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ORIGINAL ARTICLE

Prognostic Value of Serum Lactate Dehydrogenase in Patients with Nasopharyngeal Carcinoma: a Meta-Analysis

Changyun Zhai [1, *], Ke Gu [2, *], Xiaoming Zhai [3], Jianping Wang [3], Junning Zhang [3]

[*] *These authors contributed equally to this work*
[1] *Department of Oncology, Hospital of Traditional Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Yancheng, China*
[2] *Department of Radiation Oncology, Suzhou Municipal Hospital (East Branch), China*
[3] *Department of Radiation Oncology, The First Affiliated Hospital, Soochow University, Suzhou, China*

SUMMARY

Background: **Serum-lactate dehydrogenase (S-LDH) is reported to be associated with poor survival in patients with nasopharyngeal carcinoma (NPC); however, the results are inconsistent. The aim of the study was to perform a meta-analysis to evaluate the prognostic value of S-LDH in patients with NPC.**
Methods: **PubMed and Web of Science were searched for relevant studies, and the fixed-effects model was employed to pool the hazard risks (HRs) from individual studies when no substantial heterogeneity was detected; otherwise, the random-effects model was used. Heterogeneity and publication bias were also analyzed.**
Results: **A total of 18 studies involving 13,789 patients were included in the meta-analysis, serum LDH level was associated with worse outcome in NPC patients. The combined HR for overall survival (OS) was 1.86 (95% confidence interval [CI]: 1.66 - 2.08; $p < 0.01$), and the pooled HRs for disease-free survival (DFS), distant metastasis-free survival (DMFS), and distant local relapse-free survival (LRFS) were 1.64 (95% CI: 1.45 - 1.86), 2.64 (95% CI: 2.15 - 3.25), and 2.59 (95% CI: 1.74 - 3.87), respectively.**
Conclusions: **Our results suggest that higher serum LDH level is associated with worse survival in patients with NPC, which is helpful for a personalized treatment strategy for NPC patients.**
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Correspondence:
Xiaoming Zhai
Department of Radiation Oncology
The First Affiliated Hospital
Soochow University
215006 Suzhou
China
Email: zhaixmsz@163.com

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KEY WORDS

LDH, NPC, glycolysis, prognostic factor, survival, meta-analysis

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one malignant disease originating from the epithelial cells of the nasopharynx, which is relatively rare worldwide, but quite common in Southern China [1]. Radiotherapy with or without chemotherapy is the primary treatment option for NPC, and the survival rate has been improved continuously [2,3]. Nevertheless, some NPC patients are not sensitive to radiotherapy or chemotherapy and have poor outcomes. The TNM staging system is one of the most common tools used for predicting the prognosis of NPC; however, the biological variability of the tumor itself is not considered in the current TNM system, and

substantial clinical heterogeneity exists in patients with the same TNM stage, which highlights the need for better prognostic indicators for NPC [4].

LDH, an enzyme involved in aerobic glycolysis, is highly expressed in many tumor cells, known as the "Warburg effect" [5]. In our previous study, we showed that LDH-A inhibition might induce apoptosis, cycle arrest, and enhance radio-sensitivity in NPC cells, indicating that LDH-A is a potential therapeutic target in NPC treatment [6]. Moreover, increasing studies have found that serum LDH levels were associated with worse outcomes in many solid tumors [7], including renal cancer [8], melanoma [9], non-Hodgkin's lymphoma [10], and small-cell lung cancer [11]. As to NPC, multiple studies also reported that serum LDH level was a predictive indicator for poor survival. However, the results were scattered and inconsistent.

Since many confounding factors such as tumor stages, therapy methods, patient choice, and LDH detection assays may influence the results, the aim of the study was to systematically evaluate the association between serum LDH and the prognostic value of in patients with NPC.

