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Prognostic significance of pretreated serum lactate dehydrogenase level in nasopharyngeal carcinoma among Chinese population

A meta-analysis

Mingwei Zhang, MD[a], Shushan Wei, MD[b], Li Su, MD[a,c,d], Wenlong Lv, MD[a,c,d], Jinsheng Hong, MD[a,c,d,*]

Abstract

Background: A large number of studies have investigated the prognostic value of pretreated lactate dehydrogenase (LDH) level in nasopharyngeal carcinoma (NPC) patients while the role of it was inconsistent and inconclusive. Hence, the aim of the current study was to conduct a meta-analysis of all published studies to quantify the prognostic impact of pretreated serum LDH in NPC for Chinese population.

Objectives: The aim of the current study was to conduct a meta-analysis of all published studies to quantify the prognostic impact of pretreated serum lactate dehydrogenase (LDH) in nasopharyngeal carcinoma (NPC) for Chinese population.

Methods: The PubMed, Medline, Embase, and Web of Science databases were searched for studies that assessed survival outcome and LDH in NPC. Overall survival (OS) was the primary survival outcome. Distant metastasis-free survival (DMFS) and disease-free survival (DFS) were secondary outcomes. The pooled hazard ratios (HRs), associated with 95% confidence intervals (95% CIs), were combined to calculate overall effects. The Cochran Q and I^2 statistics were used to assess heterogeneity. When apparent heterogeneity was observed, sensitivity and meta-regression analyses were performed to explore its origin.

Results: Sixteen studies, which included 14,803 patients, were enrolled in the current meta-analysis to yield statistics. Overall, the pooled HR for OS in 11 eligible studies with high LDH level was 1.79 (95% CI = 1.47–2.12), and the pooled HR for DMFS in 9 eligible studies with high LDH level was 1.85 (95% CI = 1.48–2.22). Meanwhile, the pooled HR for DFS in 5 eligible studies with high LDH level was 1.63 (95% CI = 1.34–1.91). Egger test and funnel plots revealed that the publication bias in the current meta-analysis was insignificant.

Conclusions: The present meta-analysis demonstrated that high pretreated LDH level is significantly associated with poorer OS, DMFS, and DFS, suggesting that pretreated LDH could sever as a prognostic factor in NPC among Chinese population.

Abbreviations: CI = confident interval, DFS = disease-free survival, DMFS = distant metastasis-free survival, HIF = hypoxia-inducible factor, HR = hazard ratio, LDH = lactate dehydrogenase, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, OS = overall survival, PFS = progression-free survival.

Keywords: Chinese population, meta-analysis, nasopharyngeal carcinoma, prognostic value, serum lactate dehydrogenase, survival outcome

1. Introduction

Nasopharyngeal carcinoma (NPC) is prevalent in southern China, with an incidence rate approaching 30 per 100,000 persons.[1] Radiotherapy is the primary therapeutic strategy, and concurrent radiochemotherapy is the standard treatment for locoregionally advanced nonmetastatic NPC.[2–4] Nevertheless, the local recurrence occurs ranging from 5% to 15% in patients, and distant metastasis occurs between 16% and 34% in patients.[5–10] Unfortunately, patients with distant metastasis have been demonstrated with even worse survival outcome, the progression-free interval (PFS) was only 7.3 to 10 months.[11–13] Because the application of additional treatment could cure or prolong the survival time in 10% to 20% of patients with local or distant progression,[14] thus there is pressing need to identify the high-risk patients with poor prognosis so that novel and intensive protocols could be initiated earlier to improve survival.

Currently, the American Joint Committee on Cancer TNM classification is the most commonly used staging system as well as the authoritative reference to therapeutic strategy.[15] However, the staging system is based on anatomic information, which resulted in large variations in the clinical outcomes of patients

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[a] Department of Radiotherapy, First Affiliated Hospital of Fujian Medical University, [b] First Affiliated Hospital of Fujian Medical University, [c] Key Laboratory of Radiation Biology (Fujian Medical University), Fujian Province University, [d] Fujian Key Laboratory of Individualized Active Immunotherapy, Fujian Medical University, Fuzhou, Fujian, People's Republic of China.

