

# Prognostic significance of serum lactate dehydrogenase in patients with breast cancer: a meta-analysis

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**Background:** Multiple studies have assessed the prognostic significance of serum lactate dehydrogenase (LDH) in patients with breast cancer, but their results remain controversial. This study aimed to evaluate the prognostic value of LDH in breast cancer by meta-analysis.

**Methods:** Electronic searches for relevant articles were conducted in PubMed, Embase and Web of Science databases. The HR and their 95% CI were used to assess the prognostic value of serum LDH. Stata Statistical Software 12.0 was applied for statistical analysis.

**Results:** A total of 11 studies involving 6,102 patients were subjected to final analysis. Our results showed that higher serum LDH had significant effect on poor overall survival (HR, 1.88; 95% CI, 1.68–2.11) and progression-free survival (HR, 1.98; 95% CI, 1.46–2.68). Moreover, the results of subgroup analyses were consistent with that of overall outcomes. No significant heterogeneity and publication bias were found in this study.

**Conclusion:** Serum LDH could act as a prognostic factor for patients with breast cancer. Future data are needed to validate and update our results.

**Keywords:** breast cancer, lactate dehydrogenase, prognosis, biomarker, meta-analysis

## Introduction

Breast cancer is the most common cancer in women and the second leading cause of cancer-related deaths in females, with an estimated 1.67 million new cases and 0.52 million cancer deaths occurred in 2012 worldwide.<sup>1</sup> Although significant achievements have been made in therapeutic strategies, the clinical outcome of breast cancer patients remains unsatisfactory due to recurrence, metastasis or treatment-resistant. Identifying factors related to aggressive phenotypes and prognosis of breast cancer is essential for disease surveillance and precise therapy.

Breast cancer is a heterogeneous disease and presents with different clinical and biological characteristics. Nowadays, TNM staging system is widely used for cancer prognosis. However, survival of breast cancer patients after chemotherapy varies greatly, even within the same stages.<sup>2</sup> Several clinicopathological factors such as age of the patient, menopause status, tumor size, lymph node status, tumor grade, estrogen receptor, progesterone receptor, epidermal growth factor receptor 2 (HER-2) and Ki-67 expression parameters have been developed for making treatment plan.<sup>3</sup> Recently, more and more serum biomarkers were identified as prognostic factors for breast cancer, including circulating microRNAs, inflammatory factors and stem cell markers.<sup>4–6</sup> These easily

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detected and objective markers may provide new prognostic information for patients with breast cancer.

It is now generally accepted that the metabolism of cancer cells differs from that of normal cells. Under normal oxygen concentrations, tumor tissues, but not adjacent normal tissues, exhibit a high rate of glucose consumption. This phenomenon has been widely exploited for the diagnosis and staging of human solid cancers. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) utilizes the differences between glucose uptake of cancer cells and normal cells to make an imaging technique for detecting tumors. Besides, cancer cells preferentially metabolize glucose by glycolysis to generate energy even in the presence of adequate oxygen.<sup>7</sup> Lactate dehydrogenase (LDH) is the most important metabolic enzyme involved in glycolysis as it can convert pyruvate to lactate at the end of glycolysis.<sup>8</sup> LDH is a 140-kDa tetramer molecule that exists in five major isoenzymes, numbered LDH-1 through LDH-5, formed by the association of two different types of 35 kDa subunits, M (Muscle) and H (Heart), encoded by *LDHA* and *LDHB* genes, respectively. Increased levels of this protein are in fact released in blood as a consequence of massive cell death and are associated with acute diseases. High levels of LDH in serum are also measured during neoplastic diseases, as a consequence of tissue destruction caused by the cancerous growth. The prognostic value of serum LDH level has been identified in different types of cancers.<sup>9–11</sup> The international prognostic index, a common clinical tool used to predict outcomes in patients with non-Hodgkin's lymphoma, contains five risk factors including serum LDH level.<sup>12</sup> In addition, serum LDH level is included in TNM staging system for melanoma.<sup>13</sup> Thus, serum LDH which can be detected in clinical practices may allow widespread clinical use and contribute to prognosis estimation.

