Prognostic Significance of Pretreatment Albumin to Alkaline Phosphatase Ratio in Human Cancers: A Meta-Analysis

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Research

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Abstract

Purpose: To investigate the prognostic value of pretreatment albumin to alkaline phosphatase ratio (AAPR) in human cancers.

Methods: Several electronic databases were searched up to Jan 4, 2020 for relevant studies. The prognostic value of AAPR were assessed by pooled hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs). The endpoint events included the overall survival (OS), disease-free survival (DFS), cancer-specific survival (CSS) and progression-free survival (PFS).

Results: A total of 15 articles involving 20 studies with 6062 cancer patients were included. Our results proved that low pretreatment AAPR was related with poor OS (HR=1.83, 95% CI: 1.66-2.02; P<0.001), DFS (HR=1.97, 95% CI: 1.49-2.61; P<0.001), CSS (HR=1.88, 95% CI: 1.37-2.56; P<0.001) and PFS (HR=1.74, 95% CI: 1.24-2.43; P=0.001). In addition, the significant correlation between pretreatment AAPR and OS was not affected by the treatment strategy and tumor pathological type.

Conclusion: Low pretreatment AAPR is related to poor prognosis in human cancers, and AAPR could be served as a promising prognostic indicator in cancer patients.

Introduction

Because of the improvement of diagnostic techniques, growing population and the aging of population [1], more people are diagnosed with cancer. In the United States, cancer became the second leading cause of death. There are 1,806,590 new cancer cases and 606,520 cancer deaths being projected to occur in 2020 [2]. Till now, there are the numerous prognostic markers of human cancers being researched. But most of those tests have some drawbacks, such as the expensive cost and unavailability before the treatments. Therefore, identifying a new cheap and available prognostic marker may be helpful in treating human cancers.

The albumin and alkaline phosphatase (ALP) are abundant and easily available protein in human serum. Albumin, as a major component in serum, is usually used to assess nutritional status and changes of immune system in cancer patients. Besides, as a prognostic indicator, hypoalbuminemia has also been widely considered in human cancers, such as lung cancer [3], lymphoma [4], renal cancer [5]. ALP, the other component of serum protein, is a hydrolase enzyme which can remove phosphate groups. ALP level increasing can be observed in liver, bone, and kidney diseases[6]. ALP has been proved to be related with advanced cancer status [7, 8]. Recently, the albumin to alkaline phosphatase ratio (AAPR) is diffusely explored as a prognostic marker in human cancers.

However, the prognostic value of pretreatment AAPR in human cancers has not been clearly identified yet. Therefore, we performed this meta-analysis to clarify the prognostic role of pretreatment AAPR in human cancers patients.

Method

Search Strategy

A systematic search was performed in PubMed, EMBASE (via OVID) and Web of Science for eligible studies assessing the potential prognostic value of the pretreatment AAPR in human cancers up to January 4, 2020. The search strategy used in PubMed was as follows: (tumor OR cancer OR carcinoma OR neoplasm) AND (AAPR OR albumin to alkaline phosphatase ratio)

Inclusion and exclusion criteria

Inclusion criteria were as follows : (1) articles investigating the prognostic impact of pretreatment AAPR on human cancers and cancer patients were diagnosed pathologically; (2) serum albumin and ALP concentrations were collected before any treatment, including the surgery, chemoradiotherapy, neoadjuvant chemoradiotherapy and targeted therapy and other anti-tumor therapy; (3) the outcomes included overall survival (OS), disease-free survival (DFS), cancer-specific survival (CSS) or progression-free survival (PFS); (4) hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) were reported or could be calculated from Kaplan-Meier curves; (5) full texts were accessible and in English.

Exclusion criteria were as follows: (1) letters, reviews, case reports, conference abstracts and animal trials; (2) insufficient data to calculate the HRs with 95% CIs; (3) if data sets were overlapped or duplicated, only the latest study was included.

Data collection

Data was collected from each included study, including first author name, publication year, country, sample size, TNM stage, treatment method, tumor type, cut-offs of AAPR, survival outcome, source of HR and HR with 95% CIs. If HRs and 95% CIs were not directly provided in included studies, then they would be calculated from Kaplan-Meier survival curves according to the methods described by Tierney et al. [9]. During this process, two investigators filtrated the information independently and eliminated disagreements by discussing.

Quality assessment

Two independent authors evaluated the quality of included studies using the Newcastle-Ottawa Scale (NOS) [10]. Studies earning a score of 6 or higher were recognized as high-quality studies.

Statistical Analyses

We used the STATA 12.0 version software to conduct statistical analysis. HRs with 95% CIs were pooled to assess the relationship between pretreatment AAPR and prognosis. Heterogeneity among included studies was measured by the Cochrane's Q test and Higgin's I^2 statistic. If significant heterogeneity was found representing as P 0.10 or/and I^2 50% the random-effect model was used for the meta-analysis, otherwise the fix-effect model was used [11]. We conducted the sensitivity analysis to evaluate the stability of pooled results by excluding each single study from the meta-analysis. Begg's funnel plot and Egger's test were applied for the evaluation of publication bias and P 0.05 with asymmetry funnel plot indicated significant publication bias [12, 13]; and then the Duval's nonparametric trim and fill method was use for the calculation of the potentially unpublished articles [14].

Results

Study selection process

Three hundred and fifty-three records were identified through the three electronic databases. After removing 141 duplicated records, 10 publications were excluded, including meeting abstracts, case reports, animal experiments and reviews. By reading full-text of remained 18 studies, we excluded 3 articles because of the insufficient data or the overlapping data. Finally, 15 articles were included for this meta-analysis.

Characteristics of included studies

The characteristics of the included studies were shown in Table 1. In the current research, 15 retrospective articles with 6,062 cancer patients were included [15–29]. Because of the subgroup analysis in three articles [15, 17, 19], we regarded them as 2 or 3 independent studies. The publication dated from 2015 to 2019, and the number of cancer patients ranged from 82 to 746. Most of included studies were from China and 9 kinds of tumor were involved. The cutoff values of AAPR ranged from 0.23 to 0.68. The other information was presented in Table 1.

Table 1
Basic characteristics of included studies.

