

Higher pretreatment lactate dehydrogenase concentration predicts worse overall survival in patients with lung cancer

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Abstract

Background: The aim of this study was to systematically evaluate the prognostic role of pretreatment lactate dehydrogenase (LDH) concentration for survival in patients with lung cancer through performing a meta-analysis.

Methods: PubMed, EMBASE, Cochrane Library, Web of Science, and China National Knowledge Infrastructure were searched for potentially relevant literature. The study and patients' characteristics were extracted. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were pooled to estimate the prognostic role of LDH in patients with lung cancer.

Results: Fourteen studies with 4084 patients were included. Higher pretreatment LDH concentration was significantly associated with an increased risk of overall mortality in patients with lung cancer (HR = 1.49, 95% CI, 1.38–1.59). Subgroup analysis of studies also resulted in a significantly increased risk of mortality in patients with small cell lung cancer (SCLC, HR = 1.54, 95% CI, 1.43–1.67) or nonsmall cell lung cancer (NSCLC, HR = 1.25, 95% CI, 1.06–1.46), with high pretreatment LDH concentration. No significant between-study heterogeneity was observed ($I^2 = 12.0\%$, $P = .321$). No significant publication bias was found ($P = .352$) in the meta-analysis.

Conclusion: The results suggested that higher pretreatment LDH concentration was associated with worse overall survival in patients with lung cancer. The findings may assist future research on anticancer therapy by targeting LDH and help predict prognosis in lung cancer patients. However, high-quality studies are required to further research and support these associations. Moreover, confounding factors such as patient ethnicity and tumor type should be considered in future studies.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, HR = hazard ratio, LDH = lactate dehydrogenase, NOS = Newcastle–Ottawa Scale, NSCLC = nonsmall cell lung cancer, OS = overall survival, SCLC = small cell lung cancer.

Keywords: lactate dehydrogenase, lung cancer, prognosis, survival

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.^[1] Among patients with lung cancer, approximately 85% are nonsmall cell lung cancer (NSCLC).^[2] About 15% are small cell lung cancer (SCLC), which is the most aggressive type

of lung cancer.^[3] Treatments for lung cancer patients mainly include surgery, chemotherapy, radiotherapy, and target therapy in recent years.^[3,4] With improvement in diagnosis and treatment, the prognosis of lung cancer remains poor. The 5-year survival rates of NSCLC and SCLC were lower than 15%^[1] and only 1% to 3%,^[4] respectively. Also, the prognosis widely varies, so it is worthwhile to explore prognostic biomarkers for patients with lung cancer.

In recent years, serum lactate dehydrogenase (LDH) concentration was found to play a prognostic role in many tumors, such as Ewing sarcoma, urologic cancers, malignant mesothelioma, and nasopharyngeal carcinoma, and so on.^[5–9] Some researchers also investigated the prognostic role of LDH in patients with lung cancer, but the results were not conclusive. Some studies demonstrated that higher LDH was associated with poorer prognosis in lung cancer patients.^[10–14] However, some researchers found that this association was not significant.^[4,15,16] Due to the controversy, we aimed to perform a meta-analysis to systematically evaluate the prognostic role of LDH in patients with lung cancer.

2. Methods

2.1. Search strategy

As this is a meta-analysis, ethical approval was not necessary. PubMed, EMBASE, Cochrane Library, Web of Science, and

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China National Knowledge Infrastructure (CNKI) were searched for potentially eligible studies (last update ran on April 5, 2018). The following keywords were used: (“lung neoplasms” OR “lung cancer” OR “lung carcinoma”) AND (“lactate dehydrogenase”) AND (“prognosis” OR “outcome” OR “survival” OR “mortality”) (Table 1). Additional literature was located through screening reference lists of previous systematic reviews and included studies. No language restrictions were adopted.

2.2. Study selection

Two investigators performed the study selection process independently, and disagreements were resolved by consensus. Studies were considered eligible if they met all of the following inclusion criteria: the patients were diagnosed with lung cancer by histopathological examination; the LDH of the patients were measured; patients were followed up for survival outcomes; and enough data were reported to estimate the prognostic value of LDH in lung cancer patients. Study types were not restricted: retrospective/prospective or random clinical studies/observational studies. However, reviews, case reports, conference abstracts, unrelated articles, and studies without enough data were excluded.