MATERIALS AND METHODS

Publication selection

We performed the meta-analysis in accordance with the PRISMA statement [12]. We identified relevant studies by searching PubMed from 1956 to July 1, 2016. The keywords 'LDH' or 'lactate dehydrogenase' combined with 'NPC' or 'nasopharyngeal carcinoma' were used. Only publications in English were included, and the references in the included articles were also reviewed to identify more relevant studies.

Selection criteria

The studies were included in our meta-analysis, only when they met the following criteria: 1) Studies with prospective or retrospective design evaluating the prognostic impact of LDH; 2) The study subjects were patients with NPC confirmed by pathology or cytology examination; 3) Serum LDH levels were examined and dichotomized as "high" and " low" value; 4) The endpoints included overall survival (OS), disease-free survival (DFS), distant metastasis–free survival (DMFS) or local relapse-free survival (LRFS). Each endpoint was defined as follows: OS was defined as the time from diagnosis to the date of death or the last follow-up if the patients were still alive. DFS was defined as the time from diagnosis to the time of local failure/distant metastasis or the date of death or when censured at the latest date. LRFS and DMFS were defined as the times from the diagnosis to the date of local recurrence or distant metastases, respectively, or the date of death or when censured at the latest date; 5) Hazard ratios (HRs) for the association between serum LDH level and the endpoints were reported or could be calculated from the original data.

Data extraction

The identified studies were reviewed by two independent authors, and the following information was extracted, including the name of first author, publication year, country, number of patients, disease stage, treatment method, cutoff value of LDH level, LDH positive ratio, and endpoints. Multivariable adjusted HRs with their 95% confidence intervals (CIs) were preferred to those from univariate analyses. In some studies, HRs were not reported directly; however, Kaplan–Meier survival curves were presented in the articles. In this case, survival rates at specified times were extracted to reconstruct HR estimates, according to the methods by Parmar MK [13] and Tierney JF [14]. Two independent authors analyzed the survival curves using Engauge Digitizer version 2.11 (free software downloaded from http://sourceforge.net) to reduce errors. Differences were resolved by a third author.

Statistical methods

HRs with their 95% CIs from each study were extracted to obtain the pooled results. Q and I^2 statistics were employed to examine the heterogeneity among studies. If $p < 0.1$ or $I^2 > 25\%$, heterogeneity was considered to be substantial and the random-effects model was used to combine the individual HRs [15], otherwise, the fixed effects model was used. Traditionally, HR > 1.00 indicated a worse outcome for the group with higher serum LDH level, and the association between serum LDH level and the prognosis of NPC was considered to be statistically significant, when the 95% CI for did not overlap 1. In addition, we also carried out a sensitivity analysis by removing one study each time, to evaluate the stability of the results. Publication bias was examined by funnel plots [16] and the Egger test [17], $p < 0.10$ was considered to be statistically significant. If publication bias existed, we used 'trim and fill' to correct such bias [18]. All statistical analyses were carried out using STATA 12.0 software (Stata Corporation, College Station, TX, USA).

RESULTS

Study selection and characteristics

In total, 78 citations relevant to the keywords were identified, and 2 studies were found from the references. Thus, 18 studies were finally eligible for the meta-analysis (Figure 1). The main characteristics of these studies were listed in Table 1. Most studies were conducted in China, a high-prevalence area of NPC, and one study was carried out in Turkey [19].

Overall, 13,789 patients were included in the meta-analysis, with sample sizes ranging from 73 to 4,630 patients. Most studies involved all disease stages, and 5 studies only included advanced-stage disease (IV stage). Patients with early-stage diseases in the original

Table 1. Main characteristics of studies included in the meta-analysis.

