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ORIGINAL RESEARCH

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

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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.

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The enzyme ALP can physiologically dephosphorylate compounds under alkaline pH environment.[9] Serum ALP level is a widely used parameter for liver disease, bone disease burden, and treatment effects.[10] It is acknowledged that the elevation in ALP level is positively related to the rise of bone activity like osteosarcoma.[11] 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.[12] 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).[13] 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[MeSH]" OR "prostate cancer") AND "alkaline phosphatase" or "ALP" AND ("prognosis[MeSH]" OR "survival" OR "outcome"). 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.[14] The Jadad composite scale was utilized to assess randomized controlled trials (RCTs).[15] 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 (I^2) was also calculated to evaluate heterogeneity. An I^2 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

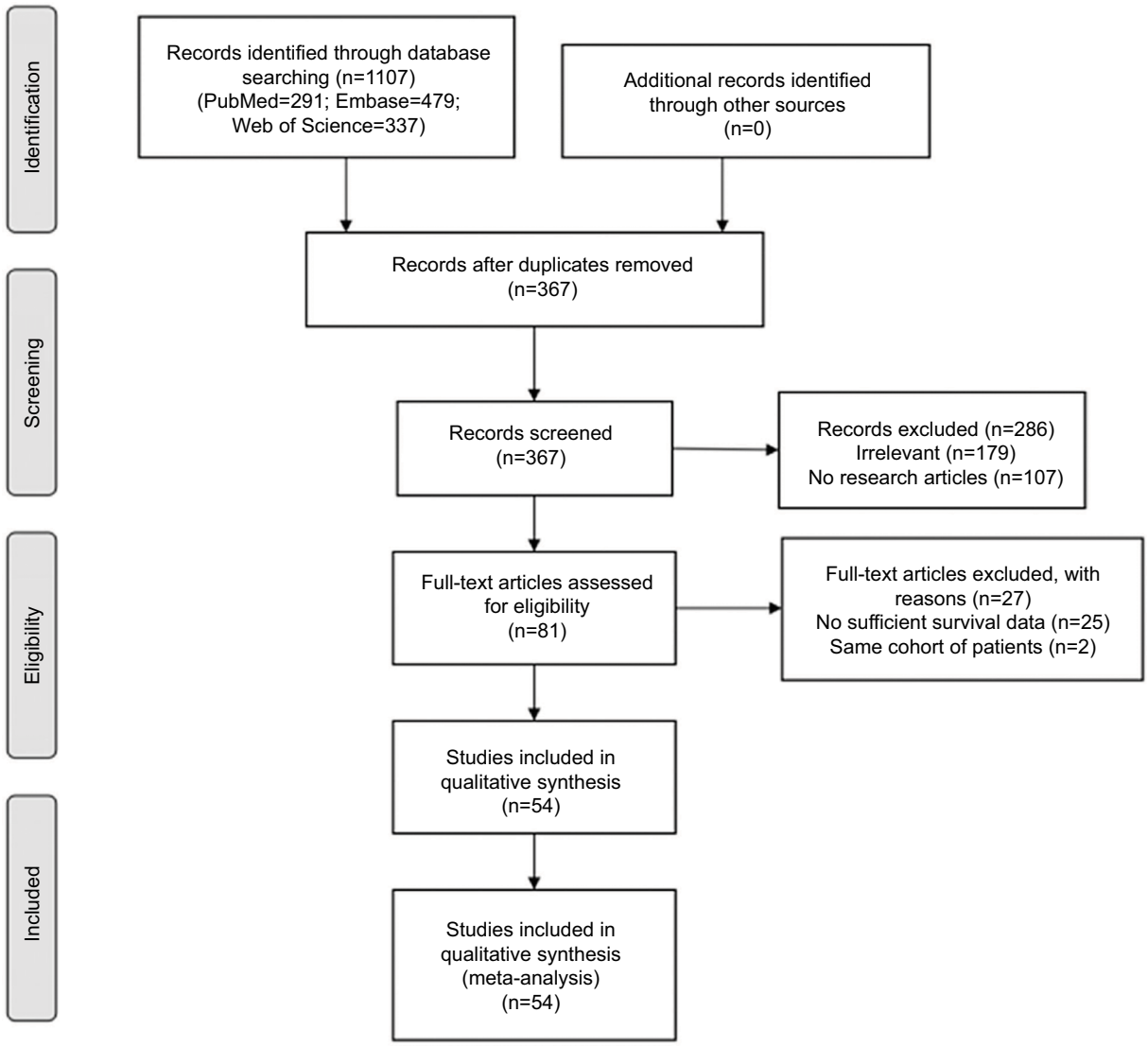

Figure 1 Flow chart of literature search and study selection.