2.3. Data extraction

The data extraction process was also performed by 2 authors independently, with any disagreements being discussed. The primary data included hazard ratio (HR) for overall survival (OS)

with 95% confidence interval (95% CI). Multivariate analyses data were extracted over univariate analyses data. The basic characteristics of the studies and patients were also extracted, including first author, publication year, country, the number of patients, sex of patients, age of patients, tumor subtype, and so on.

2.4. Study quality assessment

The Newcastle–Ottawa Scale (NOS) criteria were used to assess the quality of the included studies.^[17] The NOS scale assessed 3 perspectives of the study: subject selection; comparability of subject; and exposure (for case–control studies)/outcome (for cohort studies). The NOS scores ranged from 0 to 9, and studies with 7 scores or more were considered as high-quality studies.

2.5. Statistical analysis

Forest plots were constructed to estimate the pooled prognostic value of LDH in patients with lung cancer. The pooled HR was considered significant if the *P* value was less than .05. The between-study heterogeneity was also assessed, with $I^2 > 50\%$ or $P < .10$ indicating significant heterogeneity. Random effect models were used and sensitivity analysis was performed if significant heterogeneity existed. Subgroup analyses were also performed according to patient source and tumor type. Publication bias was assessed by Begg^[18] and Egger tests,^[19] with $P > .10$ implying no significant publication bias. The statistical analyses were performed by STATA 11.0 (STATA Corporation, College Station, TX).

Table 1

Search strategies.

Databases	Search strategies
PubMed	(1) “lung neoplasms” [Mesh] OR lung cancer OR lung carcinoma (2) lactate dehydrogenase (3) “prognosis” [Mesh] OR outcome OR survival OR mortality (4) 1 AND 2 AND 3
EMBASE	(1) “lung tumor”/exp OR “lung tumor” (2) “lung neoplasms”/exp OR “lung neoplasms” (3) “lung cancer”/exp OR “lung cancer” (4) “lung carcinoma”/exp OR “lung carcinoma” (5) “lactate dehydrogenase”/exp OR “lactate dehydrogenase” (6) “prognosis”/exp OR “prognosis” (7) “outcome”/exp OR “outcome” (8) “survival”/exp OR “survival” (9) “mortality”/exp OR “mortality” (10) 1 OR 2 OR 3 OR 4 (11) 6 OR 7 OR 8 OR 9 (12) 5 AND 10 AND 11
Cochrane Library	(1) Mesh descriptor lung neoplasms explode all trees (2) (lung cancer) OR (lung carcinoma) (3) Mesh descriptor L-lactate dehydrogenase explode all trees (4) lactate dehydrogenase (5) Mesh descriptor prognosis explode all trees (6) (survival) OR (outcome) OR (mortality) (7) 1 OR 2 (8) 3 OR 4 (9) 5 OR 6 (10) 7 AND 8 AND 9
Web of Science	(1) TS=(lung neoplasms OR lung cancer OR lung carcinoma) (2) TS=(lactate dehydrogenase) (3) TS=(prognosis OR outcome OR survival OR mortality) (4) 1 AND 2 AND 3
CNKI	Search strategy in Chinese. Includes search terms similar to the terms used in PubMed.

CNKI = China National Knowledge Infrastructure.

3. Results

3.1. Literature research

The initial literature search identified 2127 citations. Among them, 589 were duplicated and were removed. The rest 1538 studies were screened by titles and abstracts, and 1492 were excluded according to the inclusion and exclusion criteria. The rest 46 studies were assessed in full text and 32 were further excluded. Eventually, 14 articles^[4,10–16,20–25] met the inclusion criteria and were included. The study selection process is shown in Fig. 1.

3.2. Study characteristics

The basic characteristics of the 14 included studies are summarized in Table 2. The studies were published between 2004 and 2018, and 12 of them were published in the last 5 years. The studies were conducted in 7 different countries. Two of them were prospective studies. A total of 4084 patients were included. In each study, the number of male patients was higher than that of female patients. The tumor types mainly included NSCLC and SCLC. The survival outcomes were all OS, and the HRs were all from multivariate analyses. Among the 14 studies, 10 studies concluded that higher LDH was associated with worse survival in lung cancer patients. The NOS scores were all above 7, suggesting the qualities of the studies were good.