The prognostic value of serum LDH level in breast cancer patients has been investigated in several studies.<sup>5,9,14–22</sup> However, it is still difficult to confirm the prognostic role of serum LDH in breast cancer. First, the sample sizes in some published studies are small.<sup>5,18</sup> Second, the existing studies are conflicting in their results. Some studies suggested that serum LDH was associated with poor prognosis in breast cancer,<sup>5,9,14</sup> whereas other studies failed to demonstrate such correlations.<sup>16,19</sup> Therefore, we performed a meta-analysis to evaluate the prognostic role of serum LDH in patients with breast cancer.

## Methods

### Study design

We developed a protocol that defined search strategy, inclusion criteria, information extraction, and analysis plan based on the Cochrane Handbook for Systematic Reviews of Interventions.<sup>23</sup> The checklist requirements of this meta-analysis adhere to the PRISMA statements.<sup>24</sup>

### Literature search

Electronic searches for relevant articles in PubMed, Embase, and Web of Science databases published up to November 30, 2018 were conducted. The search strategy was generated by combining key words related to LDH ("lactate dehydrogenase" or "LDH"), breast cancer ("breast cancer" or "breast carcinoma"), and prognosis ("prognosis" or "prognostic"). Moreover, we manually searched the reference lists of relevant articles for additional publications. We did not limit the search through the use of any restrictions.

### Quality assessment

We assessed study quality according to the method developed by Hayden.<sup>25</sup> It was based on the identification of six sources of potential study bias that should be assessed in a review of prognostic studies: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis. The quality assessment score of each section was on a scale of 0 to –2, and 12 was the maximum total score in each every study. Studies scoring 10 or more were considered high quality.

### Inclusion criteria

Studies were included in this meta-analysis if they met the following criteria: 1) all patients recruited in the study were diagnosed with breast cancer; 2) the serum level of LDH was measured; 3) the prognostic value of LDH was tested in the article; 4) only English-language studies were included; 5) the HR and their 95% CI were described or could be statistically extracted from the study; 6) when several articles were from the same patient population, the newest or most informative single article was included.

### Information extraction

The following information was extracted from each study: first author's last name, publication year, country of origin, number of patients, tumor types, cutoff level of LDH, and survival data (HR and its 95% CIs for overall survival

(OS) and progression-free survival (PFS)). When HRs and their 95% CIs were not given explicitly in an article, these statistical variables were calculated from available numerical data using methods reported by Parmar<sup>26</sup> and Tierney.<sup>27</sup>

## Statistical analysis

HRs and their 95% CIs were adopted to estimate the prognostic value of serum LDH. The individual HR estimates were combined into an overall HR, and the results were presented graphically in the form of a forest plot. Pooled effect sizes were considered to be significantly different if their 95% CIs did not include 1 ( $P < 0.05$ ). HR  $> 1$  implied a poor survival for the higher LDH group. The Cochran  $Q$  test and  $I^2$  test were performed to assess the heterogeneity between studies.<sup>28</sup> When the Cochran  $Q$  test  $P$ -value was  $\leq 0.10$  and  $I^2$  test  $I^2$  value was  $\geq 50\%$ , statistically significant heterogeneity was considered to be present. When heterogeneity was absent, fixed effects models were employed; otherwise, random effects models were adopted. Subgroup analyses were conducted according to clinical stages of breast cancer. Funnel plots, Begg's test and Egger's test were performed to test publication bias. An asymmetry of the funnel plot with a  $P$ -value of  $< 0.05$  was regarded as a significant publication bias. All analyses were carried out by using Stata Statistical Software, version 12.0 (Stata Corporation, College Station, TX, USA).

## Results

### Search results

Literature search and eligibility assessment were performed independently by two reviewers and disagreements among them were resolved by consensus. Figure 1 illustrates the process of study selection; 724 studies were initially found by our search strategy. After the article titles and abstracts were checked, 19 articles were reviewed in detail.<sup>5,9,14–22,29–36</sup> Eight papers were excluded from the meta-analysis,<sup>29–36</sup> leaving 11 studies which fulfilled the eligibility criteria (Table 1).<sup>5,9,14–22</sup> Among these excluded studies, seven could not provide sufficient survival data for extracting HR<sup>29–35</sup> and the other one was excluded because an identical patient cohort had been used in other selected study.<sup>36</sup> The total number of patients was 6,102, ranging from 70 to 2,425 cases per study. Seven studies focused on metastatic breast cancer<sup>5,17–22</sup> and three studies dealt with non-metastatic breast cancer.<sup>14–16</sup> There were two studies reported triple-

