



Meta-Analysis

The role of lactate dehydrogenase levels on non-small cell lung cancer prognosis: a meta-analysis

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Abstract: The role of serum lactate dehydrogenase (LDH) on the clinical outcomes of non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) treatment remained to be elucidated. Therefore, we did this meta-analysis. We searched databases including PubMed, EMBASE, and Cochrane Library till to June, 2017. The relationships between the LDH levels and overall survival (OS) and progression free survival (PFS) were assessed by calculating hazard ratios (HRs) and 95% confidence intervals (CIs). The association between the LDH levels and disease control rate (DCR) was calculated by odds ratio (OR) and 95% CI. Seven studies were included in the meta-analysis. As for DCR, the result from this meta-analysis was not positive (OR=0.71; 95% CI 0.21 – 2.37; P=0.57). As for PFS, the result of the meta-analysis indicated that elevated LDH was significantly associated with shorter PFS (HR=1.88; 95%CI, 1.37–2.59). When studies were stratified by ethnicity, significant association was also observed in Asian group (HR=2.36; 95%CI, 1.57–3.55). As for OS, patients with high levels of LDH showed significantly shorter OS (HR=2.44; 95%CI, 1.84–3.23). In the subgroup by race, significant associations were found in Asian group (HR=2.62; 95%CI, 1.61–4.26) and Caucasian population (HR=2.36; 95%CI, 1.66–3.34). In conclusion, this meta-analysis suggested that elevated LDH level was associated with the poor PFS and OS of NSCLC patients receiving EGFR-TKIs treatment.

Key words: Non-small cell lung cancer; Lactate dehydrogenase; Meta-analysis; Prognosis.

Introduction

Lung cancer is the leading cause of death in patients with malignant tumors in China (1). Approximately 85% of patients presenting with lung cancer have non-small cell lung cancer (NSCLC) (2). At least 30% of non-small cell lung cancer (NSCLC) patients could not receive operation at the first time of diagnosis. Thus, NSCLC has a high prevalence and high mortality.

The first-line treatments for these patients with epidermal growth factor receptor (EGFR) mutation are molecular targeted therapy (3). The most common EGFR mutations, such as exon19 deletion and exon 21 L858R mutation, are important predictors to the response of EGFR tyrosine-kinase inhibitors (TKIs) treatment (4). In the previous clinical studies, NSCLC patients with EGFR mutation responded better to frontline platinum-doublet chemotherapy (5). Receiving EGFR-TKIs as the first-line treatment, the median progression free survival (PFS) was 12–16 months (6). However, only 70–80% patients with EGFR-TKIs treatment will receive such good PFS (7, 8). Lactate dehydrogenase (LDH) is

an enzyme which could catalyze the hydrogentransfer reaction between lactic acid and pyruvic acid (9). Many studies have investigated the association between serum LDH levels and cancer prognosis, including small cell lung cancer (10). However, the role of serum LDH on the clinical outcomes of NSCLC patients with EGFR-TKIs treatment remained to be elucidated (11–16). Therefore, we did this meta-analysis to resolve this question. To the best of our knowledge, this was the first meta-analysis on the effect of LDH in NSCLC patients treated with EGFR-TKIs.

Materials and Methods

Publication search

We searched databases including PubMed, EMBASE, and Cochrane Library till to June, 2017. We ran searches based on the following terms: (lung cancer or lung carcinoma or non-small cell lung cancer or NSCLC) and (lactate dehydrogenase or LDH) and (epidermal growth factor receptor or EGFR). The references of the retrieved articles were also hand searched at the

same time to identify additional published articles.

Inclusion and exclusion criteria

The inclusion criteria of eligible studies were as following: (1) evaluated the association between the LDH levels and clinical outcomes of NSCLC patients with EGFR-TKIs treatment; (2) sufficient data to calculate hazard ratio (HR) and 95% confidence interval (CI) for overall survival (OS) and PFS, and sufficient data to calculate odds ratio (OR) and 95% CI for disease control rate (DCR). We excluded the following studies: (1) reviews, letters, conference abstracts, and case reports; (2) articles that did not offer useful data; (3) overlapping studies.