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[16–69] 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[16]	USA	2007–2008	RCT	488	70 (63–75)	118 (40.3–370.2)
Goldkorn et al 2014[17]	USA	NR	RCT	470	69 (63–76)	68 (13–355)
Schellhammer et al 2013[18]	USA	2003–2009	RCT	512	71	50.1
Humphrey et al 2006[19]	USA	1996–1998	RCT	390	70 (64–75)	129 (50–339)
Halabi et al 2014[20]	USA	NR	RCT	705	69	79
Qu et al 2013[21]	China	2005–2011	Re	115	68 (51–82)	90.5 (0.1–4,066)
Mikah et al 2016[22]	Germany	2009–2014	Re	84	69 (62.3–76)	174 (55–500)
Klaff et al 2016[23]	Sweden	1992–1997	Pro	319	69	233
				483	71	
Miyamoto et al 2012[24]	Japan	1992–2002	Pro	94	72.5 (47–90)	1,015.6 (8.5–18,948)
Kita et al 2013[25]	Japan	2005–2008	Re	57	71 (57–80)	51.3 (0.03–1,450)
Bilen et al 2017[26]	USA	2010–2012	Re	48	67 (51–84)	8.9 (2–477)
Omlin et al 2013[27]	UK	2003–2011	Re	183	62 (41.8–77.3)	120 (0.97–11,343)
Nakashima et al 2000[28]	Japan	NR	Pro	114	73	NR
Templeton et al 2014[29]	UK	2001–2011	Pro	357	71 (44–90)	162 (56–496)
van Soest et al 2015[30]	the Netherlands	2011–2014	Pro	114	68 (49–83)	182 (12.5–5,000)
Sonpavde et al 2014[31]	USA	2008–2010	Pro	873	68 (39–90)	130 (0.1–5,927)
Halabi et al 2003[32]	USA	1992–1998	Pro	760	71	126
Shiota et al 2014[33]	Japan	2008–2013	Re	97	71 (51–85)	136.9 (3.1–10,860)
Oh et al 2017[34]	USA	2011–2014	Re	629	72	310
Brasso et al 2006[35]	Denmark	1993–1996	Pro	153	72 (54–89)	270 (10–7,730)
Chi et al 2016[36]	Canada	2008–2009	Pro	762	69 (42–95)	128.8 (0.4–9,253.0)
Nozawa et al 2015[37]	Japan	2008–2010	Pro	52	72 (55–86)	249.4
Pienta et al 1997[38]	USA	1993–1996	Pro	62	67 (47–80)	378 (0.7–2,007)
Reynard et al 1995[39]	UK	1986–1993	Pro	85	71 (47–89)	NR
Thatai et al 2004[40]	USA	1991–2001	Pro	145	70 (52–82)	NR
Vesalainen et al 1995[41]	Finland	1971–1992	Pro	188	71.5 (39.9–92)	NR
Etchebehere et al 2016[42]	USA	2013–2015	Pro	110	70 (43–89)	37 (0.4–2,433)
George et al 2001[43]	USA	1996–1998	Pro	197	68 (62–75)	150 (48–418)
Buttigliero et al 2017[44]	Italy	2004–2016	Re	71	68 (48–85)	47 (0.2–3,310)
Shigeta et al 2016[45]	Japan	2007–2014	Re	106	73 (52–95)	31.7 (0.3–751.45)
Wyatt et al 2004[46]	USA	1988–1995	Re	380	65.1	NR
Ramankulov et al 2007[47]	Germany	NR	Pro	90	64	25.4
Sonpavde et al 2012[48]	Canada	2000–2002	Pro	601	68 (36–92)	144 (0.06–40,740)
Halabi et al 2004[49]	USA	1992–2002	Pro	1,183	71 (65–76)	106 (37–310)
Oh et al 2011[50]	USA	1998–2006	Pro	302	62	22.6 (5.2–95.1)
Izumi et al 2012[51]	Japanese	2006–2010	Pro	30	65.5 (46–83)	200 (6–4,370)
Hammerich et al 2017[52]	USA	1989–2010	Re	89	62.4 (6.7)	6.7 (0.8–53.2)
Cook et al 2006[53]	USA	1998–2001	RCT	278	71.7 (7.9)	282 (839)
Park et al 2012[54]	Korea	2003–2009	Re	55	72.5±7.6	209.2±424.5
Yamada et al 2010[55]	Japan	1998–2006	Re	454	74	268.7
Kamiya et al 2010[56]	Japan	2002–2008	Re	58	69±8.2	1,402.4±2,055.3
Mohammed et al 2015[57]	Saudi Arabia	2011–2015	Re	71	72±8.7	54 (0.1–16,430)
Akimoto et al 1997[58]	Japan	1979–1992	Re	56	71.8	NR
Koo et al 2015[59]	Korea	2002–2012	Re	248	NR	NR
Kato et al 2016[60]	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	1.035–1.510	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
			1.29	1.02–1.63	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	NR	NR	0.93	0.66–1.32	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
Orchiectomy	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 (16.7–186)	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)	NR	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
			1.57	0.97–2.54	OS		
			1.16	0.79–1.71	PFS		