Author [Ref]	Year	Country	Design	Duration	Follow-up (median, range)	Number of patients	Stage	Cutoff (IU/L)	Positive ratio	Treatment	Endpoints
Liaw [29]	1997	China	Retrospective	1982 - 1993	10 d - 111 m	118	IV	140	44.07%	RT with or without chemotherapy	OS
Cheng S [22]	1998	China	Retrospective	1990 - 1995	29 m (15 - 74 m)	74	III - IV	410	26.30%	CCRT	DMFS
Cheng S [21]	2006	China	Retrospective	1990 - 2002	58 m	630	I - IV	410	13.00%	RT with or without chemotherapy	LRFS
Turen S [19]	2007	Turkey	Retrospective	1995 - 2002	55 m (1 - 93 m)	61	III - IVB	460	24.60%	NCT + RT or NCT + CCRT	OS, DFS
Li G [30]	2011	China	Retrospective	2002 - 2003	84 m (3 - 98 m)	533	I - IV	240	8.30%	RT	OSO
Jin Y [31]	2012	China	Retrospective	2000 - 2008	NR	1380	IV	245	22.46%	Chemotherapy	OS
Jin Y [32]	2012	China	Retrospective	1999 - 2005	NR	799	IV	245	45.80%	Chemotherapy	OS
Zhou G [33]	2012	China	Retrospective	2003 - 2006	44.7 m (3.1 - 67.5 m)	465	I - IV	245	6.67%	Radical radiotherapy	OS, DFS, DMFS
Wan X [34]	2013	China	RCT	2002 - 2005	5 y	400	III - IV	245	8.25%	IC + CCRT and IC + RT	OS, DFS, DMFS, LRFS
Tian Y [35]	2013	China	Retrospective	2000 - 2009	17 m	85	IV	245	63.50%	Chemotherapy with or without RT	OS
Wei Z [36]	2014	China	Retrospective	2003 - 2006	51.5 m (5 - 116 m)	693	I - IV	225	18.80%	RT with or without chemotherapy	OS, DFS
Zeng L [37]	2014	China	Retrospective	2001 - 2010	22 m (2 - 125 m)	234	IV	245	34%	Chemotherapy alone or CRT	OS
Zhang W [38]	2015	China	Retrospective	2007 - 2011	38.0 m (5.4 - 60.2 m)	600	I - IV	245	5%	IMRT with chemotherapy	OS, DFS, DMFS
Tang L [39]	2015	China	Retrospective	2007 - 2009	55.9 m (1.3 - 90.8 m)	4630	I - IV	245	6.10%	RT with or without chemotherapy	DFS
Huang P [40]	2015	China	RCT	2002 - 2005	133.3 m (130.8 - 135.7 m)	400	II - IV	168.5	45.30%	IC + CCRT and IC + RT	OS, DFS, DMFS
Li A [41]	2015	China	Retrospective	2001 - 2009	88.4 m (4.2 - 150.6 m)	520	I - IV	245	13.70%	IMRT	DMFS
Zhou G [42]	2016	China	Retrospective	2009 - 2012	44.7 m (3.1 - 67.5 m)	1428	I - IV	245	6.20%	CRT	OS, DFS, DMFS
Wang J [20]	2016	China	Retrospective	2007 - 2012	34 m (3 - 72 m)	739	I - III	240	10.96%	RT with or without chemotherapy	OS, DFS, DMFS

Abbreviations: Ref - references, m - months, y - years, RCT - random clinical trial, RT - radiotherapy, NCT - neoadjuvant chemotherapy, CRT - chemoradiotherapy, CCRT - concurrent chemoradiotherapy, IC - induction chemotherapy, IMRT - Intensity Modulated Radiation Therapy, OS - overall survival, DFS - disease-free survival, DMFS - distant metastasis-free survival, LRFS - local relapse-free survival.