3.3. Association between LDH concentration and overall mortality risk

After pooling the results of the 14 studies together, higher pretreatment LDH concentration was significantly associated with an increased risk of overall mortality in patients with lung

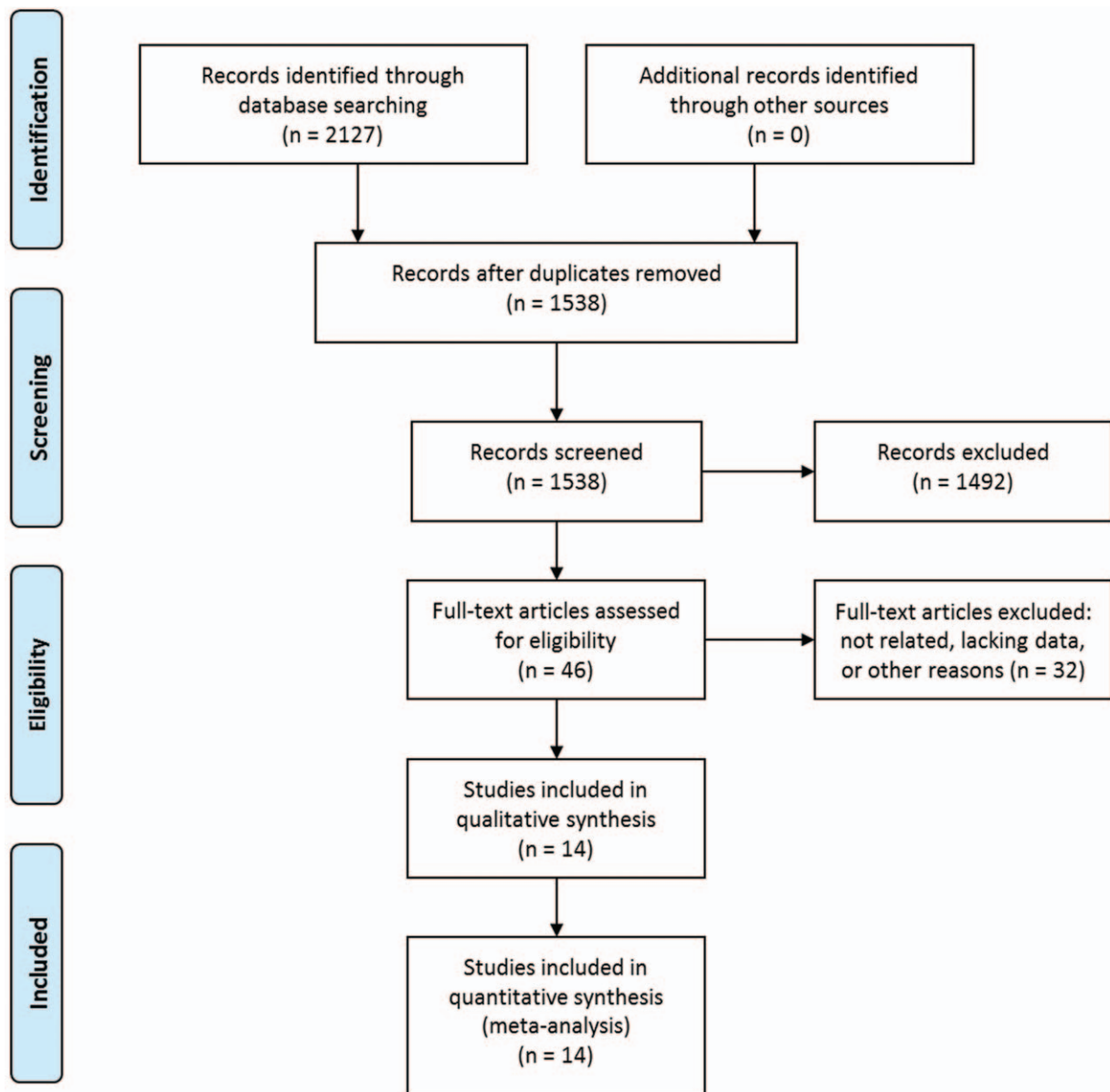


Figure 1. Selection process of studies.

cancer (HR = 1.49, 95% CI, 1.38–1.59) (Fig. 2). No significant between-study heterogeneity was observed ($I^2 = 12.0\%$, $P = .321$).