[*] Correspondence: Jinsheng Hong, Department of Radiotherapy, First Affiliated Hospital of Fujian Medical University, Chazhong Road No. 20, Fuzhou 350005, Fujian, People's Republic of China (e-mail: 13799375732@163.com).

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with the same stage receiving similar treatment protocols, suggesting that the current staging system is not comprehensive enough for predicting survival outcome and reflecting the biological heterogeneity of NPC patients. As an essential part of tumor biological behavior, there were different metabolic programs between cancer cells and normal cells.[16] In the process of malignant transformation, the elevated aerobic glycolysis is one of the primary metabolic alterations. Lactate dehydrogenase (LDH), which catalyzing the reversible conversion of pyruvate to lactate, plays a vital role in anaerobic glycolysis.[17] LDH as a feasible serum biomarker has been identified as an adverse prognostic factor for several tumors, including nonsmall cell lung cancer,[18] colorectal cancer,[19] prostate cancer,[20] and other solid tumors.[21,22]

Numerous studies have investigated the correlation between elevated pretreated LDH level and survival outcome in NPC.[23–38] Nevertheless, the results were inconsistent and controversial in regards to the magnitude of the prognostic impact of LDH in NPC. It is generally acknowledged that meta-analysis is a powerful statistic tool to overcome the limitation of different sample sizes from individual studies and to generate the best estimation.

Therefore, the aim of the current study was to conduct a meta-analysis of all eligible published studies to quantify the prognostic value of pretreated serum LDH in NPC.

2. Materials and methods

2.1. Search strategy

PubMed, Medline, Embase, and Web of Science databases were searched for studies assessing survival outcome and the LDH in NPC. All relevant studies reported up to March 3, 2016. The searching keywords were as follows: "nasopharyngeal neoplasm*" or "cancer* of nasopharynx" or "nasopharyngeal cancer*"or "nasopharyngeal tumor*" or "nasopharyngeal carcinoma" or "neoplasm* of nasopharynx" and "L-Lactate dehydrogenase" or "lactate dehydrogenase" or "LDH." This meta-analysis was reported in accordance with the preferred