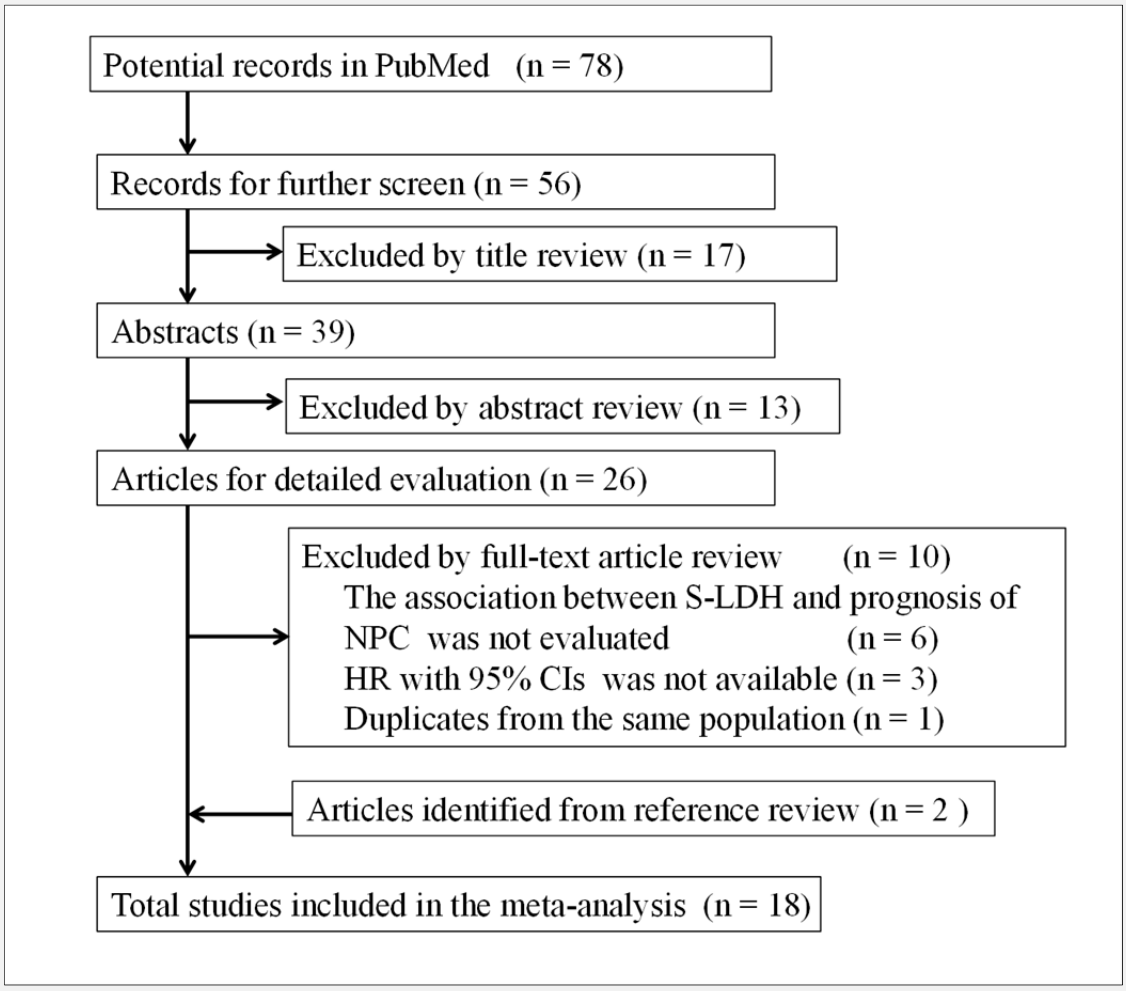

Figure 1. Flowchart summarizing the selection of studies for this meta-analysis.

studies were mainly treated with radiotherapy (conventional RT, 3D-RT or IMRT) combined with chemotherapy (neoadjuvant, adjuvant or concurrent) or without chemotherapy, while patients with distant metastasis primarily received chemotherapy.

The S-LDH level was significantly higher in patients with advanced-stage diseases than in patients classified as early-stage diseases. Serum LDH levels were tested before treatment in most studies, and elevated S-LDH level was defined as > 240 - 245 U/L. However, in one study by Wang J et al., the LDH levels were detected during the follow-up after treatment [20], and in two studies, the cutoff value of LDH level was 410 U/L [21, 22]. We also noticed that in the study by Liaw et al. [29], the positive ratio of LDH was relatively high (44.07%), which was possibly caused by the low cutoff value. The proportion of patients with elevated LDH levels ranged from 5.00% to 63.50%, with a median of 16.25%. After combining all studies, the overall rate of increased LDH levels was 14.15%. In most studies, HRs were reported directly from multivariate Cox analysis; however, in one study by Turen S et al., HRs were obtained from Kaplan-Meier survival curves [19].