Author	Publication year	Country	Sample size	TNM stage	Treatment	Tumor type	Cut-offs of AAPR	Outcome	Source of HR	NOS score
Chan [15]	2015	China	217	I-III	Surg	HC	0.23, 0.68	OS, DFS	R	8
Chan [15]	2015	China	256	I-III	Surg	HC	0.23, 0.68	OS, DFS	R	8
Chan [15]	2015	China	425	I-IV	Non-surg	HC	0.23, 0.68	OS	R	8
Nie [16]	2017	China	209	IV	CT	NC	0.447	OS, PFS	R	7
Pu [17]	2017	China	220	I-III	Surg	PDA	0.46	OS	R	7
Pu [17]	2017	China	134	I-III	Surg	PDA	0.46	OS	R	7
Cai [18]	2018	China	237	I-IV	Palliative therapy	HC	0.38	OS	R	7
Chen [19]	2018	China	372	I-IV	CT	HC	0.439	OS	R	7
Chen [19]	2018	China	202	I-IV	CT	HC	0.439	OS	R	7
Chen [19]	2018	China	82	I-IV	CT	HC	0.439	OS	R	7
Tan [20]	2018	China	692	NR	Surg	UC	0.58	OS, DFS, CSS	R	6
Kim [21]	2019	Korea	100	I-IV	RT (+ CT)	NC	0.4876	OS, PFS	R	7
Li D [22]	2019	China	290	IV	Non-surg or palliative therapy	NSCLC	0.36	OS	R	7
Li S [23]	2019	China	310	I-IIIA	Surg	NSCLC	0.57	OS, DFS	R	8
Li X [24]	2019	China	122	LS	RT	SCLC	0.61	OS, PFS	R	6
Long [25]	2019	China	746	I-III	Surg	BC	0.525	OS	R	6
Xia [26]	2019	China	419	NR	Surg	RCC	0.39	OS, CSS	R	7
Xiong [27]	2019	China	303	I-IV	Surg	CCA	0.41	OS, DFS	R	6

TNM: tumor-node-metastasis; AAPR: albumin-to-alkaline phosphatase ratio; HR: hazard ratio;NOS: Newcastle-Ottawa Scale; LS: limited stage; NR: not reported; R□reported; Surg: surgery; CT: chemotherapy; RT: radiotherapy; HC: hepatocellular carcinoma; NC: nasopharyngeal carcinoma; PDA: pancreatic ductal adenocarcinoma; UC: urothelial carcinoma; BC: breast cancer: RCC: renal cell carcinoma; CCA: cholangiocarcinoma; CC: cervical cancer; OS: overall survival□DFS: disease-free survival; PFS: progression-free survival; CSS: cancer-specific survival.

Author	Publication year	Country	Sample size	TNM stage	Treatment	Tumor type	Cut-offs of AAPR	Outcome	Source of HR	NOS score
Zhang C [28]	2019	China	230	IB-IIA	Surg	CC	0.68	OS, DFS	R	8
Zhang L [29]	2019	China	496	I-III	Surg	NSCLC	0.64	OS, DFS	R	8

TNM: tumor-node-metastasis; AAPR: albumin-to-alkaline phosphatase ratio; HR: hazard ratio;NOS: Newcastle-Ottawa Scale; LS: limited stage; NR: not reported; R□reported; Surg: surgery; CT: chemotherapy; RT: radiotherapy; HC: hepatocellular carcinoma; NC: nasopharyngeal carcinoma; PDA: pancreatic ductal adenocarcinoma; UC: urothelial carcinoma; BC: breast cancer: RCC: renal cell carcinoma; CCA: cholangiocarcinoma; CC: cervical cancer; OS: overall survival□DFS: disease-free survival; PFS: progression-free survival; CSS: cancer-specific survival.

Association between pretreatment AAPR and OS

Totally, all included studies involving 6062 patients compared OS between low AAPR and high AAPR groups. The fix-effects model was used because of low heterogeneity (I^2 = 16.7%, P = 0.246). The pooled meta-analysis results revealed that low pretreatment AAPR was related to poor OS (HR = 1.83, 95%CI: 1.66–2.02, P < 0.001).

We conducted subgroup meta-analysis based on the treatment strategy and tumor type to further clarify the results. The subgroup analysis results revealed that the prognostic value of pretreatment AAPR were not affected by these two factors. And pretreatment AAPR did show high prognostic significance in different tumors included the hepatocellular carcinoma, nasopharyngeal carcinoma, pancreatic ductal adenocarcinoma and lung cancer according to the pooled results. (Table 2)

Table 2. Meta and subgroup analyses.

	No. of studies	HR	95% CI	P value	I^2(%)	$P_{heterogeneity}$
Overall survival	20	1.83	1.66-2.02	<0.001	16.7	0.246
Treatment						
Surgery	11	2.08	1.77-2.45	<0.001	15.2	0.299
Non-surgery	9	1.70	1.50-1.92	<0.001	0.0	0.525
Tumor type					0.0	0.643
Hepatocellular carcinoma	7	1.75	1.52-2.02	<0.1	18.5	0.268
Nasopharyngeal carcinoma	2	2.59	1.44-4.64	0.001	0.0	0.926
Pancreatic ductal adenocarcinoma	2	2.11	1.40-3.19	<0.001	69.5	0.020
Lung cancer	4	2.03	1.36-3.02	0.001		
Urothelial carcinoma	1	1.59	1.19-2.13	0.002		
Breast cancer	1	2.24	1.03-4.88	0.043		
Renal cell carcinoma	1	2.75	1.27-5.95	0.011		
Cholangiocarcinoma	1	2.88	1.19-2.78	0.002		
Cervical cancer	1	3.02	1.24-7.41	0.015		
Disease-free survival	7	1.97	1.49-2.61	<0.001	65.2	0.008
Cancer-specific survival	2	1.88	1.37-2.56	<0.001	27.0	0.242
Progression-free survival	3	1.74	1.24-2.43	0.001	0.0	0.570

HR: hazard ratio; CI: confidence interval.