(*Continued*)

Table 1 (*Continued*)

Study ID	Country	Duration	Type	Sample size	Median age (years)	Median serum PSA (ng/mL)
D'Amico et al 2005[61]	USA	1991–2001	Pro	281	72	NR
Bando et al 2017[62]	Japan	2014–2016	Re	66	NR	NR
Pelger et al 1996[63]	the Netherlands	NR	Re	112	73	NR
Han and Hong 2014[64]	Korea	2002–2013	Re	61	69 (54–84)	299.0 (10.6–12,467.0)
Goodman et al 2011[65]	USA	2007–2009	Pro	33	66 (51–80)	57 (5.3–3,956)
Matsuyama et al 2014[66]	Japan	NR	Re	279	71 (48–91)	35.2 (0.05–3,134)
Fizazi et al 2015[67]	USA	2006–2009	RCT	1,900	71 (38, 93)	59.5 (0.0–14,076.8)
Rahbar et al 2018[68]	Germany	2014–2016	Re	104	70 (64–76)	361 (80–755)
Sartor et al 2017[69]	UK	NR	Pro	400	NR	NR

Abbreviations: NR, not reported; HR, hazard ratio; Pro, prospective; Re, retrospective; ALP, alkane phosphatase; BAP, bone-specific ALP; PSA, prostate-specific antigen; OS, overall survival; PFS, progression-free survival; CSS, cancer-specific survival; RCT, randomized controlled trial.

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 (I^2=75.4%, 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 (I^2=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.[70] The high ALP level has been

Treatment	Median follow-up (months)	Cutoff value (U/L)	HR	95% CI	Outcome	Multivariate analysis	Study quality (NOS score)
Taxotere, thalidomide, atrasentan, ketoconazole, and alendronate.	16.8	NR	1	0.8–1.2	OS	Yes	8
Cabazitaxel and docetaxel	10.3	300	1.73	0.80–3.85	PFS	Yes	7
Orchiectomy	22	200	3.5	1.90–6.45	PFS	Yes	7
Chemotherapy	NR	NR	1.003	1.001–1.005	PFS	Yes	7
Radical prostatectomy and radiation therapy	11.2	NR	4.33	1.53–12.21	PFS	No	6
Docetaxel	NR	189	2.95	1.15–8.85	OS	Yes	7
Denosumab and zoledronic acid	20 (18–21)	143/low	0.664	0.559–0.789	OS	Yes	7 (Jadad)
^{177}Lu-PSMA-617 RLT	14	220/low	0.55	0.30–0.98	OS	Yes	7
Radium-223	17.8	NR/low	0.45	0.34–0.61	OS	Yes	7