Overall survival (OS)

Among all the studies, 14 studies reported the association between serum LDH levels and overall survival of NPC. After pooling all the results, a combined RR of 1.86 (95% CI: 1.66 - 2.08) was obtained with the fixed-effects model, indicating that higher level of S-LDH was associated with worse overall survival. A low heterogeneity was observed among studies (I^2 = 19.1%, Q = 16.07, p = 0.245).

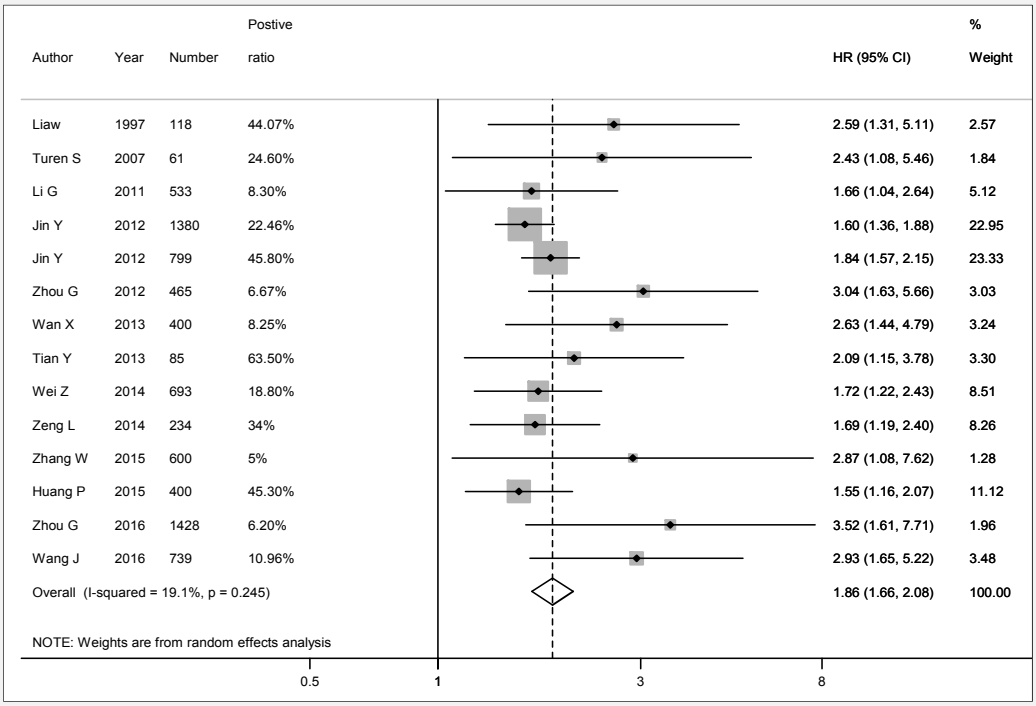

Figure 2. Meta-analysis of the association between S-LDH level and overall survival of NPC patients.