Association between pretreatment AAPR and DFS

Seven studies with 2504 patients explored the predictive role of pretreatment AAPR on DFS. Pooled meta-analysis results demonstrated that lower pretreatment AAPR was significantly associated with poor DFS. (HR = 1.97, 95% CI: 1.49–2.61, $P < 0.001$) with significant heterogeneity ($I^2 = 65.2\%$ $P = 0.008$). (Table 2; Fig. 3)

Association between pretreatment AAPR and CSS

Two studies with 1111 patients explored the predictive role of pretreatment AAPR on CSS. Pooled meta-analysis results proved that lower pretreatment AAPR was associated with poor CSS (HR = 1.88, 95% CI: 1.37–2.56, $P < 0.001$) with low heterogeneity ($I^2 = 27.0\%$, $P = 0.242$). (Table 2; Fig. 4)

Association between pretreatment AAPR and PFS

Three studies with 431 patients explored the predictive role of pretreatment AAPR on PFS. Pooled meta-analysis results demonstrated that lower pretreatment AAPR was related with poor PFS. (HR = 1.74, 95% CI: 1.24–2.43, $P = 0.001$) without any heterogeneity ($I^2 = 0.0\%$, $P = 0.570$). (Table 2; Fig. 5)

Sensitivity analysis and publication bias

Through excluding each single study individually from the meta-analysis, we further evaluated the impact of each study on the pooled results. The results suggested that our results were stable (Fig. 6).

The Begg's funnel plot was asymmetric (Fig. 7a) and the *P* value for Egger's test was 0.001, which indicated significant publication bias. Then the nonparametric trim and fill method was applied and the filled funnel plot showed that there were 9 potentially unpublished articles (Fig. 7b); furthermore, the meta-analysis combining included studies and 7 unpublished articles showed that the 7 potentially unpublished studies did not cause a significant impact on the overall results (HR = 1.67, 95% CI: 1.53–183; *P* 0.001).

Discussion

Our quantitative meta-analysis investigated the prognostic value of pretreatment AAPR in human cancers. The pooled estimates of 20 studies involving 6,062 patients proved that patients with low pretreatment AAPR had poorer OS (HR = 1.83, 95% CI: 1.66–2.02; *P* 0.001), DFS (HR = 1.97, 95% CI: 1.49–2.61; *P* 0.001), CSS (HR = 1.88, 95% CI: 1.37–2.56; *P* 0.001) and PFS (HR = 1.74, 95% CI: 1.24–2.43; *P* = 0.001). In addition, the subgroup analysis indicated the therapy strategy and tumor pathological type did not affect the predictive role of pretreatment AAPR on OS.

It is widely known that pretreatment serum albumin level is a promising biomarker representing the nutrition status of the body and a number of publications have demonstrated that low level of serum albumin is an independent prognostic factor for cancer patients [30–32]. As a phosphate monoester hydrolase, ALP is found to play an important role in removing phosphate groups and catalyzing hydrolysis under the alkaline conditions [33]. It is abundant in multiple organs or tissues especially the bone, liver, placenta and bile duct [34]. The concentration of serum ALP usually increases in some pathological conditions like the bone metastases. Thus, ALP has been used to monitor patients for bone metastasis. It has been manifested the that serum ALP level and its change can play a role in predicting therapy effects and prognosis in cancer patients with bone metastasis in some studies and high level of serum ALP is associated with poor survival [35–37].

Hence, it is suggested that both serum albumin and ALP might play roles in reflecting disease progression and predicting long-term survival in cancer patients. We believe that the ratio combining them together would show higher prognostic value than each of them. Thus, for the first time, we conducted the current meta-analysis based on available relevant studies and demonstrated that low pretreatment AAPR was an independent and reliable prognostic risk factor in cancer patients.

Although we got relatively certain conclusions according to the pooled results, we consider that there are still many fields about the prognostic value of pretreatment AAPR deserving more investigation. With the exception of the study conducted by Kim et al. [21], all the other studies are from China. Therefore, the predictive role of pretreatment AAPR for survival of cancer patients in other countries or regions needs to be further clarified. Only one study explored the prognostic role of AAPR in urothelial, breast, renal cell, cervical cancer and cholangiocarcinoma [20,25–28,], although they all reported positive results. Thus, more relevant researches are needed to verify their findings. The cut-offs of pretreatment AAPR differs in included studies. The optimal thresholds of AAPR in patients with different tumors, TNM stage, age, etc. should be determined in future relevant investigations.

However, our meta-analysis still has some limitations. First, all included studies are retrospective and most of them are from the same country (China), therefore, there might be some bias. Second, due to lack of original data, we were unable to conduct subgroup analysis based on other factors such as the TNM stage, age and sex. Third, significant publication bias

was detected in our meta-analysis, although potentially unpublished studies should not cause an impact on the pool results.

Conclusions

In conclusion, we demonstrated that cancer patients with low pretreatment AAPR had worse survival than patients with high pretreatment AAPR. Pretreatment AAPR could contribute to the assessment of risk and formulation of therapy strategy for human cancers in clinical work.

Abbreviations

TNM: Tumor-node-metastasis; AAPR: Albumin-to-alkaline phosphatase ratio; HR: Hazard ratio□CI: Confidence interval; NOS: Newcastle-Ottawa Scale; LS: Limited stage; HC: Hepatocellular carcinoma; NC: Nasopharyngeal carcinoma; PDA: Pancreatic ductal adenocarcinoma; UC: Urothelial carcinoma; BC: Breast cancer: RCC: Renal cell carcinoma; CCA: Cholangiocarcinoma; CC: Cervical cancer; OS: Overall survival□DFS: Disease-free survival; PFS: Progression-free survival; CSS: Cancer-specific survival.

Declarations

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Authors’ contributions

YW conceived and designed the analyses. YWW and YWS performed the literature search and selection, collected data and wrote the paper. YWS and WYX performed statistical analyses. All authors contributed substantially to its revision.

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Availability of data and materials

All data are fully available without restriction.