3.4. Subgroup analysis

3.4.1. Patient source. The 14 studies were divided into Asian group (8 studies) and Caucasian group (6 studies) according to patients' source. Subgroup analysis showed that patients with higher pretreatment LDH concentration had a significantly increased risk of mortality in both Asian group (HR = 1.52, 95% CI, 1.40–1.65; $I^2 = 7.0\%$, $P = .376$) and Caucasian group (HR = 1.40, 95% CI, 1.23–1.60; $I^2 = 19.4\%$, $P = .287$) (Fig. 3).

3.4.2. Tumor type. Of the 14 studies, 10 examined SCLC, 3 examined NSCLC, and 1 examined mixed lung cancers. Subgroup analysis of studies also resulted in a significantly increased risk of mortality in patients with SCLC (HR = 1.54,

95% CI, 1.43–1.67; $I^2 = 0.0\%$, $P = .615$) or NSCLC (HR = 1.25, 95% CI, 1.06–1.46; $I^2 = 0.0\%$, $P = .723$), with high pretreatment LDH concentration (Fig. 4).

All the meta-analyses results above are summarized in Table 3.

3.4.3. Publication bias. No significant publication bias was found in the meta-analysis ($P = .352$ for Begg test and $.951$ for Egger test). The Begg plot of publication bias of the 14 studies is shown in Fig. 5.

4. Discussion

This study aimed to evaluate the prognostic role of LDH in patients with lung cancer. We performed a meta-analysis to summarize the evidence, and 14 studies were included. Our results suggested that higher LDH was associated with poorer OS in patients with lung cancer.

Table 2**Characteristics of the included studies.**

Ref.	Year	Country	Study type	N	Female	Male	Age, y	Tumor type	Multivariate	Conclusion	NOS score
Ando et al ^[20]	2004	Japan	Retrospective	57	9	48	Mean 66	SCLC	Yes	Results not conclusive	7
de Jong et al ^[21]	2007	Netherlands	Retrospective	156	63	93	Median 63	SCLC	Yes	High LDH correlates with worse OS	8
Almasi et al ^[22]	2013	Denmark	Prospective	85	—	—	—	SCLC	Yes	High LDH correlates with worse OS	9
Fiegl et al ^[10]	2014	Austria	Retrospective	484	158	326	Median 62.1	SCLC	Yes	High LDH correlates with worse OS	8
Kang et al ^[23]	2014	Korea	Retrospective	187	25	162	Median 68	SCLC	Yes	High LDH correlates with worse OS	8
Ulas et al ^[24]	2014	Turkey	Retrospective	462	57	405	Median 58	NSCLC	Yes	High LDH correlates with worse OS	8
Wang et al ^[14]	2014	China	Retrospective	499	124	375	Mean 59	SCLC	Yes	High LDH correlates with worse OS	9
Hong et al ^[25]	2015	China	Retrospective	919	284	635	Median 56	SCLC	Yes	High LDH correlates with worse OS	8
Inal et al ^[12]	2015	Turkey	Prospective	72	16	56	—	Mixed	Yes	High LDH correlates with worse OS	7
Zhou et al ^[13]	2015	China	Retrospective	367	51	316	Median 59	SCLC	Yes	High LDH correlates with worse OS	9
Fukui et al ^[15]	2016	Japan	Retrospective	83	10	73	Median 71	SCLC	Yes	Results not conclusive	8
Kasapoglu et al ^[16]	2016	Turkey	Retrospective	199	60	139	Median 64	NSCLC	Yes	Results not conclusive	8
Lee et al ^[14]	2016	Korea	Retrospective	394	148	246	Median 65	NSCLC	Yes	High LDH correlates with worse OS	8
Fan et al ^[4]	2018	China	Retrospective	120	34	86	Mean 63	SCLC	Yes	Results not conclusive	8

LDH=lactate dehydrogenase, NOS=Newcastle–Ottawa Scale, NSCLC=non-small cell lung cancer, OS=overall survival, SCLC=small cell lung cancer.