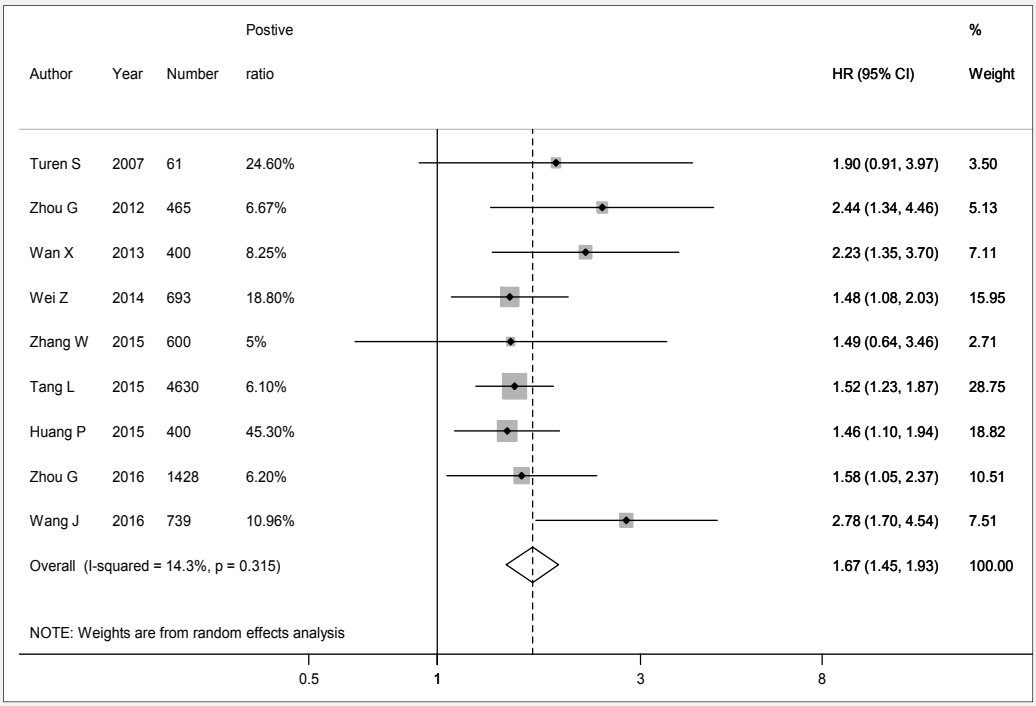

Figure 3. Meta-analysis of the association between S-LDH level and DFS of NPC patients.