Data extraction and quality assessment

The following information was extracted from all obtained publications: first author name, year, race, age, histology, stage, Eastern Cooperative Oncology Group performance status (ECOG PS), EGFR mutation, sample size, duration of follow-up, clinical outcomes, and covariates. The quality of each study was evaluated according to the Newcastle-Ottawa quality assessment scale (17).

Statistical analysis

The relationships between the LDH levels and OS and PFS were assessed by calculating HR with 95% CI. The association between the LDH levels and DCR was calculated by OR and 95% CI. When the P value for Cochran’s Q statistic was less than 0.1, and a significant heterogeneity existed across the included studies, the random effects model (DerSimonian and Laird method) was used for meta-analysis (18, 19), or else the fixed effects model (Mantel–Haenszel method) was used (19, 20). The subgroup analysis was carried out by race. Funnel plots was undertaken to assess the potential publication bias. All statistical tests were used by the Reviewer Manager software 5.1 (Nordic Cochrane Center, Copenhagen, Denmark).

Results

Study characteristics

A total of 19 papers were retrieved after the first search, and 12 of them were excluded from the analysis. As a result, 7 studies that met the inclusion criteria were included in the meta-analysis. The data collection flow chart was shown in Figure 1. The characteristics of all studies were included in Table 1. Four studies were performed in Asian and 3 studies were conducted in Caucasian. Four studies provided the data of DCR and OS, 3 studies provided the data of PFS.

LDH levels and clinical outcomes

As for DCR, the result from this meta-analysis was not positive (OR=0.71; 95% CI 0.21 – 2.37; P=0.57; Figure 2). As for PFS, the result of the meta-analysis indicated that elevated LDH was significantly associated with shorter PFS (HR=1.88; 95%CI, 1.37–2.59; Figure 3). When studies were stratified by ethnicity, significant association was also observed in Asian group (HR=2.36; 95%CI, 1.57–3.55). As for OS, patients with high levels of LDH showed significantly shorter OS

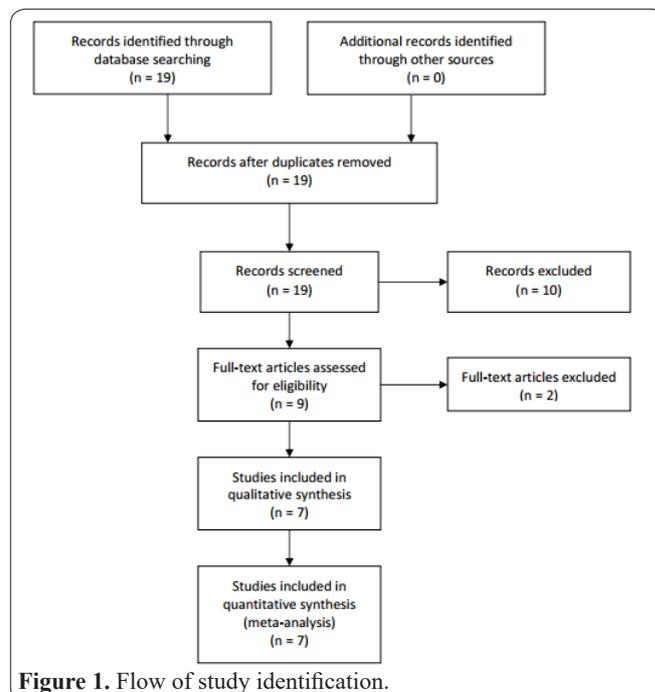


Figure 1. Flow of study identification.

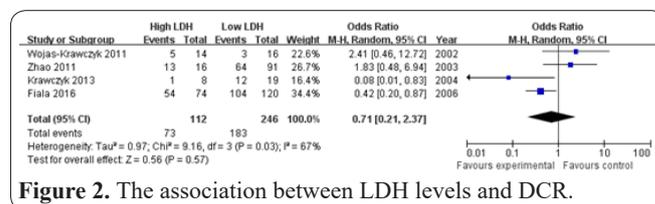


Figure 2. The association between LDH levels and DCR.

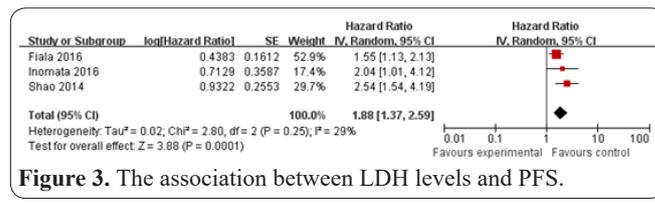


Figure 3. The association between LDH levels and PFS.