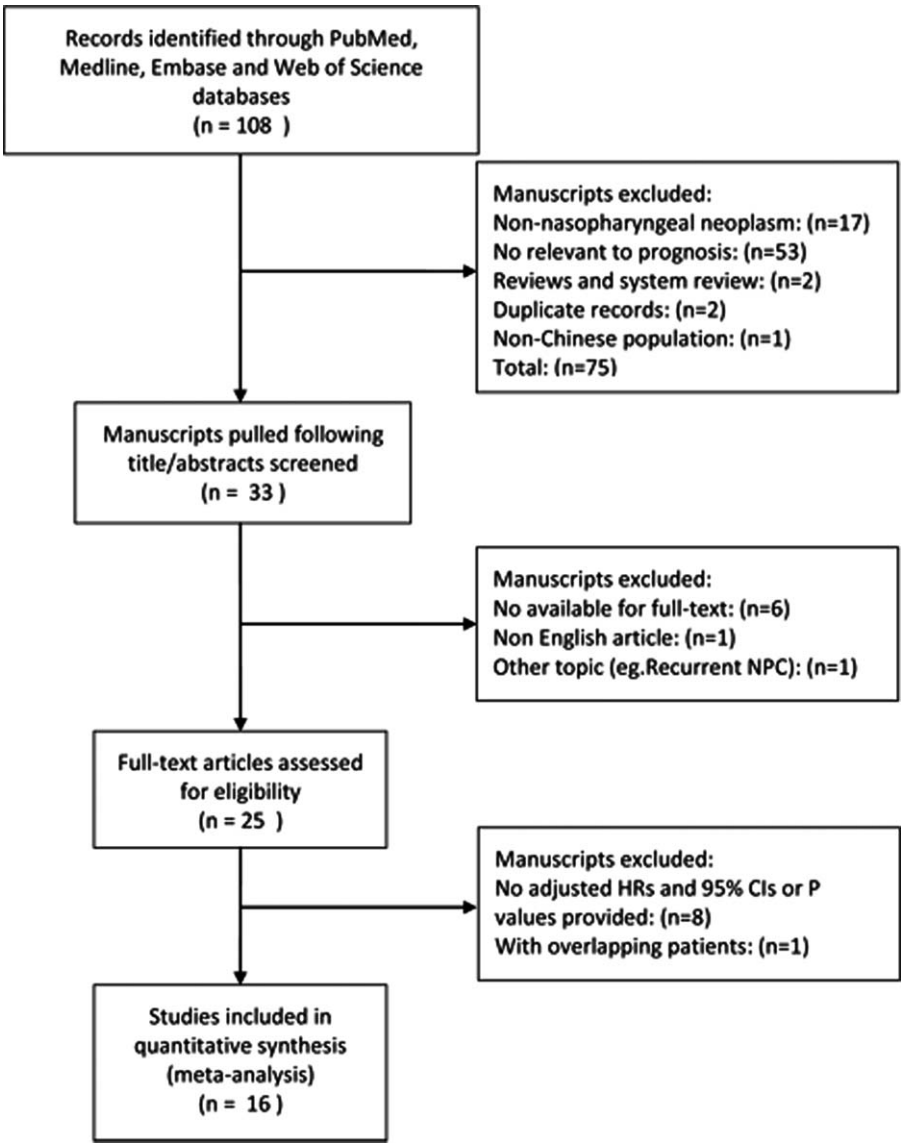

Figure 1. The procedure of selection for eligible studies.

reporting items for PRISMA statements.[39] The full search strategy was shown in Figure 1.

2.2. Data selection

Only literature published in English was enrolled in the current study, no consideration for abstracts or reports. The inclusive criteria for our meta-analysis were as follows: retrospective or prospective study; the neoplasm was pathologically confirmed as NPC; the racial was confined to Chinese population; the associations between pretreated LDH level and survival outcomes were listed in included studies; multivariate proportional hazards models that adjusted for major clinical factors were enrolled in statistical analysis; the study provided the multivariate hazard ratios (HRs) associated with 95% confidence intervals (CIs) or a *P* value for overall survival (OS) or distant metastasis-free survival (DMFS) or disease-free survival (DFS); and >6 points of Newcastle-Ottawa Scale (NOS) score were considered eligible for inclusion.

2.3. Data extraction

OS was the primary survival outcome, whereas DMFS and DFS were secondary outcomes. The relevant data were independently extracted by 2 authors (MZ and SW), including the name of first author, publication year, numbers of cases, metastatic status (nondisseminated or disseminated), study type (prospective or retrospective), follow-up time, adjusted variable, cutoff value of pretreated LDH, and HRs associated with 95% CIs for OS, DMFS, and DFS as applicable. HRs and 95% CIs were extracted from multivariate analyses that adjusted for major prognostic factors. In case of doubt or controversy between the 2 authors involved in data extraction and search strategy, this was discussed with a third independent senior oncologist (JH).

2.4. Quality assessment

The NOS was used for quality assessment.[40] The 3 aspects of NOS criterion were listed as follows: selection of subject 0 to 4, comparability of subject 0 to 2, and clinical outcome 0 to 3. The range of NOS scores was from 0 to 9, and a score ≥7 defined as "good quality."

2.5. Ethical statement

This article does not contain any studies with human participants or animals performed by any of the authors.

2.6. Statistical analysis

The STATA software version 12 (StataCorp LP, College Station, TX) was used to perform statistical analysis in the current study. HRs associated with 95% CIs were combined to calculate overall effects. The utility of Cochran Q and I^2 statistics were for assessing the heterogeneity. When no significant heterogeneity was observed among the included studies ($I^2 \leq 50\%$), the fixed-effects model was used for statistical analysis. When an apparent heterogeneity was observed among the eligible studies ($I^2 > 50\%$), the random-effects model was used for statistical analysis.[41] Also, sensitivity and meta-regression analyses were applied to explore the origin of heterogeneity. Publication bias was assessed by visual inspection of Begg funnel plot and the possibility of publication bias was conducted by Egger test.[42] Conventionally, the adverse prognosis for the group with high LDH level was presented with HR >1 as well as the associated 95% CI did not overlap with 1. A 2-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Description of studies

By searching the databases in PubMed, Medline, Embase, and Web of Science, 108 potentially relevant articles were identified. Based on the inclusive criterion, 16 eligible studies were enrolled in current meta-analysis.[23–38] The predominant characteristics of 16 eligible studies are shown in Table 1. A total of 14,803 patients were enrolled, ranging from 85 to 4630 patients per study (median 526). In the assessment of the quality of the included studies, the average NOS scores from 2 reviewers were 7.5 and 7.4. All included studies were defined as "good quality."

