa in the future. Moreover, BAP will also be a potential prognostic marker in PCa, which needs verification as well.
Conclusion
In spite of the limitations mentioned above, the results of this study present the conclusion that high serum ALP is significantly associated with poor OS and PFS of PCa, but there is no obvious relation between ALP and CSS. ALP level is an efficient and convenient biomarker for PCa prognosis.

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Author contributions
YS and BH were involved in project development; DL and HL helped to collect and manage data; DL, HL, and XH analyzed the data; DL wrote/edited the manuscript; YS and BH helped in critical revision of the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Disclosure
The authors report no conflicts of interest in this work.

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