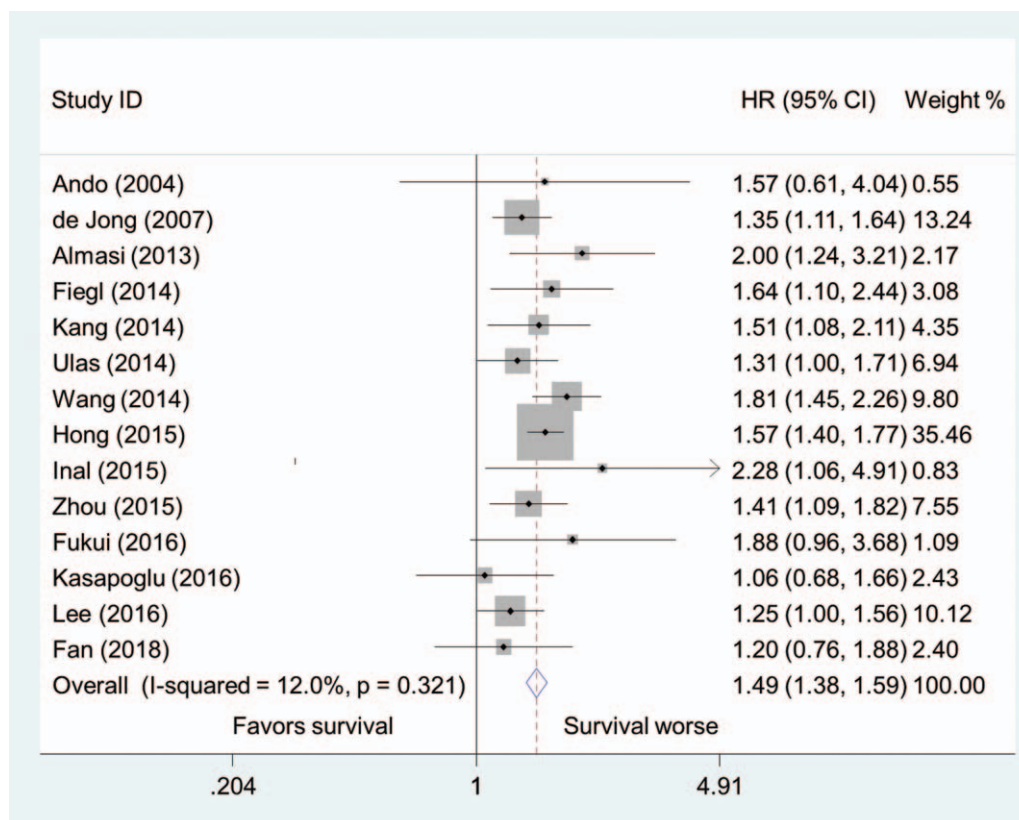


Figure 2. Pooled hazard ratio of higher pretreatment LDH concentration for overall survival in patients with lung cancer.

Subgroup analyses were also performed to further explore the role of LDH in patients with lung cancer. In both Asian group and Caucasian group, higher LDH was found to be associated with worse OS in patients with lung cancer. The pooled HR in the Asian group was slightly higher than that in the Caucasian group, suggesting that LDH might better predict the prognosis in Asian populations. As to different tumor types, the pooled HRs were all significant, and the pooled HR was the highest in patients with

mixed lung cancer and the lowest in patients with NSCLC. These findings suggested that LDH might not be a good prognostic marker in patients with NSCLC. However, due to the limited number of studies in the subgroups, caution should be applied as to the subgroup analyses results, and more studies are needed to verify these findings.

LDH is distributed in many tissues of the human body. LDH is an enzyme that catalyzes the reaction between lactic acid and