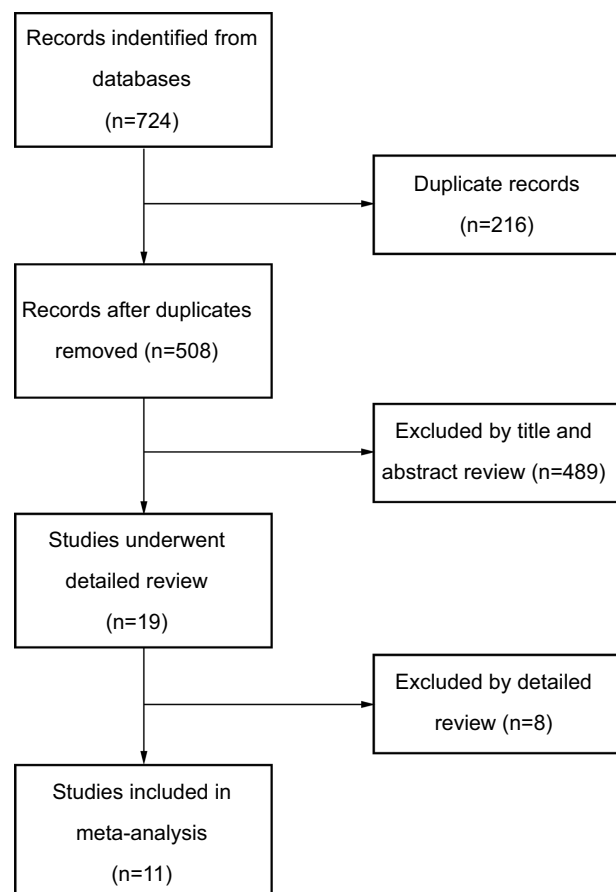


Figure 1 Flow diagram of study selection.

negative breast cancer.<sup>9,14</sup> The majority of these studies tested serum LDH before treatment. Ten studies assessed OS<sup>5,9,14–16,18–22</sup> and five studies evaluated PFS<sup>9,14,16,17,19</sup> in patients with breast cancer. The quality assessment scores of included studies ranged from 7 to 11. No one obtained a perfect score of 12, and six scored less than 10.

### Survival analysis

We used OS and PFS as clinical outcomes in this meta-analysis. The combined HR for OS was 1.88 (95% CI, 1.68–2.11;  $P = 0.000$ ), indicating that higher serum LDH had a significant effect on poor survival in patients with breast cancer (Figure 2). Similar to the results of OS, our study revealed that serum LDH was a predictor for short PFS time (HR, 1.98; 95% CI, 1.46–2.68;  $P = 0.000$ ; Figure 3). The heterogeneity test showed no significant heterogeneity in analysis dealing with OS ( $I^2 = 17.9\%$ ,  $Q$  test  $P = 0.279$ ) but a slight heterogeneity in analysis regarding PFS ( $I^2 = 50.2\%$ ,  $Q$  test  $P = 0.09$ ).

**Table 1** Characteristics of studies included in this meta-analysis

Reference	Country	Patient number	Tumor type	Testing time	Cutoff level	Clinical factors	Quality score
Jia et al (2018) <sup>9</sup>	China	131	TNBC	Baseline	250 U/L	OS, PFS	11
Petekkkaya et al (2017) <sup>5</sup>	Turkey	77	Metastatic BC	Diagnosis	480 U/L	OS	11
Chen et al (2016) <sup>14</sup>	China	253	Nonmetastatic TNBC	Pretreatment	165 U/L	OS, PFS	10
Liu et al (2015) <sup>15</sup>	USA	2,425	Nonmetastatic BC	Pretreatment	469 U/L	OS	9
Petekkkaya et al (2014) <sup>16</sup>	Turkey	652	Nonmetastatic BC	Postoperation	480 U/L	OS, PFS	10
Bidard et al (2012) <sup>17</sup>	France	267	Metastatic BC	Baseline	ULNV	PFS	10
Brunetto et al (2010) <sup>18</sup>	UK	70	Metastatic BC	Not reported	Normal	OS	9
Er et al (2008) <sup>19</sup>	USA	132	Liver-metastatic BC	Pretreatment	Normal	OS, PFS	9
Pierga et al (2001) <sup>20</sup>	France	1,430	Metastatic BC	Pretreatment	330 U/L	OS	8
Ryberg et al (2001) <sup>21</sup>	Denmark	469	Metastatic BC	Pretreatment	450 U/L	OS	8
Yamamoto et al (1998) <sup>22</sup>	Japan	196	Metastatic BC	Registration	Normal	OS	7

**Abbreviations:** TNBC, triple-negative breast cancer; BC, breast cancer; ULNV, upper limit of normal value; OS, overall survival; PFS, progression-free survival.