Ethics approval and consent to participate

This paper did not use the experimental data from human subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

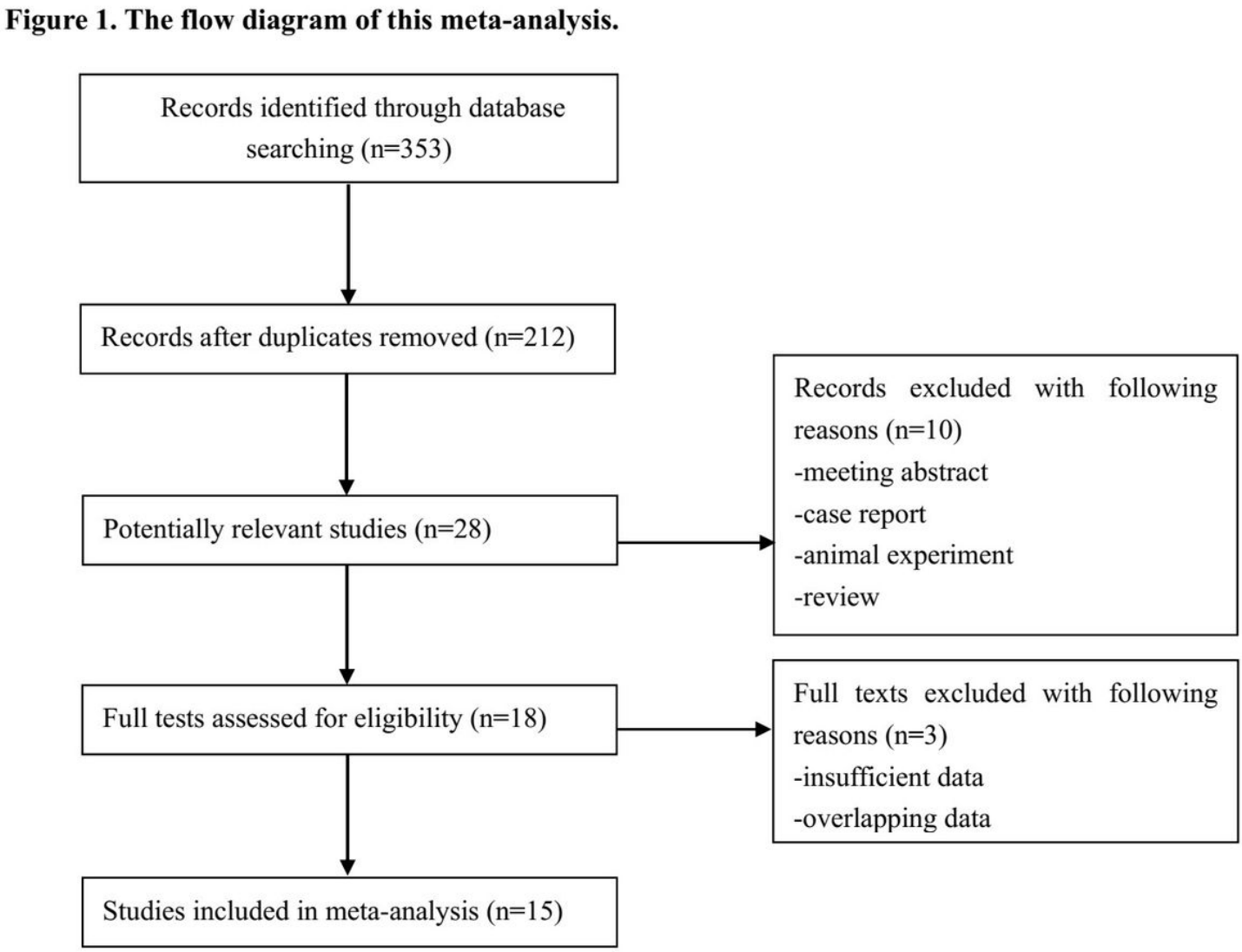

Figure 1

The flow diagram of this meta-analysis.