3.2. OS

Eleven studies including 7846 patients reported HRs for OS. No significant heterogeneity was observed in the included 11 studies ($I^2 = 27.3\%$, $P = 0.185$); thus, the fixed-effects model was applied. Overall, the pooled HR for OS in 11 eligible studies with high LDH level was 1.79 (95% CI = 1.47–2.12). Figure 2 illustrates the Forest plot of all studies. Subsequently, in the subgroup analysis of metastatic status, the adverse impacts of high LDH level on OS were still presented in 2 groups. The HRs were 1.81 (95% CI = 1.39–2.23) for nondisseminated NPC and 1.73 (95% CI = 1.55–1.92) for disseminated NPC (Fig. 3), suggesting that high LDH level was an adverse prognostic factor for OS in both nondisseminated and disseminated NPC patients. In addition, Egger test and funnel plot (Fig. 4) revealed that the publication bias in the current meta-analysis was insignificant ($P = 0.085$).

3.3. DMFS

Nine studies including 7313 patients reported HRs for DMFS. Significant heterogeneity was observed in the included 9 studies ($I^2 = 60.2\%$, $P = 0.010$); thus, the random-effect model was applied. Overall, the pooled HR for DMFS in 9 eligible studies with high LDH level was 1.85 (95% CI = 1.48–2.22). The Forest plot was shown in Figure 5. To explore the origin of heterogeneity, sensitivity analysis and meta-regression model were used. The pooled HR was stable in sensitivity analysis and no significant alteration was found when omitted a single study (Fig. 6). Subsequently, a univariate meta-regression analysis including a total of 9 studies was conducted. In aggregate, no significant association was observed among year of publication, LDH cutoff value, study type, and the HR for DMFS ($P = 0.204$, 0.335, and 0.971, respectively).

3.4. DFS

Five studies containing 7523 patients reported HRs for DFS. No significant heterogeneity was observed in the included 7 studies ($I^2 = 0.0\%$, $P = 0.615$); thus, the fixed-effect model was applied. Overall, the pooled HR for DFS in 7 eligible studies with high LDH level was 1.63 (95% CI = 1.34–1.91). The Forest plot was shown in Figure 7.

4. Discussion

A large number of studies have investigated the prognostic value of pretreated LDH levels in NPC patients while the role of it was inconsistent and inconclusive.[23–38] Therefore, we reviewed the

Table 1

Characteristics of eligible sixteen studies other than seventeen studies.