## Subgroup analysis

We also performed the subgroup analyses to evaluate the prognostic role of serum LDH in patients with different clinical stages. When we limited the analysis to the six studies dealing with metastatic breast cancer, the combined HR was 1.91 (95% CI 1.71–2.13;  $P=0.000$ ) without inter-study heterogeneity ( $I^2=2.3\%$ ,  $Q$  test  $P=0.402$ ; Figure 4). In the non-metastatic breast cancer subgroup, higher serum LDH indicated a poor OS with a pooled HR of 1.76 (95% CI 1.18–2.62;  $P=0.006$ ) and an acceptable heterogeneity ( $I^2=47.8\%$ ,  $Q$  test  $P=0.147$ ; Figure 5). All subgroup analyses showed statistically significant association between serum LDH and patients' survival, indicating that serum LDH was able to suggest poor survival of patients with breast cancer.

## Publication bias

We assessed the publication bias by visually assessing a funnel plot for asymmetry and by quantitatively performing Begg's test and Egger's test. As shown in Figure 6, there was no clear evidence of funnel plot asymmetry by visual assessment. Moreover, publication bias statistics displayed in Table 2 indicated that no publication bias was detected either from Begg's test or Egger's test.

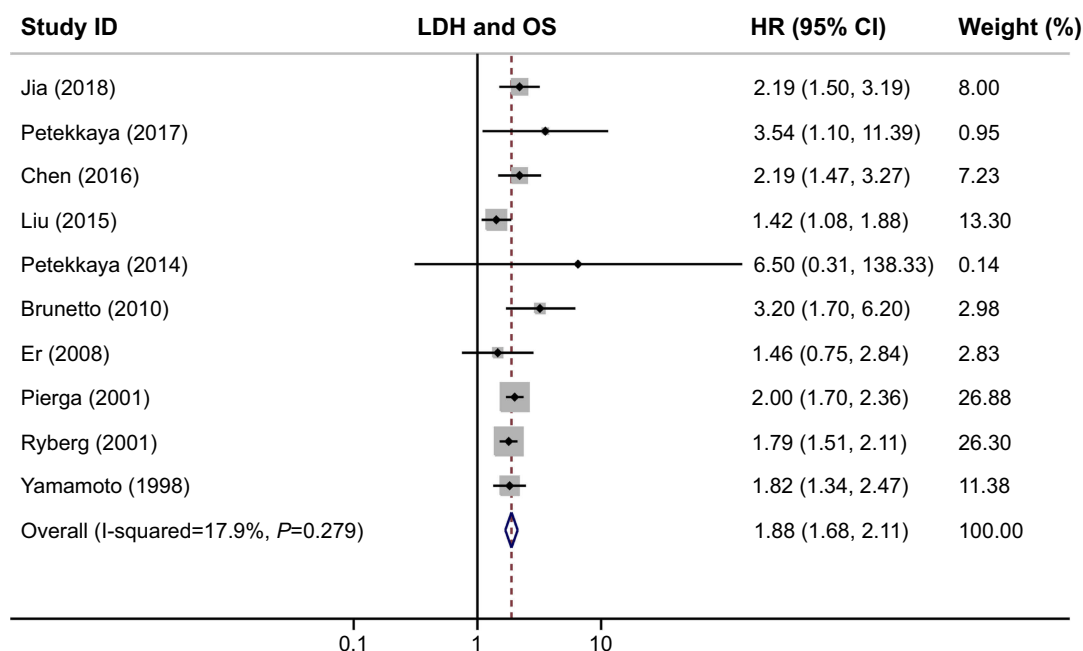
## Discussion

The prognostic value of serum LDH has been investigated extensively in various tumors.<sup>37–39</sup> These studies suggested that serum LDH could predict poor survival of

cancer patients. In breast cancer, the association between serum LDH and clinical outcome has also been widely studied. However, it is still difficult to confirm the prognostic value of serum LDH in breast cancer as the existing studies are often small and conflicting in their results. In this study, we provided the evidence that serum LDH could act as an available prognostic factor for OS and PFS in patients with breast cancer.