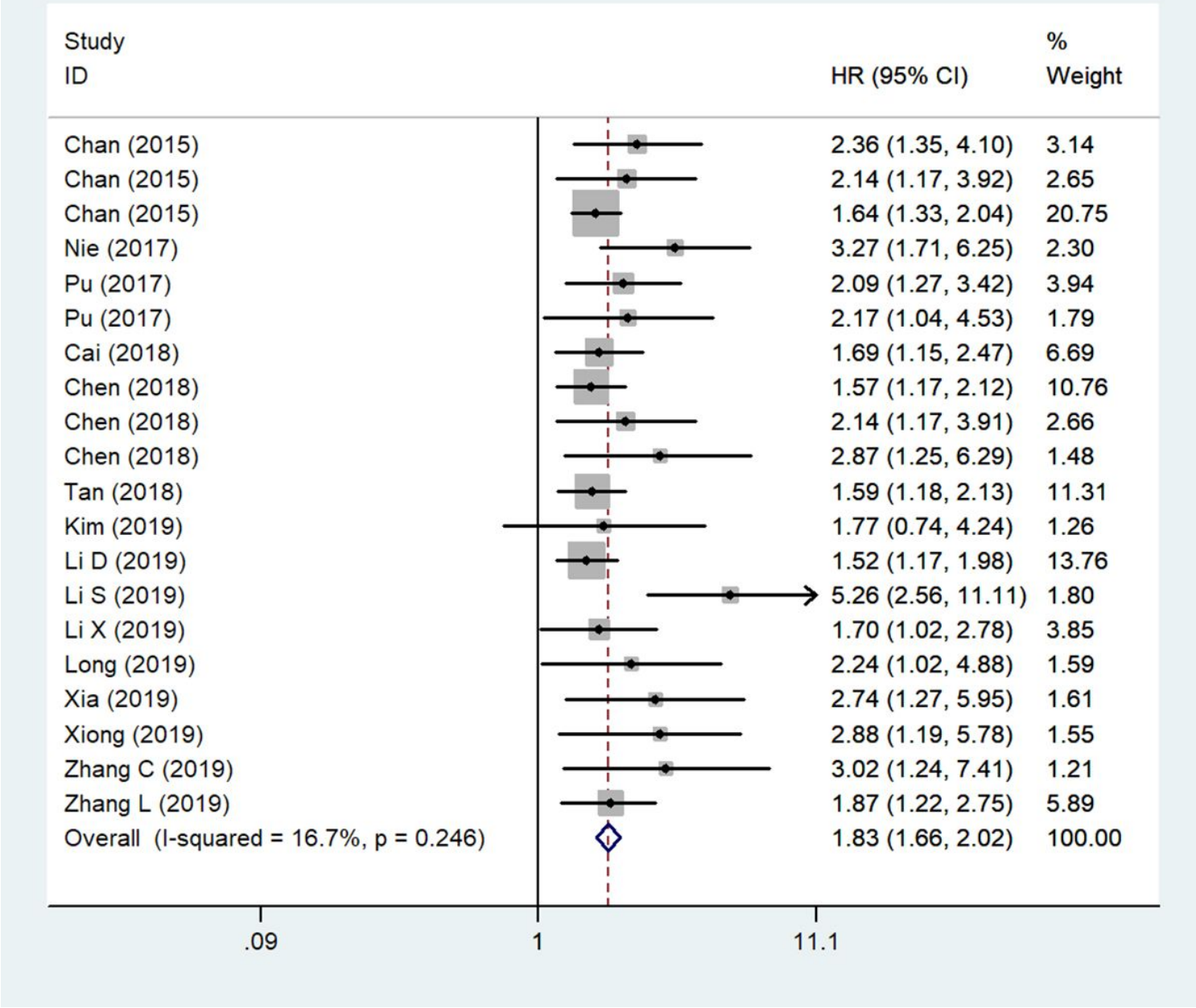

Figure 2

Forest plot of the association between pretreatment albumin to alkaline phosphatase ratio and overall survival.

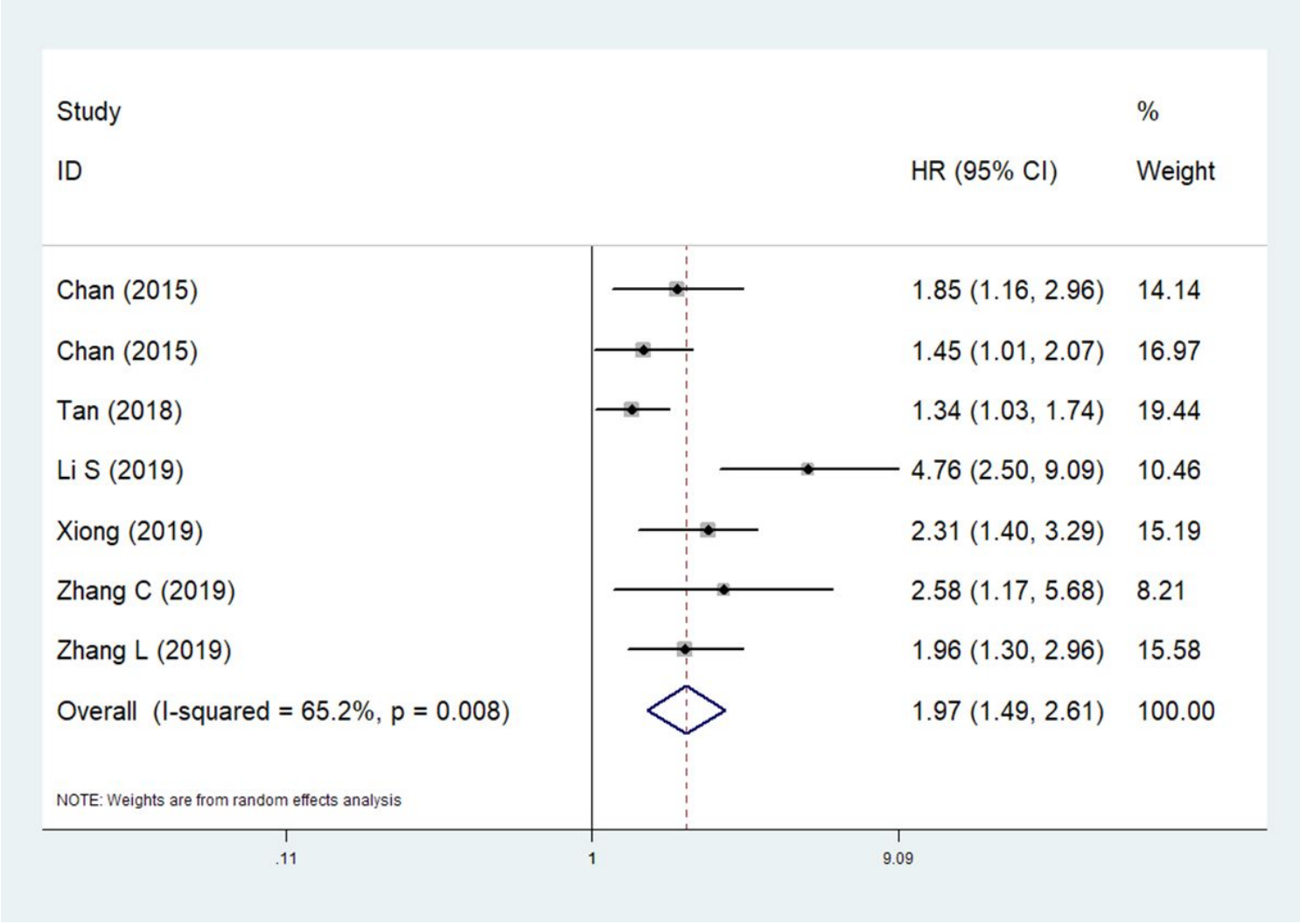

Figure 3

Forest plot of the association between pretreatment albumin to alkaline phosphatase ratio and disease-free survival.