No.	First author	Year	Sample size	Stage	Study type	LDH cutoff, IU/L	Outcome	Follow-up month (s)	Adjusted factor
1	Zhou et al[38]	2016	1428	NM	R	245	DFS/DMFS	44.7 (3.1–67.5)	Age, sex, T stage, N stage, pretreatment LDH, posttreatment LDH chemotherapy (present vs absent)
2	Tang et al[37]	2016	4630	NM	R	245	DFS	55.9 (1.3–90.8)	Age, sex, T stage, N stage, plasma EBV-DNA, pretreatment hs-CRP, LDH, HGB, BMI
3	Li et al[36]	2015	520	NM	R	245	DMFS	88.4 (4.2–150.6)	T stage, N stage, GTVnx, HGB and PLT change, pretreatment AGR, NLR, LDH
4	Huang et al[35]	2015	408	NM	P	168.5	OS/DMFS	133.3 (130.8–135.7)	Age, sex, T stage, N stage, treatment arm, total RT dose, BMI, smoking status, LDH, VCA-IgA, EA-IgA
5	Zhang et al[34]	2015	600	NM	R	245	OS/DFS/DMFS	NA	Age, sex, T stage, N stage, clinical stage, LDH, ALB, FH tumor type, chemotherapy, RT technique
6	Tang et al[33]	2015	3113	NM	R	167	OS/DFS/DMFS	Median: 51; IQR: 40–62	Age, sex, ECOG performance status, T stage, N stage, EB-DNA, CRP, LDH, ALB, BMI, smoking, cardiovascular disease, chemotherapy (yes vs no)
7	Chen et al[32]	2014	230	NM	R	240	DMFS	80 (20–126)	Age, N stage, HB, LDH, dose to primary tumor
8	Zeng et al[31]	2014	234	M	R	245	OS	22 (2–125)	KPS, liver metastasis, number of involved site, LDH, ALP, local therapy to metastases, treatment modality, response to chemotherapy, chemotherapy cycles
9	Wei et al[30]	2014	601	NM	R	225	OS	51.5 (5–116)	Age, T stage, N stage, LDH
10	Tian et al[29]	2013	85	M	R	245	OS	19 (4–124)	KPS, ALT, LDH, number of lesions, extrahepatic metastases, RT of primary tumor, cycles of chemotherapy, response to chemotherapy, local therapy of lesions
11	Wan et al[28]	2013	400	NM	P	245	OS/DFS/DMFS	NA	Age, T stage, N stage, LDH
12	Jin et al[27]	2013	689	M	R	245	OS	NA	Age, sex, specific metastatic sites, metastatic at presentation, pre-LDH, post-LDH, number of chemotherapy, number of involved sites
13	Li et al[26]	2012	533	NM	R	240	OS	84 (3–98)	Age, T stage, N stage, LDH, ALP
14	Jin et al[25]	2012	718	M	R	245	OS	NA	Age, sex, KPS, EB-DNA, VCA-IGA, LDH, ALP, WBC, HB, albumin level, present of metastatic at present, disease-free interval, number of metastatic sites, metastasis at presentation
15	Zhou et al[24]	2012	465	NM	R	245	OS/DFS/DMFS	44.7 (3.1–67.5)	Age, T stage, N stage, LDH
16	Cheng et al[23]	2001	149	NM	P	410	DMFS	48 (18–112)	Age, histological type, T stage, N stage, LDH, clivus infiltration, parapharyngeal extension

AGR = albumin-globin ratio, ALB = albumin, ALP = alkaline phosphates, BMI = body mass index, CRP = C-reactive protein, DFS = disease-free survival, DMFS = distant-metastasis free survival, ECOG PS = Eastern Cooperative Oncology Group Performance Status, FH = family history, GTVnx = gross tumor volume of nasopharynx, HGB = hemoglobin, Hs-CRP = high-sensitivity C-reactive protein, IQR = interquartile range, KPS = Karnofsky Performance Status, LDH = lactate dehydrogenase, M = metastasis, N = nodal, NA = nonapplicable, NLR = neutrophil-lymphocyte ratio, NM = nonmetastasis, OS = overall survival, P = prospective, PLT = platelet count, R = retrospective, RT = radiotherapy.

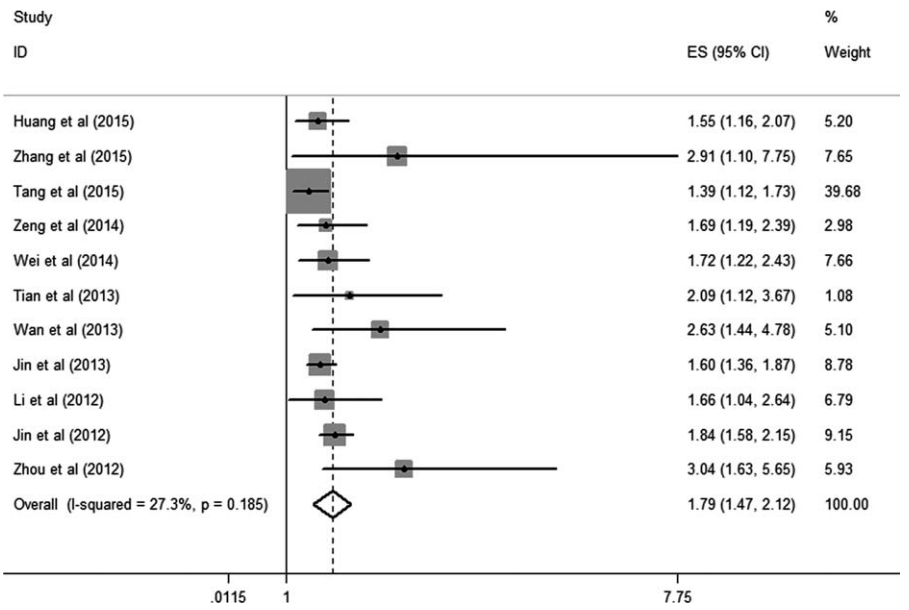

Figure 2. Forest plot illustrating HRs for OS of high serum LDH level in nasopharyngeal carcinoma. HR = hazard ratio, LDH = lactate dehydrogenase, OS = overall survival.