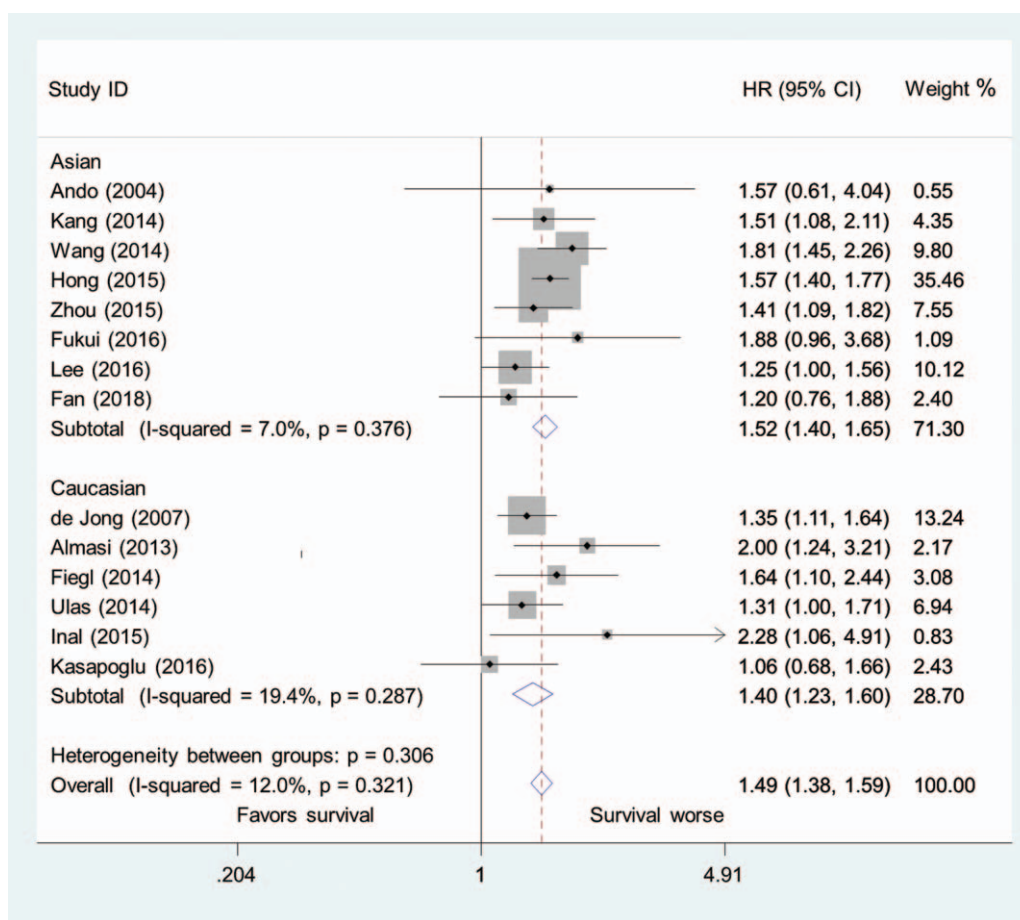


Figure 3. Pooled hazard ratio of higher pretreatment LDH concentration for overall survival in patients with lung cancer in the Asian group and Caucasian group.

pyruvic acid. The reaction between lactic acid and pyruvic acid usually occurs under anaerobic conditions, such as intratumoral environment. The concentration of serum LDH is elevated in various diseases, including many malignant tumors. High concentrations of LDH reflex anaerobic glycolytic metabolism in the tumor environment.^[14] Lee et al^[14] also found that, compared with the low metastatic score group, the patients in the high metastatic score group had significantly higher concentrations of serum LDH. Therefore, the concentrations of LDH reflect the extent of many tumors and could serve as a nonspecific marker,^[14] which might be an underlying mechanism why high concentrations of LDH are associated with worse OS of lung cancer patients.

The findings of this study may imply potential therapeutic implications (targeting LDH) in patients with lung cancer. Some researchers have investigated the effect of lowering LDH concentration in cancer patients. Yang et al^[26] investigated the effects of oxamate, a classic inhibitor of LDH-A, in both NSCLC cells and normal lung epithelial cells. They found that oxamate significantly suppressed the proliferation of NSCLC cells, and it had a much lower toxicity in normal cells. Their results suggested the potential use of targeting LDH-A in NSCLC treatment. Koukourakis et al^[27] examined the role of the addition of vatalanib, a VEGF-receptor inhibitor, to FOLFOX 4 in colorectal cancer patients with high serum LDH concentrations. Their results showed that the addition of vatalanib diminished

the effect of LDH expression on the prognosis of patients. Thus, our results further support the therapeutic potential of targeting LDH in patients with lung cancer.

Although most studies concluded that higher pretreatment LDH concentration was associated with worse OS in patients with lung cancer,^[10–14,21–25] some studies did not come to this conclusion.^[4,15,16,20] LDH is increased not only in cancer patients but also in other diseases, for example, infections, heart failure, acute pancreatitis and anemia, and so on.^[4,28] Therefore, other factors that influence LDH concentrations may result in the insignificant association between LDH concentrations and survival.^[4] In future studies, patients with other diseases that may influence the LDH concentrations should be excluded.