Table 2 Summary of the subgroup analysis results of ALP and OS prognosis for PCa

Variable	Number of studies	Number of patients	Model	Outcome (OS)		Heterogeneity	
				HR (95% CI)	*P* value	I^2 (%)	*P* value
Study type							
Prospective	20	7,082	R	1.764 (1.420–2.190)	<0.001	97.5	<0.001
Retrospective	13	2,319	R	1.581 (1.250–1.999)	<0.001	65.6	<0.001
Region							
Asia	9	1,095	R	2.771 (1.347–5.703)	0.006	93.2	<0.001
Europe	9	1,884	R	1.280 (1.069–1.532)	0.007	66.9	0.002
North America	15	6,422	R	1.637 (1.283–2.008)	<0.001	95.3	<0.001
ALP cutoff							
>178	11	1,670	R	2.734 (1.293–5.783)	0.009	98.4	<0.001
<178	11	2,453	R	1.578 (1.285–1.938)	<0.001	77.5	<0.001
Sample size							
>180	17	7,958	R	1.302 (1.161–1.459)	<0.001	90.0	<0.001
<180	16	1,443	R	2.642 (1.565–4.460)	<0.001	93.9	<0.001

Abbreviations: ALP, alkaline phosphatase; OS, overall survival; PCa, prostate cancer; R, random-effects model.

reported related to the poor survival in colorectal cancer.[71] The elevation of ALP is also an independent risk factor in the bone metastasis of gastric cancer and bladder cancer.[72,73] 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.[11] 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