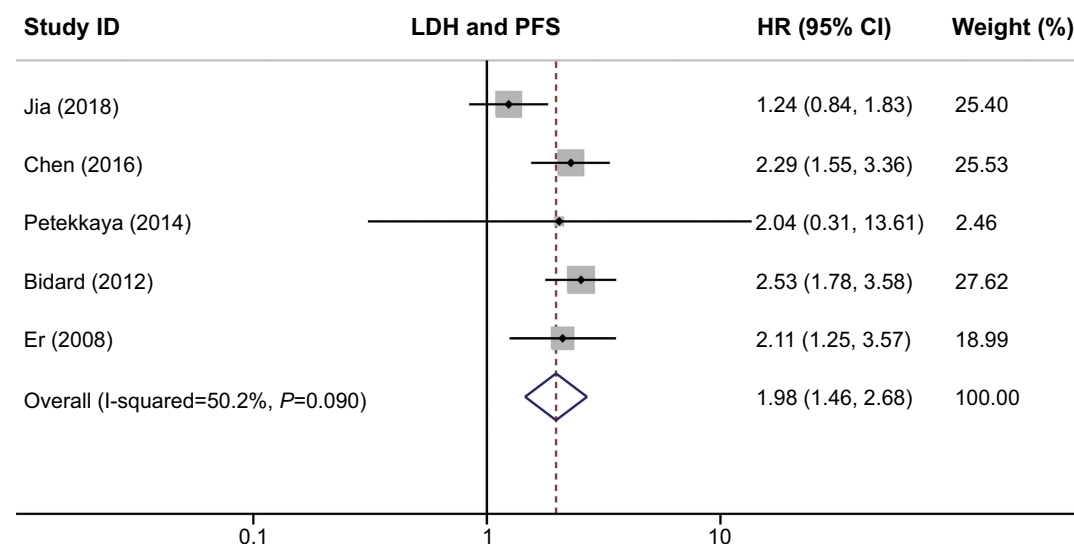
To the best of our knowledge, this is the first comprehensive meta-analysis to confirm the prognostic significance of serum LDH in breast cancer. A total of 11 studies were enrolled to investigate the effect of serum LDH on survival of breast cancer patients. We got the combined HR value of 1.88 (95% CI: 1.68–2.11;  $P=0.000$ ) for OS, which suggested that patients with higher serum LDH had a shorter OS time. In addition, a significant association was also found between serum LDH and poor PFS (HR, 1.98; 95% CI, 1.46–2.68;  $P=0.000$ ). These results hinted that serum LDH could work as a prognostic factor for patients with breast cancer.

Total serum LDH level elevation is a predictive marker of tissue damage and inflammation. Its prognostic value on the follow up of patients with malignant hematologic diseases and solid tumors is known. Serum LDH levels are used as a prognostic factor in chronic lymphocytic leukemia and metastatic melanoma.<sup>12,13</sup> High-serum LDH levels have been suggested as a marker of relapse in asymptomatic non-Hodgkin lymphoma patients and are also known to be an important factor in determining an appropriate treatment strategy. However, the underlying mechanism linking LDH to poor