Kasapoglu et al^[16] investigated the factors influencing survival in NSCLC patients with malignant pleural effusions. Interestingly, they found that the survival time was significantly longer in patients with blood LDH concentrations less than 250 U/L than those with more than 250 U/L; however, the survival time was not significantly different between the patients with pleural fluid LDH concentrations less than 250 U/L and those with more than 250 U/L.^[16] These results may suggest that blood LDH concentrations could better predict survival than pleural fluid LDH concentrations, but more research is needed to verify this.

Apart from LDH, many other factors have been found in the prognosis of lung cancer, such as plasma fibrinogen, serum hemoglobin concentration, D-dimer plasma concentration, white

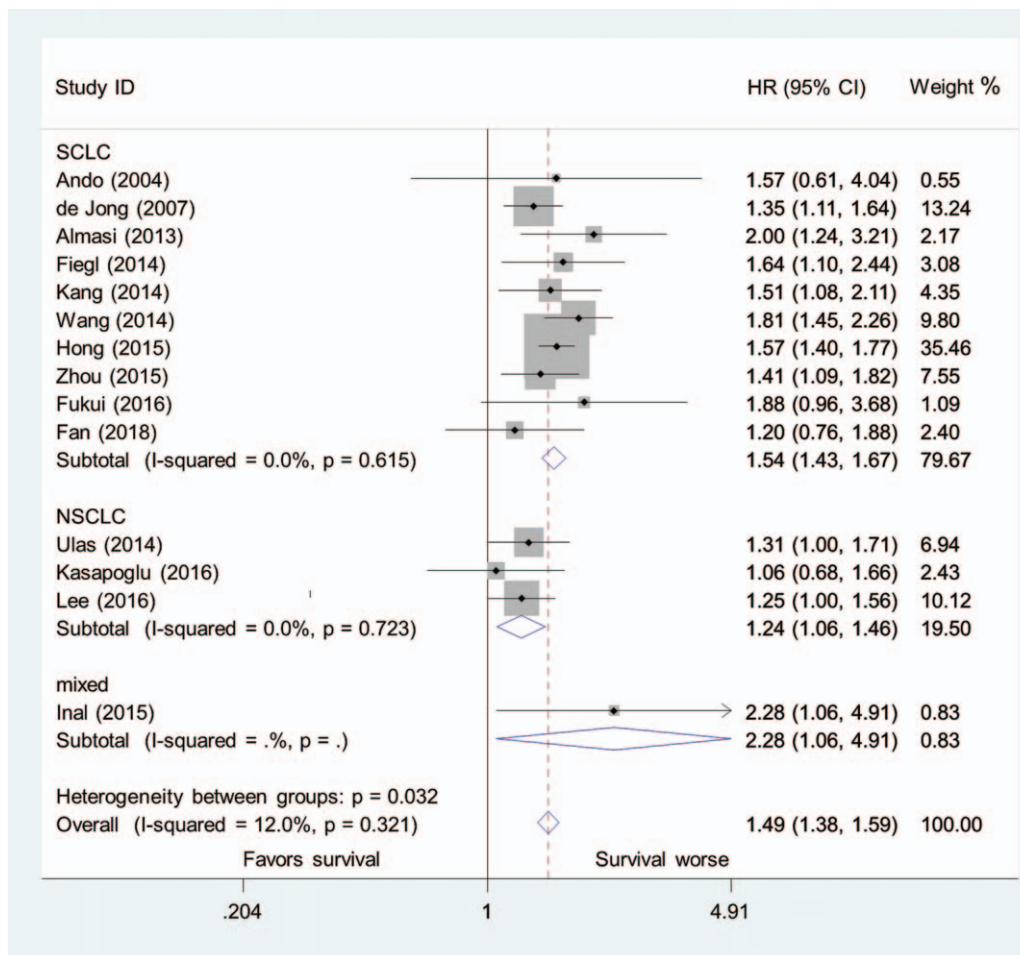


Figure 4. Pooled hazard ratio of higher pretreatment LDH concentration for overall survival in patients with SCLC, NSCLC, and mixed lung cancers.