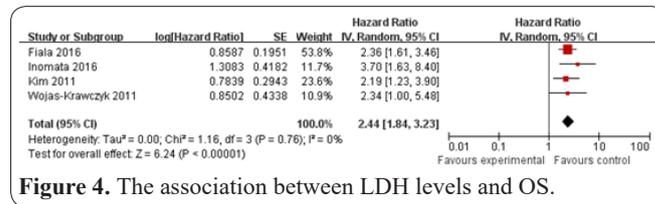


Figure 4. The association between LDH levels and OS.

Table 2. The association between LDH levels and clinical outcomes of patients with NSCLC.

Outcomes	HR/OR (95% CI)	P Value	I ² (%)
DCR	0.71 (0.21-2.37)	0.57	67
PFS	1.88 (1.37-2.59)	0.0001	0
Asian	2.36 (1.57-3.55)	<0.0001	0
OS	2.44 (1.84-3.23)	<0.00001	0
Asian	2.62 (1.61-4.26)	0.0001	5
Caucasian	2.36 (1.66-3.34)	<0.00001	0

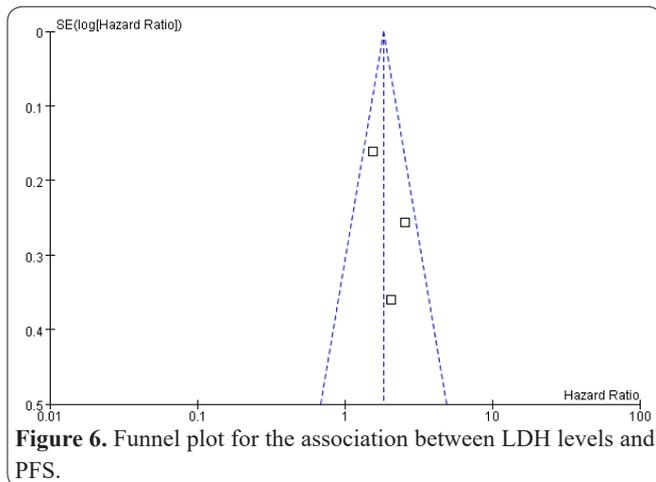
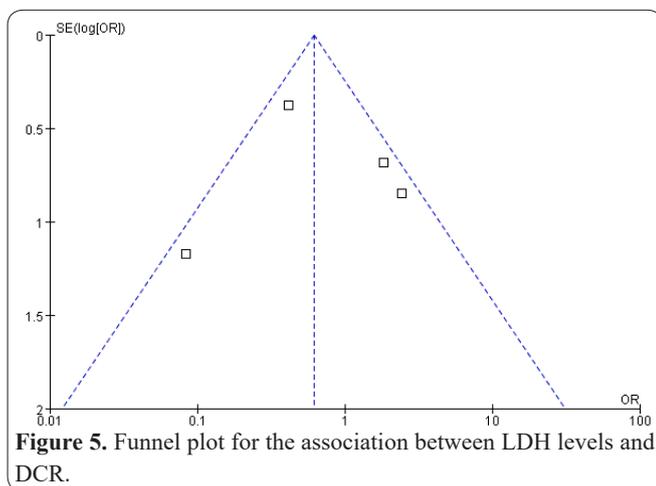
OS, overall survival; PFS, progression-free survival; DCR, disease control rate.

(HR=2.44; 95%CI, 1.84–3.23; Figure 4). In the subgroup by race, significant associations were found in Asian group (HR=2.62; 95%CI, 1.61–4.26) and Caucasian population (HR=2.36; 95%CI, 1.66–3.34). All the results are showed in the Table 2. Funnel plot was used to analyze the publication bias in this meta-analysis. No significant publication bias was found (Figures 5-7).