**Figure 2** Forest plot of HR for the association between serum LDH and OS in breast cancer.

**Abbreviations:** LDH, lactate dehydrogenase; OS, overall survival.

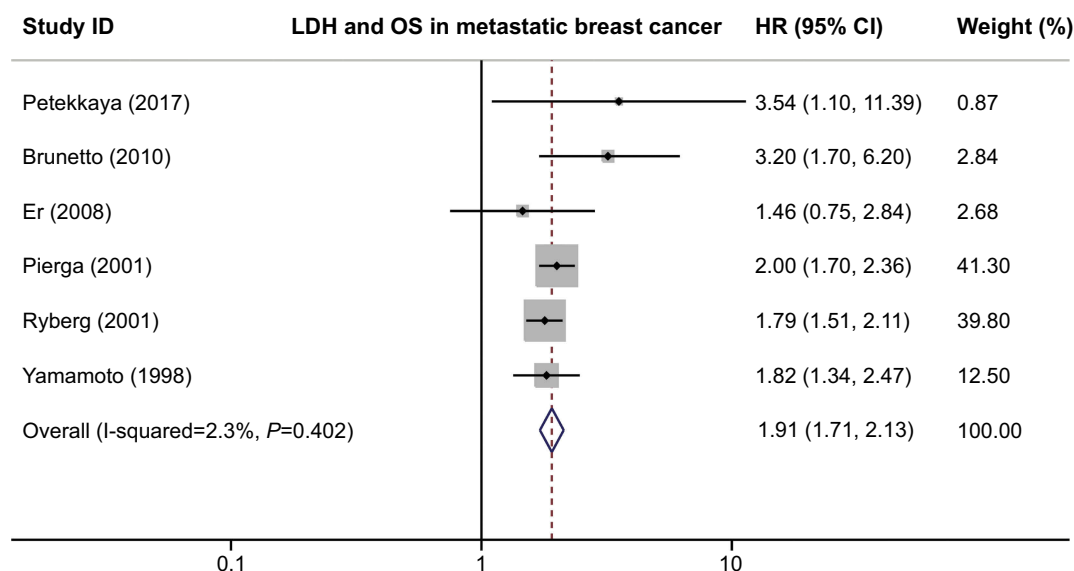


**Figure 3** Forest plot of HR for the association between serum LDH and PFS in breast cancer.

**Abbreviations:** LDH, lactate dehydrogenase; PFS, progression-free survival.

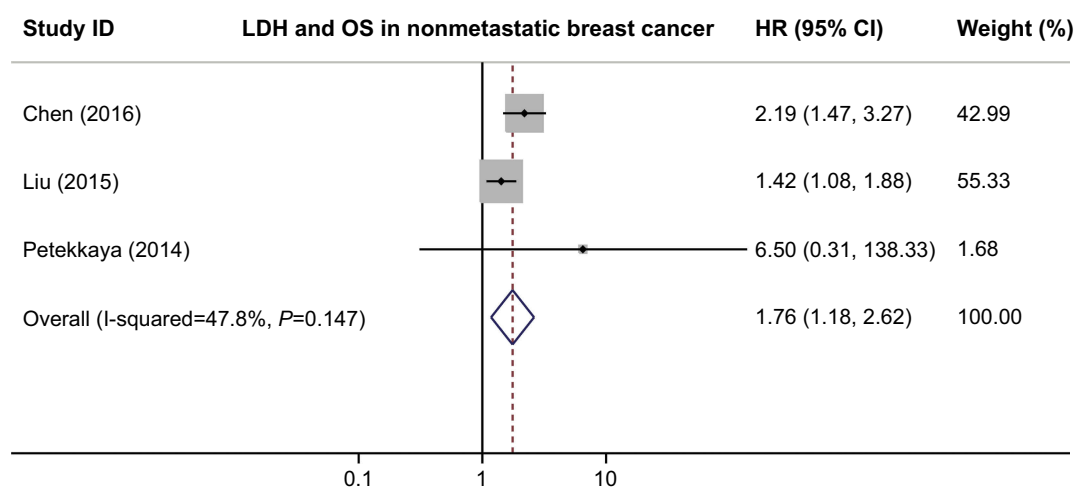
survival remains unknown. It has been hypothesized that serum LDH level may reflect the extent of hypoxia in tumor cells. Tumor cells are often starved of oxygen due to their rapid proliferation. In producing energy, cancer cells can use anaerobic glycolysis which enables them to be independent of oxygen supply. This phenomenon is known as the Warburg effect and is one of the predominant metabolic processes that occur during malignant transformation.<sup>40</sup> LDH, as the key kinase of this process, ensures the efficiency of this process

and can be detected in the serum. Besides, elevated serum LDH level was suggested to be a marker of immune suppression in cancer patients. Ding et al found that LDH allows tumor cells to suppress and evade the immune system by altering the tumor microenvironment.<sup>41</sup> Taken together, serum LDH level may reflect the hypoxia in tumor cells and immune suppression in patients which lead to poor prognosis. What's more, LDH is emerging as one of the most interesting molecular targets for the development of glycolytic inhibitors to possibly use in



**Figure 4** Forest plot of HR for the association between serum LDH and OS in breast cancer in metastatic breast cancer.