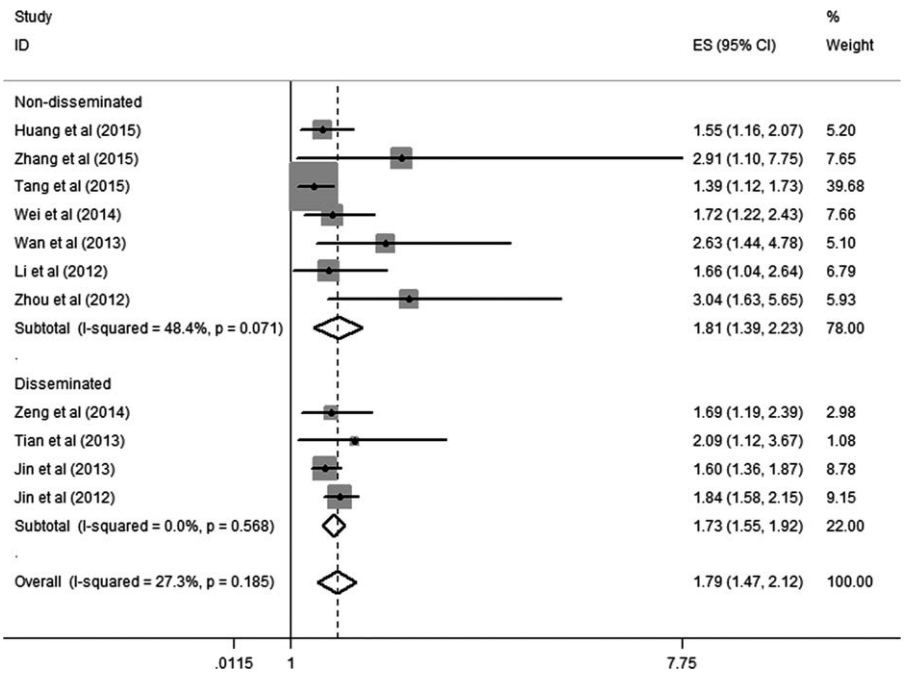

Figure 3. Forest plot illustrating HRs for OS by the subgroup analysis of metastatic status. HR = hazard ratio, OS = overall survival.

published studies and undertook a meta-analysis to derive a more precise estimation of the prognostic value of pretreated LDH in NPC. In aggregate, 16 studies including 14,803 patients were enrolled in the current meta-analysis to yield statistics. In the current study, the strong association between high LDH level and poor OS of NPC was observed. Furthermore, the significantly adverse effect of LDH on OS was also observed in the subgroup analysis by metastatic status. Correspondingly, the adverse prognostic value of pretreated LDH was also found to be significant for DFS and DMFS. Although the significant heterogeneity existed in HR for DMFS, the pooled HR is stable in sensitivity analysis. In addition, 3 dominant factors including "year of publication," "study type," and "LDH cutoff value" were enrolled in meta-regression analysis; however, no significant association was observed in HR for DMFS.

In the current analysis, our results revealed the association between high LDH level and survival outcome in NPC. In the subgroup analysis of metastatic status, the strong relationship between elevated LDH level and poor OS was still significant. Analogs to our study, a meta-analysis conducted by Chen et al also found that the pooled HR for elevated LDH level on OS was 1.92 (95% CI = 1.53–2.40) in osteosarcoma.[43] Correspondingly, a systematic review comprising 29,620 patients with solid tumors also reported that high serum LDH level is an adverse prognostic factor for OS, PFS, and DFS. In addition, the significantly strong association was still observed between high LDH level and poorer survival outcome in the subgroup analysis of disease sites and metastatic status, indicating that serum LDH could be used as a useful indicator for survival outcome.[44] However, the underlying mechanism of LDH and poor prognosis needs further investigation.