Table 1. Characteristics of the included studies

Study	Year	Race	Age (year)	Ratio of men/women	Histology	Stage	ECOG PS	EGFR mutation (%)	No. of patients	Follow-up (month)	Outcome	Quality score	Adjustment for covariates
Kim	2011	Asian	20-84	160/97	Mixed	IIIB-IV	0-2	NA	257	NA	OS	8	Skin rash, ECOG PS
Wojas-Krawczyk	2011	Caucasian	61.64±8.19	51/22	Mixed	IIIB-IV	0-3	6.8	73	31	OS, DCR	8	Sex, ECOG PS, weight loss, skin rash
Zhao	2011	Asian	31-78	69/97	Mixed	IIIB-IV	NA	NA	77	NA	DCR	8	NA
Krawczyk	2013	Caucasian	60.9±9.6	36/35	Mixed	IIIA-IV	NA	24	71	NA	DCR	8	NA
Shao	2014	Asian	25-82	77/37	Mixed	IIIB-IV	0-3	31.6	114	NA	PFS	7	Smoking, EGFR mutation status, skin rash, tissue polypeptidespecific antigen
Fiala	2016	Caucasian	28-84	200/109	Mixed	IIIB-IV	0-3	8.4	309	10.4	OS, PFS, DCR	8	Age, sex, smoking, histology, EGFR mutation status, stage, ECOG PS
Inomata	2016	Asian	49-87	30/35	Mixed	III-IV	0-3	100%	65	NA	OS, PFS	8	EGFR mutation status, stage

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival; DCR, disease control rate; NA, not available.

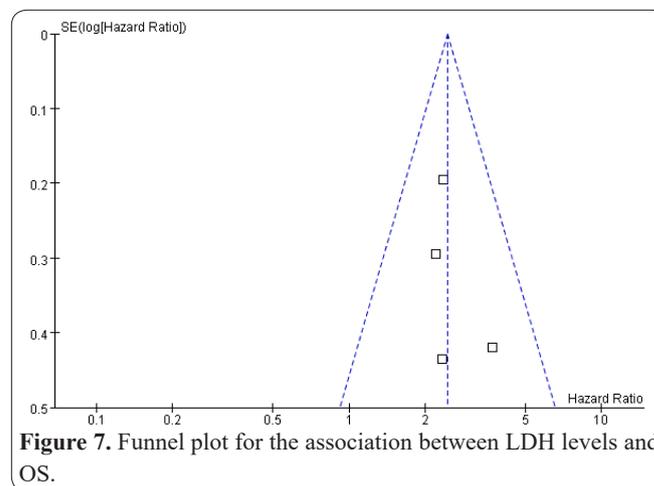


Discussion

Some studies have investigated the relation of LDH with outcomes of NSCLC patients with EGFR-TKIs treatment, but the results were still controversial. We thus analyzed this clinical question via the method of meta-analysis, and found that elevated LDH level was associated with the poor PFS and OS of NSCLC patients receiving EGFR-TKIs treatment. Therefore, LDH might be a prognostic biomarker for EGFR-TKIs treatment in NSCLC patients.

Lee *et al.* suggested that serum LDH levels was significantly correlated with whole-body tumor extent and OS in stage IV NSCLC (21). Kang *et al.* indicated that LDH was an independent prognostic factors for OS and PFS in small-cell lung cancer (22). Koukourakis *et al.* suggested that NSCLC with LDH-5 overexpression had a particularly aggressive behavior (23). Furthermore, Danner *et al.* found that in tumours greater than 3 cm, high tumour LDH-5 values associated with poorer long-term survival (24). Interestingly, high pleural LDH predicted shorter survival in patients with adenocarcinoma lung (25). However, the mechanism why LDH level was associated with the poor PFS and OS of NSCLC patients receiving EGFR-TKIs was still to be elucidated.

Some limitations in this meta-analysis should be acknowledged. First, although we searched the studies as more as we could, the number of studies was still small. Second, the data of histology and EGFR mutation status were still insufficient. Thus, we could not do subgroup analysis by these important clinical factors.



Third, all included studies were retrospective. Thus, the bias could not be excluded, although most studies used multivariate analyses and adjusted the covariates. The prospective study should be conducted to confirm the results of this meta-analysis.

In conclusion, this meta-analysis suggested that elevated LDH level was associated with the poor PFS and OS of NSCLC patients receiving EGFR-TKIs treatment.

Conflicts of interest

None

Acknowledgments

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