**Abbreviations:** LDH, lactate dehydrogenase; OS, overall survival.



**Figure 5** Forest plot of HR for the association between serum LDH and OS in nonmetastatic breast cancer.

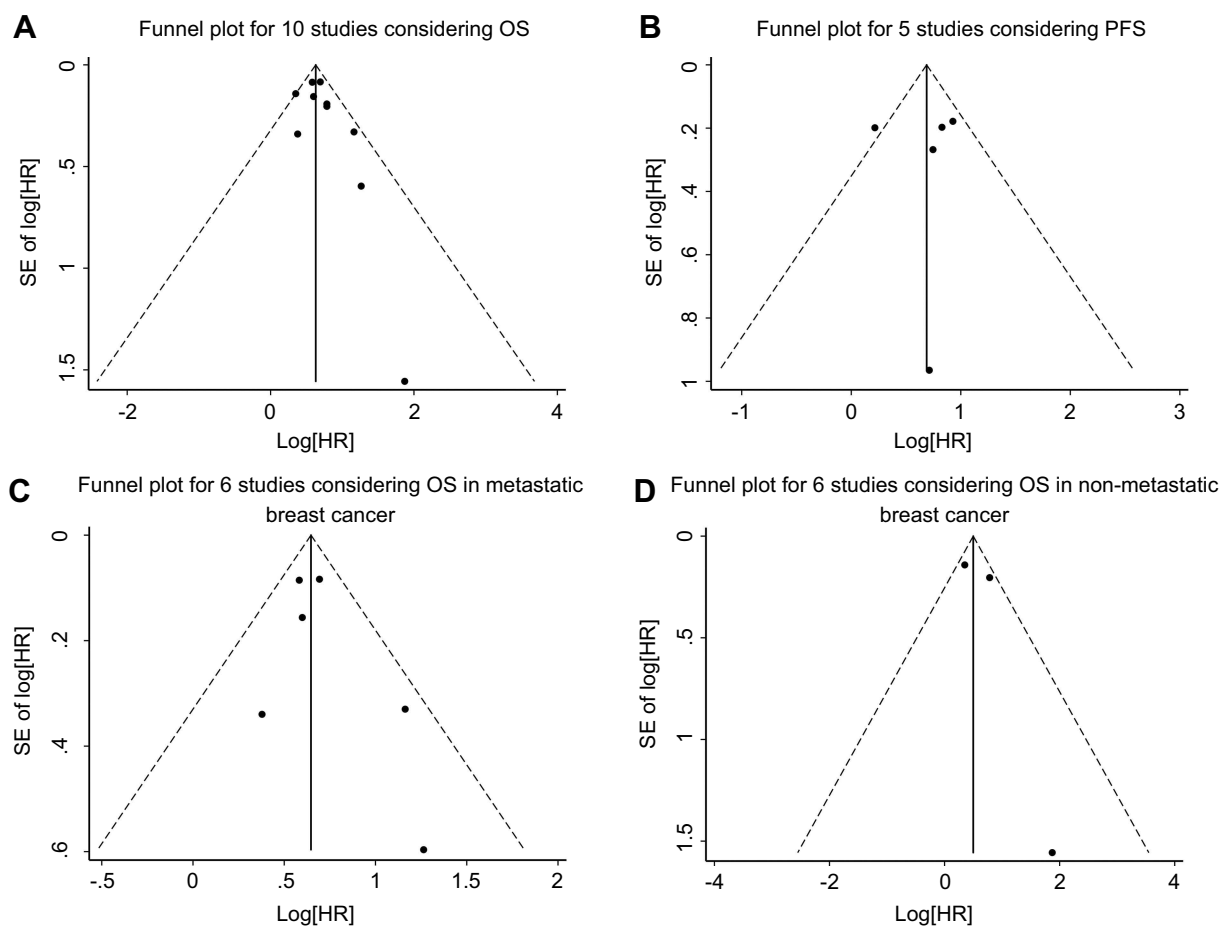
**Abbreviations:** LDH, lactate dehydrogenase; PFS, progression free survival.

cancer therapy.<sup>42</sup> Further deeper investigations toward LDH may promote its clinical utility in cancers. Thus, serum LDH correlates with poor survival and targeting LDH may be an effective way to control breast cancer.