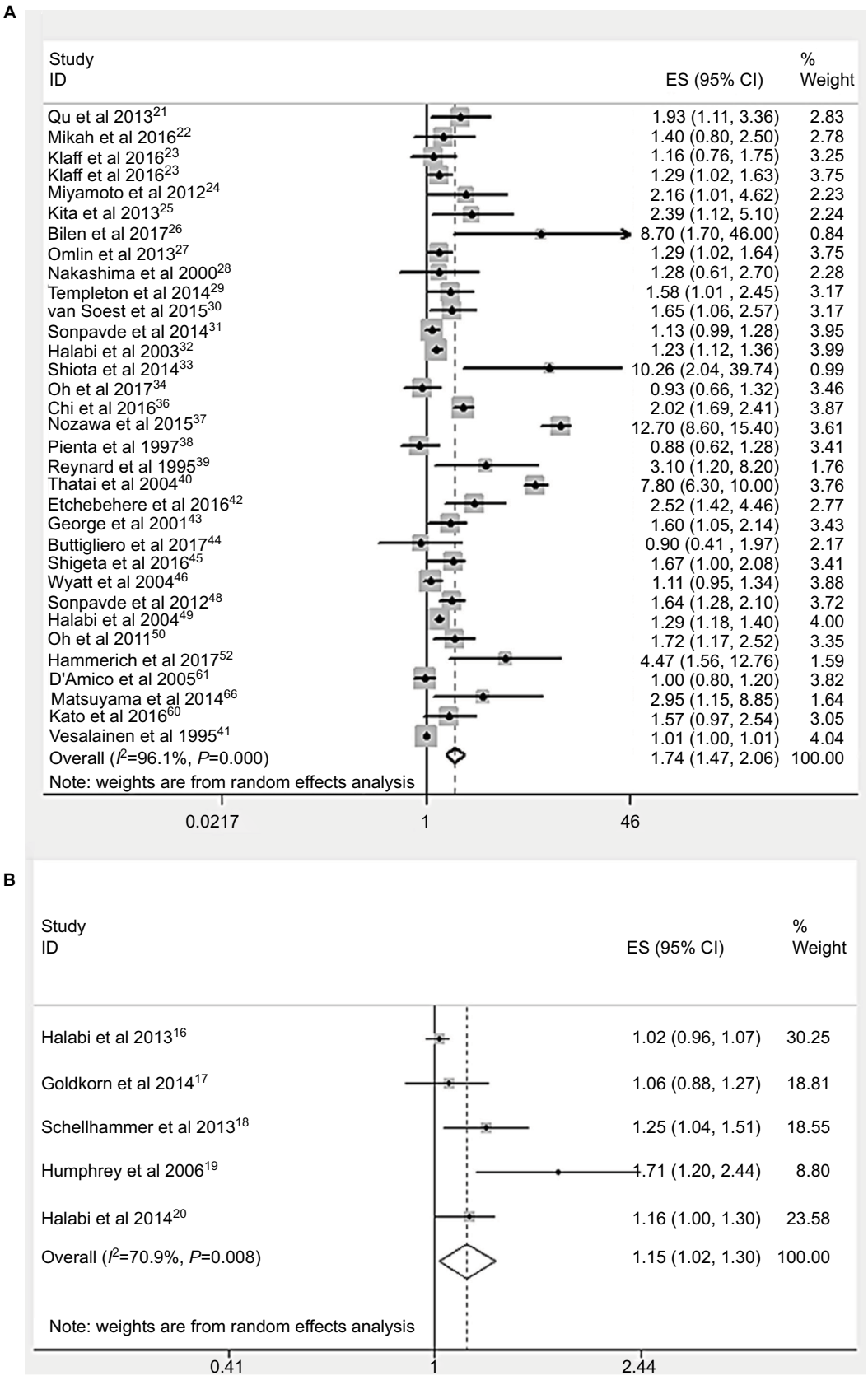

Figure 2 Forest plot of pooled HR and 95% CI of high ALP and OS prognosis.
Notes: (**A**) Observational cohorts; (**B**) RCTs.
Abbreviations: ALP, alkane phosphatase; OS, overall survival; RCT, randomized controlled trial; ES, effect size.