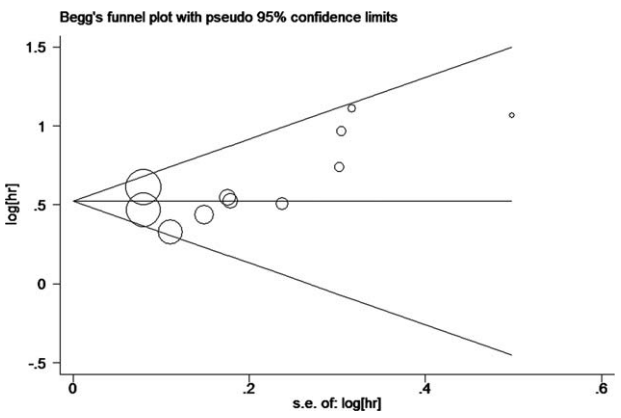

Figure 4. Visual inspection of publication bias by Begg funnel plot.

As an essentially part of tumor biological behavior, there were different metabolic programs between cancer cells and normal cells. In the process of generating energy, the anaerobic pathway of glycolysis was preferentially used by cancer cells despite the presence of oxygen, which is histologically known as Warburg effect.[16] LDH, which catalyzing the reversible conversion of pyruvate to lactate, plays a key role in anaerobic glycolysis.[17] Numerous studies have proposed several hypotheses to explain the mechanisms of LDH in malignant tumors. First, the increased level of LDH activity may result in the upregulation of lactate acid production and lower the pH of extracellular water space.[45,46] Acidic extracellular pH has been demonstrated to facilitate the decomposition of extracellular matrix by the activity of metalloproteases and enhance the activation of macrophage-mediated angiogenesis.[47,48] In addition, mitochondria may be protected from oxidative stress by lower PH, which enhanced the resistance of tumor cells to hypoxia-induced apoptosis.[49] Thus, upregulation of LDH may trigger the activation of tumor invasiveness and metastasis. Second, LDH-5, one of the most dominant isoenzymes of LDH, has been confirmed to be significantly associated with the expression of hypoxia-inducible factors (HIFs) and vascular endothelial growth factor. In that way, high pretreatment LDH levels may be an indicator of HIF-dependent

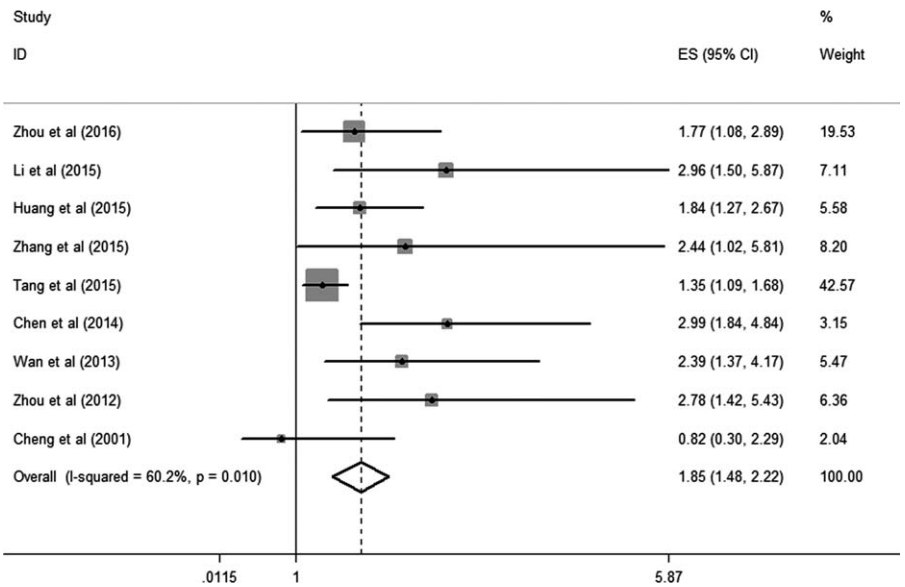

Figure 5. Forest plot illustrating HRs for DMFS of high serum LDH level in nasopharyngeal carcinoma. DMFS = distant-metastasis free survival, HR = hazard ratio, LDH = lactate dehydrogenase.

tumor angiogenesis, aggressiveness, and metastasis.[50,51] Furthermore, LDH-5 was also associated with the absence of lymphocytic infiltration at the invading tumor edge.[52] Overall, elevated serum LDH levels may be a reflection of the upregulated HIF-molecular pathway, attenuated host immunologic function, and aggressive angiogenesis, which frequently lead to adverse prognosis in malignant tumors.