Given that histological types and clinical stages of breast cancer are correlated with patient's prognosis, we conducted subgroup analyses in this study. In terms of histological types in each study, two researched patients with triple-negative breast cancer<sup>9,14</sup> and others considered patients with all pathological types. Thus, this type of subgroup analysis could not be performed. In terms of

clinical stages in each study, seven studies focused on metastatic breast cancer<sup>5,17–22</sup> and three dealt with non-metastatic breast cancer.<sup>14–16</sup> Consequently, we combined studies considering patients with different clinical stages for our subgroup analysis. When analysis was limited to metastatic breast cancer, the combined HR for OS was 1.91 (95% CI 1.71–2.13;  $P=0.000$ ). In the non-metastatic breast cancer subgroup, higher serum LDH indicated a poor OS with a pooled HR of 1.76 (95% CI 1.18–2.62;  $P=0.006$ ). The elevation of LDH usually indicates a heavy tumor burden and tumor metastasis. Mishra et al





**Figure 6** Funnel plot for the assessment of publication bias in this study. (A) Funnel plot for 10 studies considering OS. (B) Funnel plot for five studies considering PFS. (C) Funnel plot for six studies considering OS in metastatic breast cancer. (D) Funnel plot for three studies considering OS in nonmetastatic breast cancer.

**Abbreviations:** OS, overall survival; PFS, progression-free survival.

**Table 2** Results of Begg's test and Egger's test for publication bias

Analysis	Study number	Begg's test (P-value)	Egger's test (P-value)
OS for all studies	10	0.474	0.254
PFS for all studies	5	0.221	0.956
OS for metastatic BC	6	0.707	0.399
OS for non metastatic BC	3	1.000	0.526

**Abbreviations:** OS, overall survival; PFS, progression-free survival; BC, breast cancer.

performed a study to evaluate the blood levels of biochemical parameters in breast cancer with and without metastasis.<sup>43</sup> They found that breast cancer patients with metastasis had higher pre-treatment serum LDH levels than those without metastasis (mean LDH level was 730

and 433 U/L, respectively). This phenomenon may be interpreted by medical conditions in patients with advanced or metastatic stages that are more likely to be influenced by systemic effects from the cancers. The results of our subgroup analyses were consistent with that of pooled analyses and demonstrated the prognostic significance of serum LDH once again. This further proves that LDH is a reliable prognostic factor for breast cancer patients.

Estimating heterogeneity and publication bias is an essential part of a meta-analysis. In this study, heterogeneity test revealed no significant heterogeneity when analyzing the associations between serum LDH and OS. However, a slight heterogeneity appeared when assessing the value of serum LDH in predicting PFS. The heterogeneity may partly come from the variations in assessing serum LDH. The cutoff values for judging high blood levels of LDH varied in the studies, ranging from 165 U/

L<sup>14</sup> to 480 U/L.<sup>5,16</sup> Some studies applied receiver operating curve analysis to calculate optimal cutoff values for serum LDH level,<sup>14</sup> while other studies adopted the normal value<sup>18,19,22</sup> or upper limit of normal value<sup>17</sup> as cutoff values. The majority of these studies tested serum LDH before treatment, but they did not provide the detailed methods for LDH testing. The standardization of LDH testing may resolve this problem in the future, including the cutoff value, test time and test methods. Factors related to the clinical variables could also contribute to heterogeneity. In subgroup analysis, heterogeneity reduced when we combined studies considering with metastatic breast cancer, indicating that the difference in clinical stages could be another source of heterogeneity. With regard to publication bias, no clear evidence of funnel plot asymmetry was found by visual assessment. Moreover, no publication bias was detected according to both Begg's test and Egger's test. These findings suggested that our results were robust and not far from the actual situation.

However, the present meta-analysis still has some limitations. First, it is a literature-based meta-analysis, making our results less reliable than individual patient data-based analysis. Second, studies that cannot provide sufficient data to extract HR were excluded. The exclusion of these studies may make our pooled effect sizes differ from their true value on some level. Third, we only conduct subgroup analysis in terms of clinical stages. Considering these issues, our results need to be validated and updated in the near future.

## Conclusion

In view of this study, our findings showed that high serum LDH correlated with poor OS and PFS in patients with breast cancer. Thus, serum LDH can act as a prognostic factor for breast cancer, which might help to define high-risk patients and guide clinical decision-making. However, future large randomized trials are needed to improve and update our results due to the limitation of meta-analysis.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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