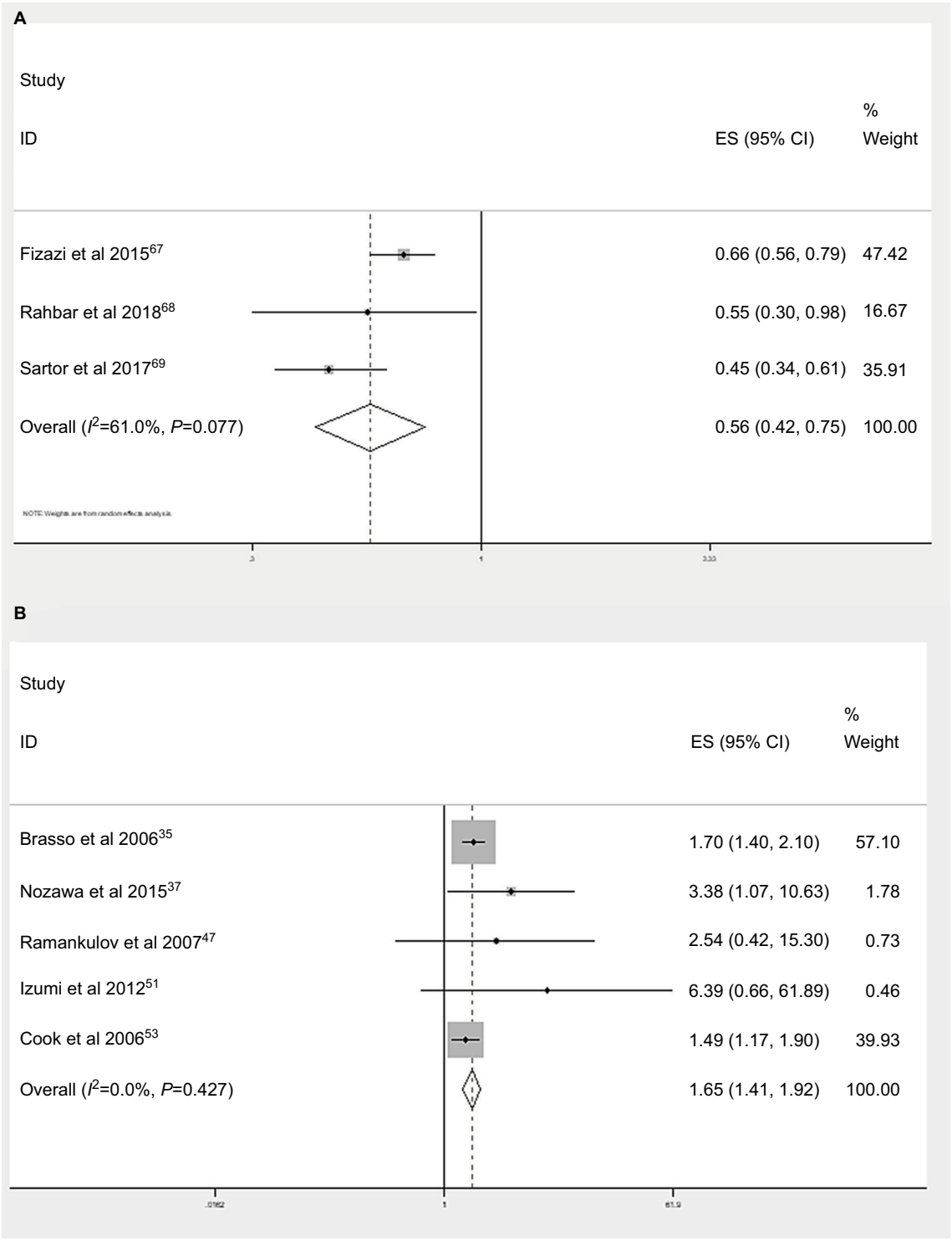

Figure 3 Forest plot of pooled HR of low ALP (**A**) or bone-specific ALP (**B**) and OS prognosis.
Abbreviations: ALP, alkane phosphatase; OS, overall survival; ES, effect size.