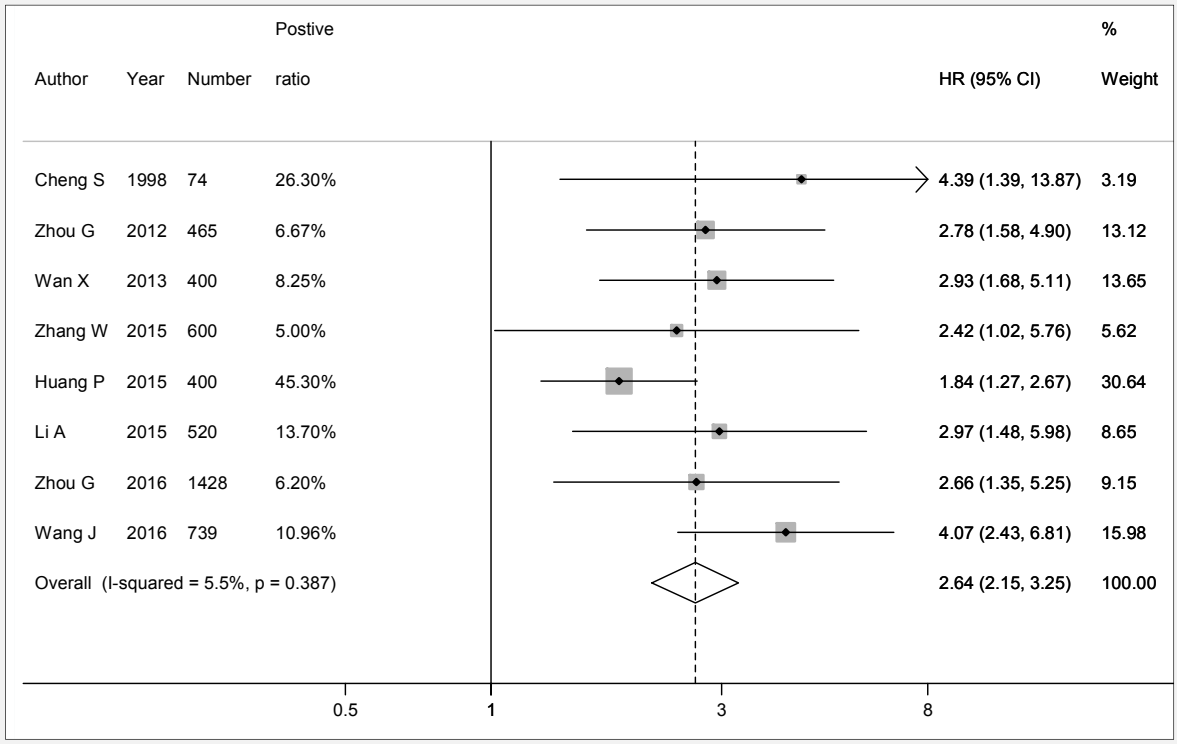

Figure 4. Meta-analysis of the association between S-LDH level and DMFS of NPC patients.

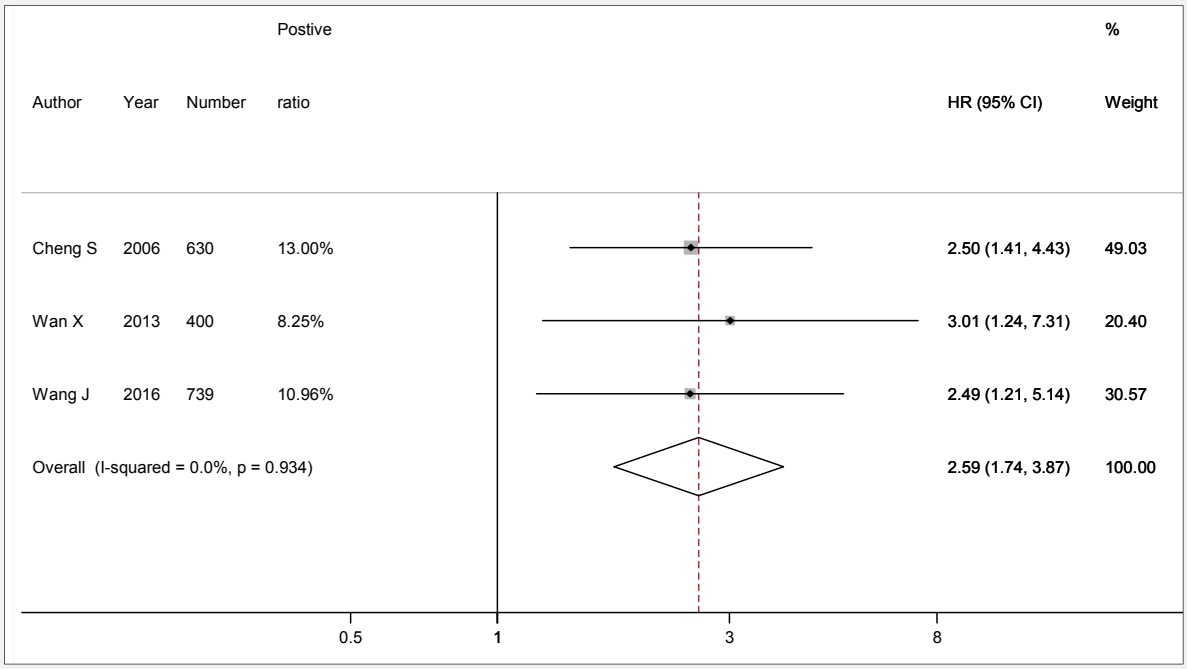

Figure 5. Meta-analysis of the association between S-LDH level and LRFS of NPC patients.

Disease-free survival (DFS)
Nine studies were included in the meta-analysis concerning the association between S-LDH levels and DFS of NPC. No substantial heterogeneity was detected between all of the studies (I^2 = 14.3%, Q = 9.34, p = 0.32), so the fixed-effects model was employed to combine all the results. The pooled HR for all 9 studies was 1.64 (95% CI: 1.45 - 1.86; p < 0.01), suggesting that S-LDH was inversely associated with DFS in NPC patients.