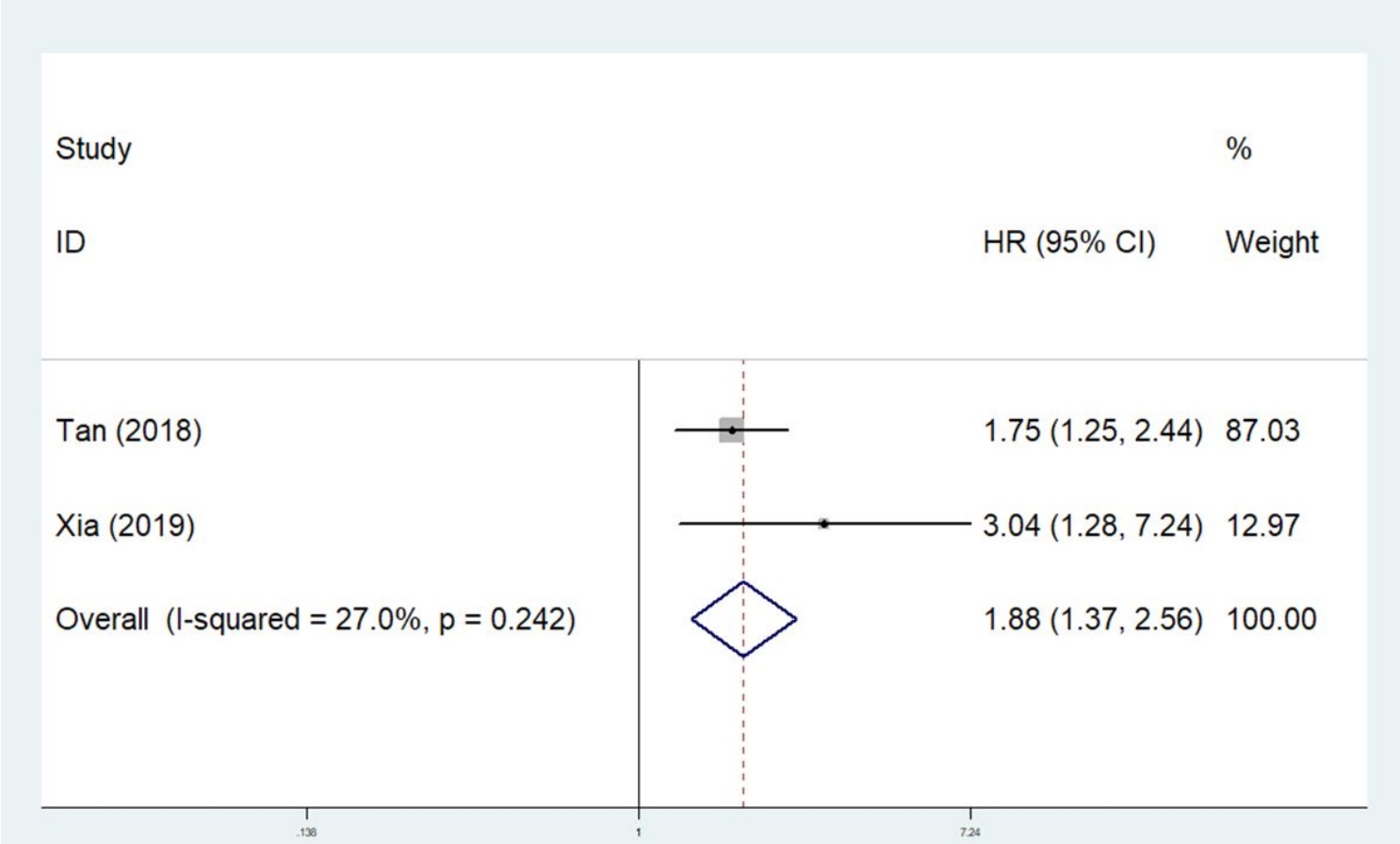

Figure 4

Forest plot of the association between pretreatment albumin to alkaline phosphatase ratio and cancer-specific survival.

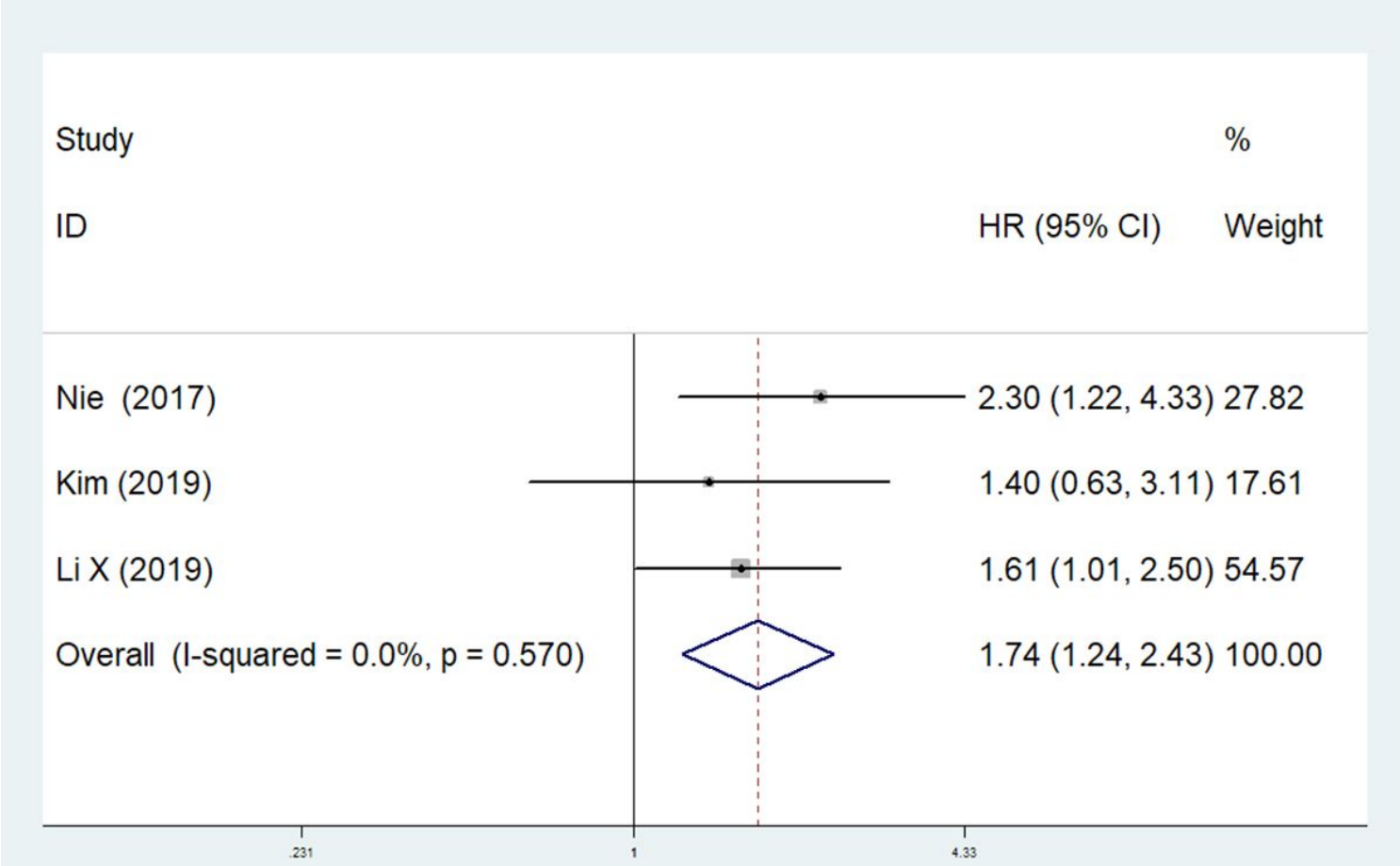

Figure 5

Forest plot of the association between pretreatment albumin to alkaline phosphatase ratio and progression-free survival.