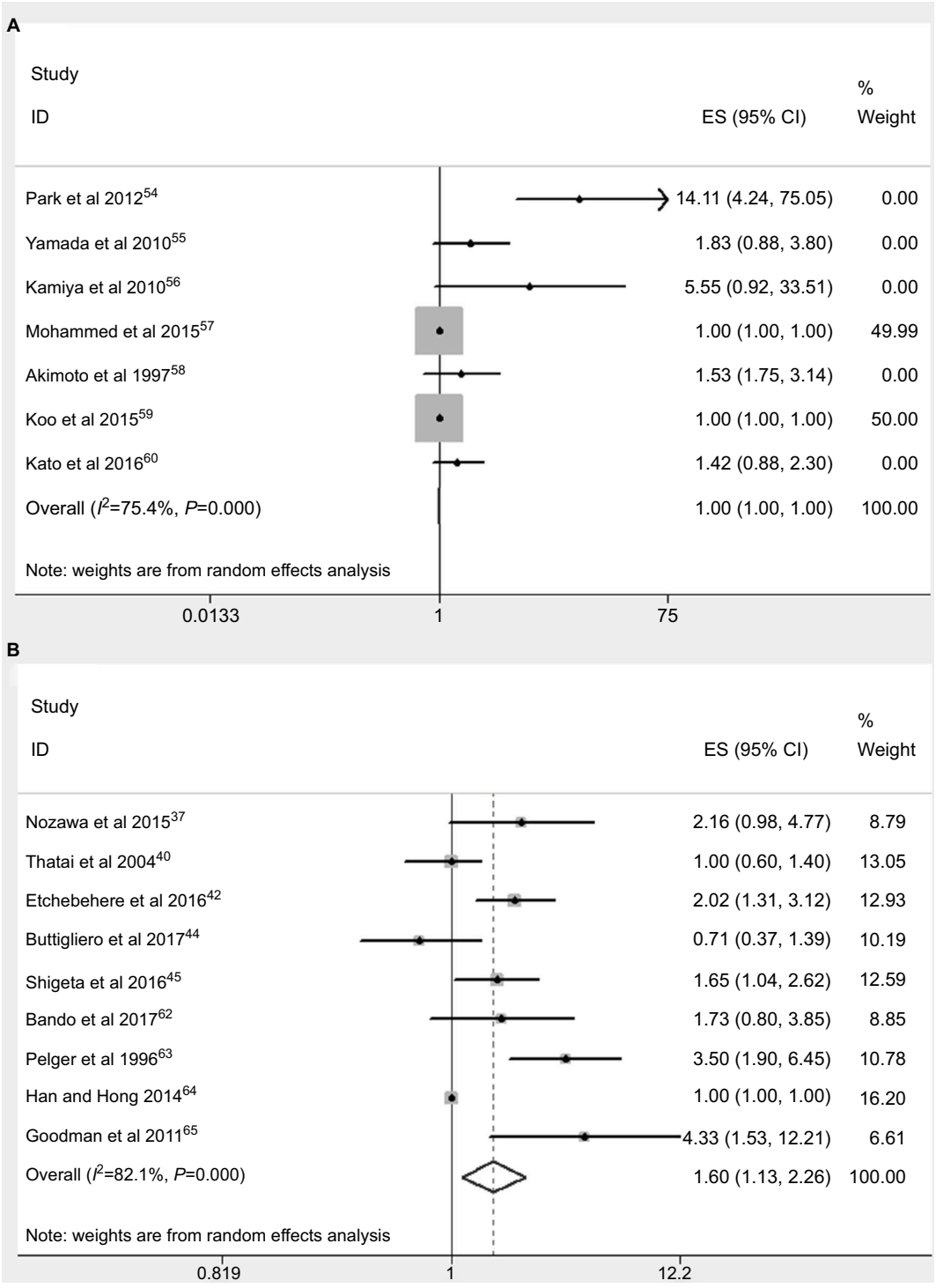

Figure 4 Forest plot of pooled HR and 95% CI of high ALP and CSS (**A**) or PFS (**B**) prognosis.
Abbreviations: ALP, alkane phosphatase; CSS, cancer-specific survival; PFS, progression-free survival; ES, effect size.