Distant metastasis-free survival (DMFS)
Our analysis of 8 studies on the association between S-LDH levels and DMFS of NPC yielded a summary HR of 2.64 (95% CI: 2.15 - 3.25), without obvious heterogeneity (I^2 = 5.5%, Q = 7.41, p = 0.39), using a fixed-effects model.

Local relapse-free survival (LRFS)
A significant positive association was also found between S-LDH levels and LRFS of NPC. The pooled HR was 2.59 (95% CI: 1.74 - 3.87), after combining the only 3 studies involved. No heterogeneity was observed (I^2 = 0.00 %, Q = 0.14, p = 0.93).

Sensitivity analyses and publication bias
The results of sensitivity analyses by removing each study one a time showed that the pooled HRs did not alter significantly, revealing the stability of the results. The funnel plots revealed an evident asymmetry, suggesting the presence of a potential publication bias. With the trim and fill method, 5, 2, 3 and 0 studies were found to be filled concerning the OS, DFS, DMFS, and LRFS, however, the results were little influenced. A language bias, inflated estimates by a flawed methodologic design in retrospective studies, and a lack of publication of small trials with opposite results might all contribute the significant publication bias.

DISCUSSION

In general, the results indicate that a higher S-LDH level is associated with worse survival in NPC patients, including OS, DFS, DMFS, and LRFS. This association was slightly stronger with regard to DMFS and LRFS. The biological explanation on the association between S-LDH and NPC is plausible. Higher metabolic rate and aerobic glycolysis, known as the "Warburg effect", are major characteristics of cancer cells, which not only provide small molecules for the growth of cancer cells, but also influence the local micro-environment [23]. LDH, a key enzyme in glycolysis, plays an important role in the Warburg effect. Recent studies showed that LDH is also involved in the process of tumor initiation and maintenance [24]. In accordance with its role in cancer cells, LDH is found to be highly expressed in cancer cells. In addition, serum LDH levels in cancer patients are higher than in the healthy population, which might be caused by the release of the enzyme from malignant cells [25]. *In vitro* studies, increasing studies indicated that targeting LDH might inhibit tumor growth and increase the sensitivity of tumor cells to chemotherapy and radiotherapy [6,26-28].
The results of this meta-analysis provide useful information for clinicians making personalized therapy decisions, indicating that patients with higher levels of S-LDH need more aggressive and effective treatment, including both local irradiation and systematic treatment. Also, our study suggests that targeting LDH may be a novel strategy for treating NPC patients, especially for those patients with higher S-LDH levels.
Our study combined the results from 18 studies and 13,789 patients, and the common endpoints were all analyzed. Moreover, the heterogeneity was very low among all the studies, supporting the stability of our results. However, several shortcomings have to be admitted in our study. Firstly, significant publication bias was observed. In our study, papers in non-English language and abstracts were not considered, and some studies with negative results or small samples tend to be unpublished, all these factors may contribute to the significant publication bias. However, after using the "trim and fill" method, we found that the positive associations were not influenced. Besides that, the sample sizes, S-LDH cutoff values, treatment methods and follow-up periods varied among the studies, these confounding factors might weaken the rationality of data synthesis. Especially, it is well known that enzyme activity depends on reaction temperature, which might result in the different cutoff values in the original studies. However, no specific information on the reaction temperatures or the manufacturers of the assay was provided in the original studies. Lastly, we used information from published data in the manuscripts, instead of original individual patient data (IPD), which also limited our ability to perform subgroup analyses and examine the sources of heterogeneity.

CONCLUSION

Our results suggest that higher levels of S-LDH are associated with worse survival of NPC patients, which is helpful for identifying those patients at an increased risk for poor clinical outcome, and providing useful information for personalized treatment. A well-designed prospective study is needed to further investigate the association between S-LDH and the survival of NPC patients.

Declaration of Interest:
The authors have declared no conflicts of interest.

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