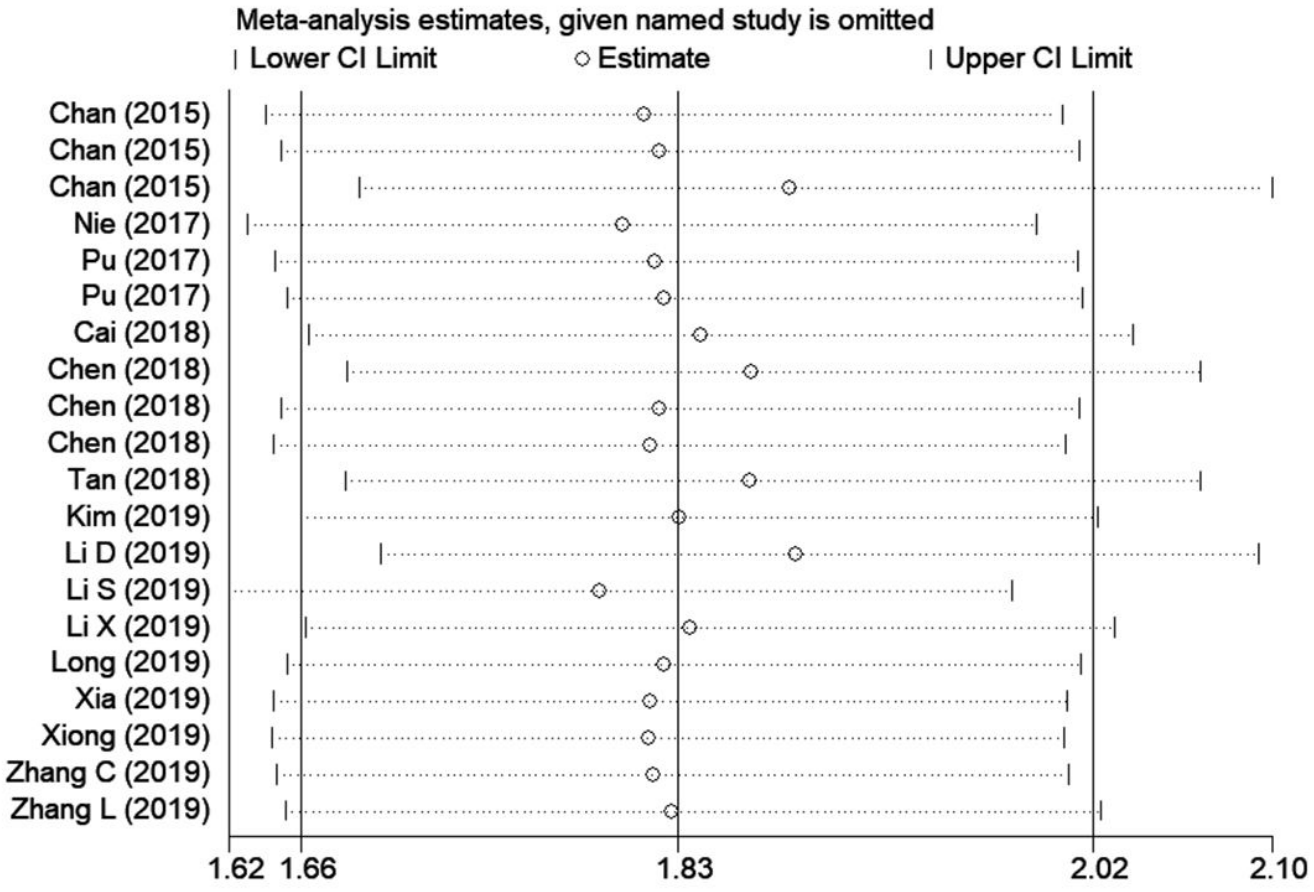

Figure 6

Sensitivity analysis of the association between pretreatment albumin to alkaline phosphatase ratio and overall survival.