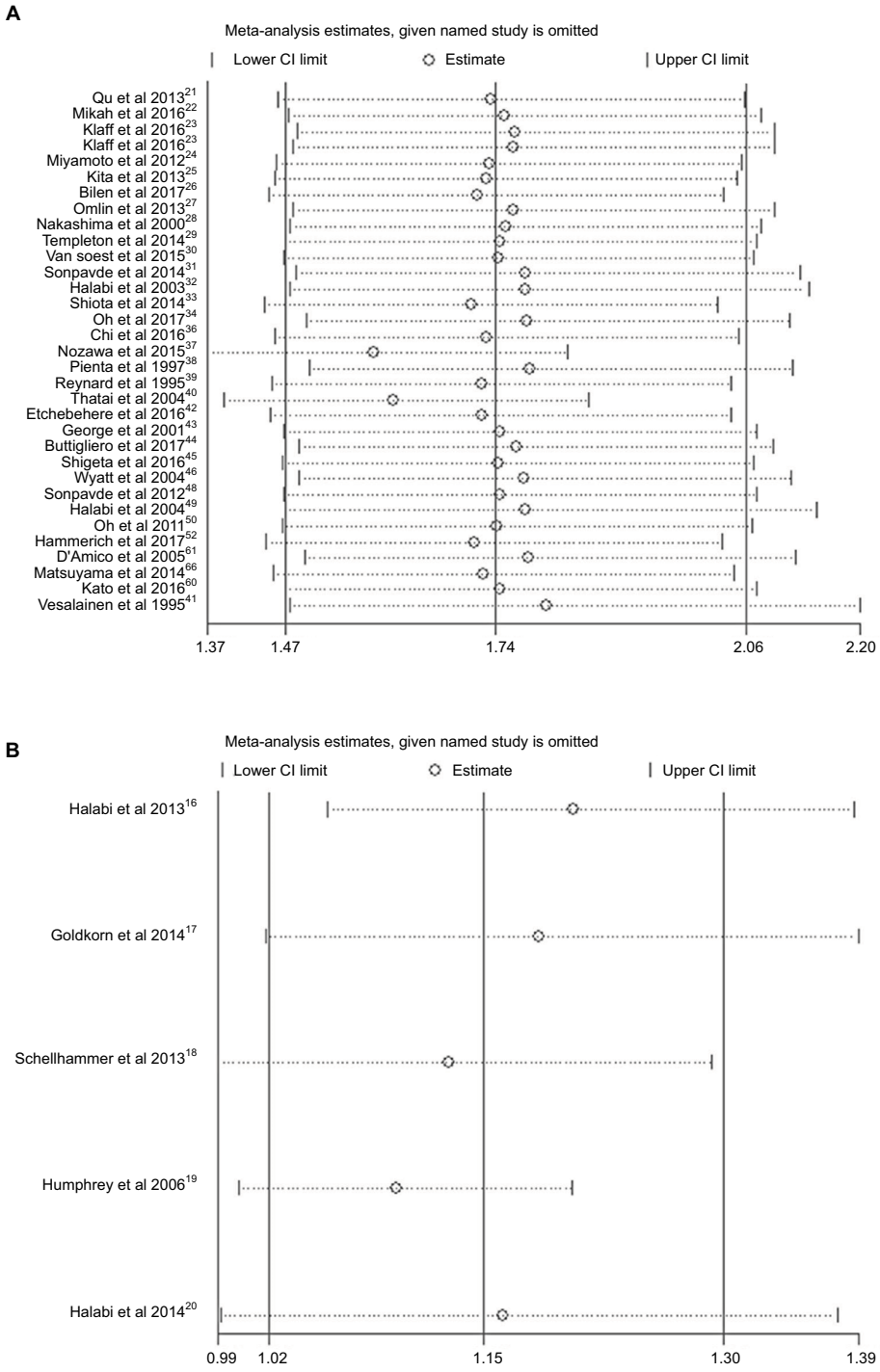

Figure 5 Sensitivity analyses of high ALP and OS prognosis.
Notes: (**A**) Observational cohorts; (**B**) RCTs.
Abbreviations: ALP, alkane phosphatase; OS, overall survival; RCT, randomized controlled trial.

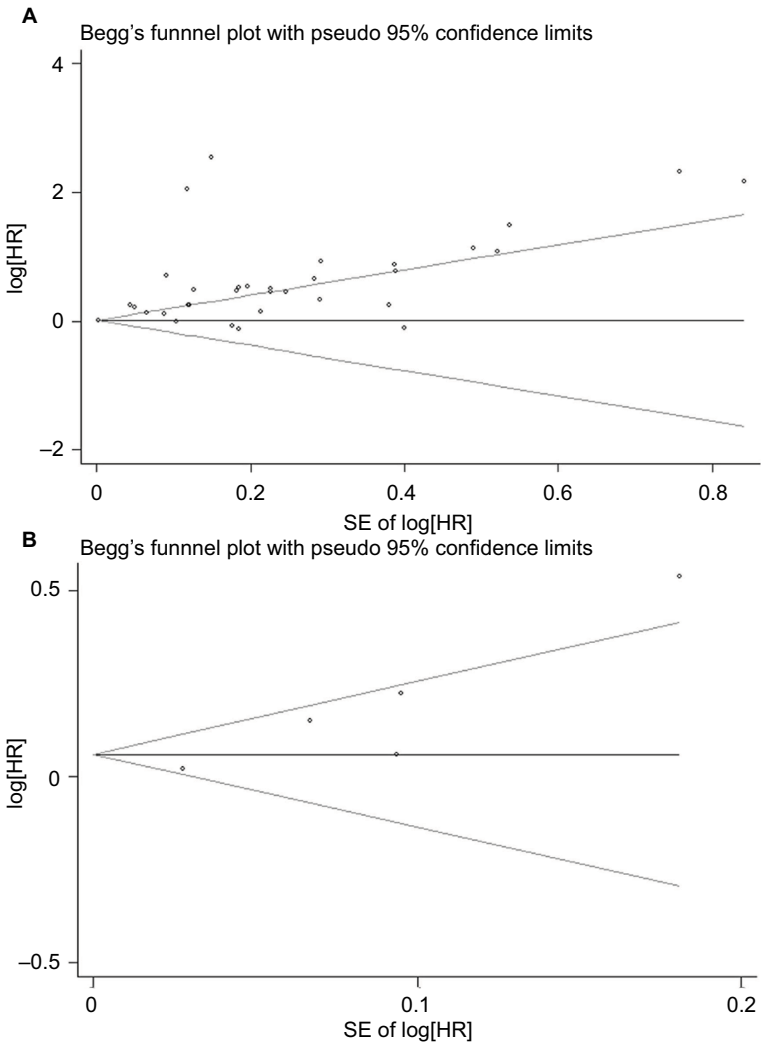

Figure 6 Funnel plots of Begg's test of high ALP and OS prognosis.
Notes: (**A**) Observational cohorts; (**B**) RCTs.
Abbreviations: ALP, alkane phosphatase; OS, overall survival; RCT, randomized controlled trial.

(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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