blood cell count, platelet count, serum albumin concentration, C-reactive protein/albumin ratio, and so on.^[4,12,13,15,16,25] The assessment of LDH is easy and inexpensive. This readily accessible and cheap prognostic factor may serve as a promising tool in clinical work. In the future, serum LDH concentrations could be used to predict the survival of lung cancer along with other well-established biomarkers through performing multidimensional assessment of the known markers to improve prognostic algorithms.^[14]

There are some limitations in our meta-analysis. First, the number of included studies in our meta-analysis was limited. And the numbers of studies in the subgroups were even smaller. Therefore, the results of this meta-analysis should be treated with

caution. More studies are needed to verify our findings. Second, the characteristics of the studies and patients between the included articles varied. For example, the ethnicity and tumor type of the patients were not the same. Furthermore, although no significant between-study heterogeneity was observed in our meta-analysis, the I^2 was not 0%, suggesting difference between the results of the studies. Besides, publication bias should not be completely excluded, although no significant publication bias was found in our meta-analysis, as it was a major concern for all meta-analyses.

In conclusion, our results suggested that higher pretreatment LDH concentration was associated with worse OS in patients with lung cancer. The findings may assist future research on

Table 3

Summary of meta-analysis results.

	N	Pooled HR (95% CI)	P	Heterogeneity (I^2 , P)	Conclusion
Overall	14	1.49 (1.38–1.59)	<.001	12.0%, .321	Positive
Asian	8	1.52 (1.40–1.65)	<.001	7.0%, .376	Positive
Caucasian	6	1.40 (1.23–1.60)	<.001	19.4%, .287	Positive
SCLC	10	1.54 (1.43–1.67)	<.001	0.0%, .615	Positive
NSCLC	3	1.25 (1.06–1.46)	.007	0.0%, .723	Positive
Mixed	1	2.28 (1.06–4.91)	.035	—	positive

CI = confidence interval, HR = hazard ratio, NSCLC = nonsmall cell lung cancer, SCLC = small cell lung cancer.

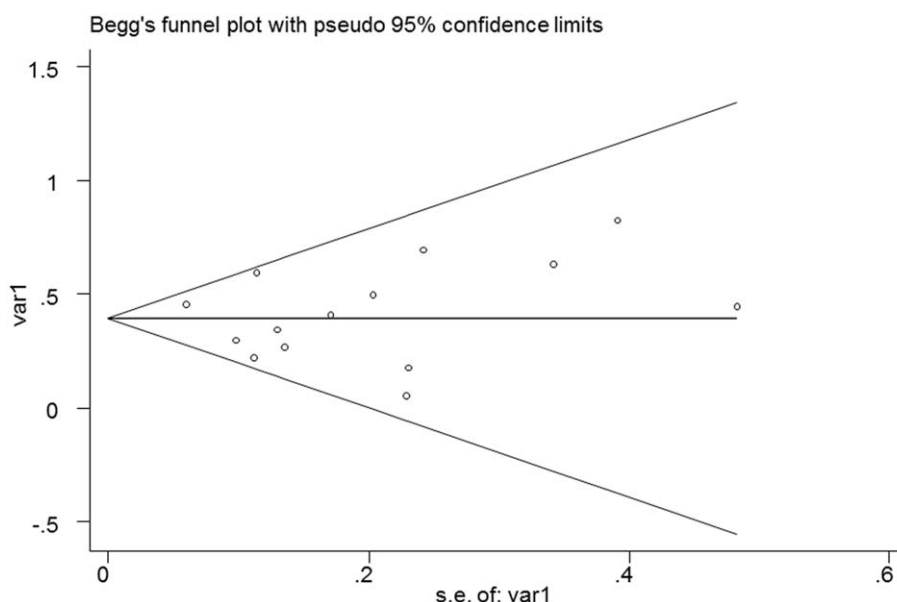


Figure 5. The Begg publication bias plot of the 14 included studies.

anticancer therapy by targeting LDH and help predict prognosis in lung cancer patients. However, due to the limited number of included studies, more well-designed studies are warranted to further verify our results.

Author contributions

Conceptualization: Taibing Deng, Yu Meng, Weimin Li.

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Validation: Jing Zhang, Yu Meng.

Writing – original draft: Taibing Deng, Jing Zhang, Yu Meng.

Writing – review & editing: Taibing Deng, Jing Zhang, Yu Meng, Yong-Zhao Zhou, Weimin Li.

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