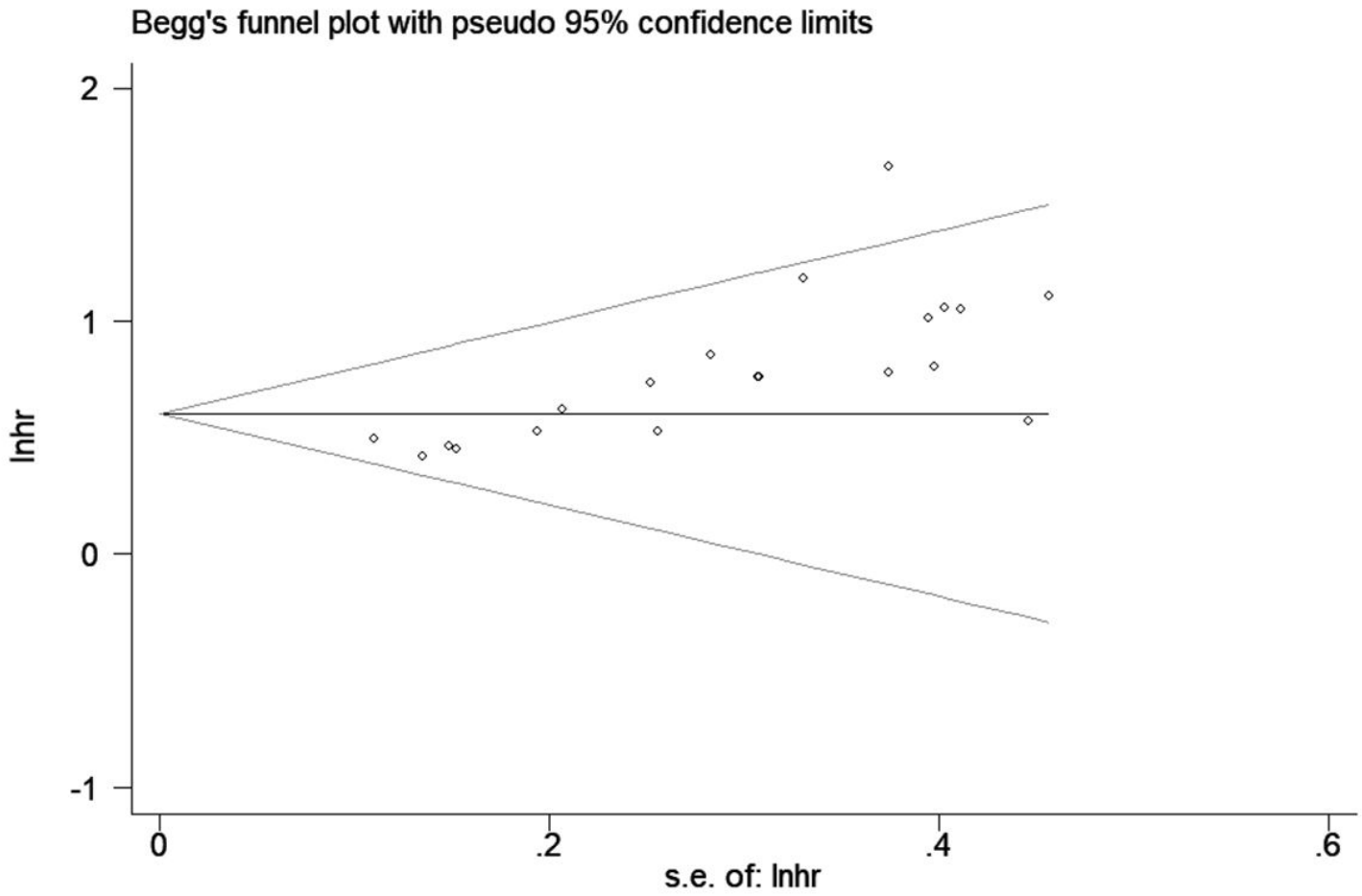

Figure 7

Begg’s funnel plots of the association of pretreatment albumin to alkaline phosphatase ratio with overall survival.

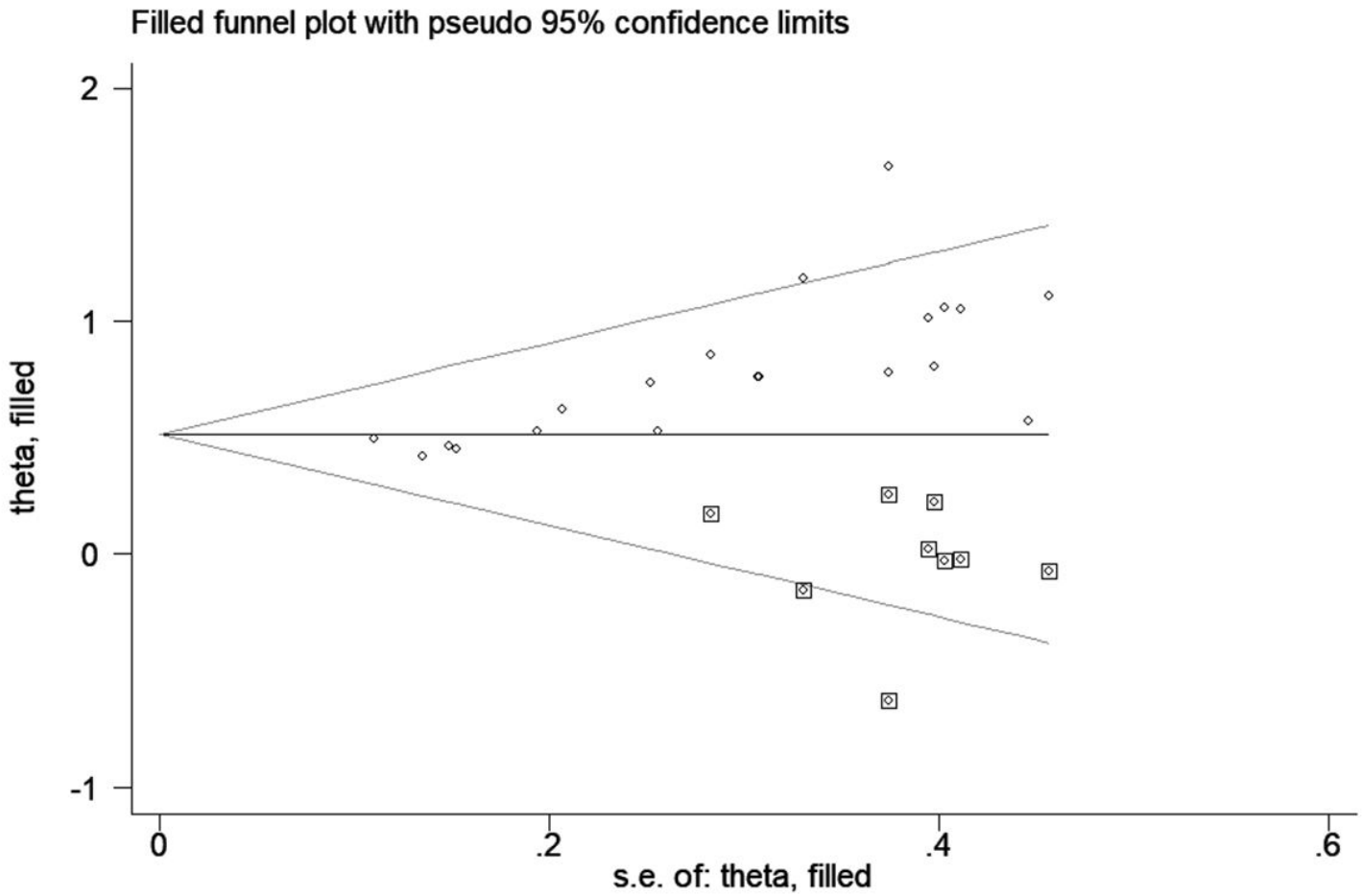

Figure 8

Filled funnel plots of the association of pretreatment albumin to alkaline phosphatase ratio with overall survival