The strength of current meta-analysis is incorporating large samples of 16 eligible studies covering >14,000 patients, and the multivariate effects that adjusted for major prognostic factors were used to calculate the HRs and 95% CIs for 3 predominant survival outcomes. In addition, our study has several important implications. First, our analysis demonstrated that the high level of pretreated LDH has a strong correlation with worse survival outcome. With the progression of molecular mechanism researches about LDH, further target investigation of LDH may provide a bright direction for individualized treatment. Zhai et al revealed that the LDH inhibition by oxamate could successfully suppress energy metabolism in NPC cells, induce G2/M arrest, and improve sensitivity to radiation in NPC.[53] Hence, further investigations of LDH inhibitions provided a new prospect for clinical practice. Second, the elevated LDH levels may be a reflection of high tumor burden and tumor invasiveness,[50,51,54] suggesting that dynamic observation of LDH levels may be a useful predictor of survival outcomes in NPC. Recently, a retrospective analysis was conducted by Zhou et al with the aim of evaluating the prognostic roles of dynamic LDH levels in NPC patients. Their results demonstrated that posttreatment LDH was the independent prognostic factor for OS. However, the limitation of the study was that they only analyze the LDH level within 4 weeks after the completion of treatment.[38] Owing to the vague definition, there is pressing need to explore the optimal time point of LDH measurement in further study.

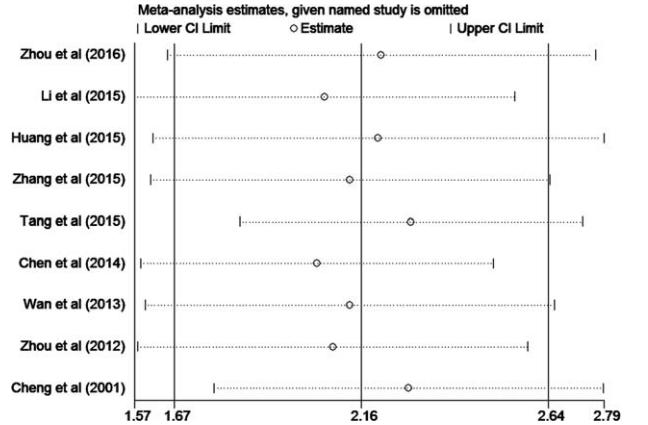

Figure 6. Forest plot for the sensitivity analysis in current meta-analysis.

However, several limitations should be noticed. First, the form of current study is a literature-based analysis, which resulted in the marginal significance of publication bias in HR for OS ($P = 0.085$). The reasons for potential publication bias may be partly attributed to the publication tendency for positive results; meanwhile, the relatively strict inclusion criterion may also contribute to it. Second, there was significant heterogeneity across the included studies in HR for DMFS ($I^2 = 60.2\%$, $P = 0.010$). Despite the utility of sensitivity analysis and meta-regression, the origin of heterogeneity could not be fully traced. Third, the definition of LDH cutoff values in each center is inconsistent. Hence, it is urgent to establish the standard and unified LDH cutoff value. Further investigations involving the unified LDH cutoff are needed to achieve more meaningful results. In addition, some special areas needed to be focused, such as the establishment of the prognostic value of LDH and its subtypes in same tumor stage.

In conclusion, the present meta-analysis demonstrated that high pretreated LDH level is significantly associated with poorer OS, DFS, and DMFS, suggesting that pretreatment LDH could serve as a prognostic factor in NPC among Chinese population. To strengthen our findings, prospective researches with a standardized definition of LDH cutoff value are needed to authenticate the relationship between high pretreatment LDH level and survival outcome of NPC.

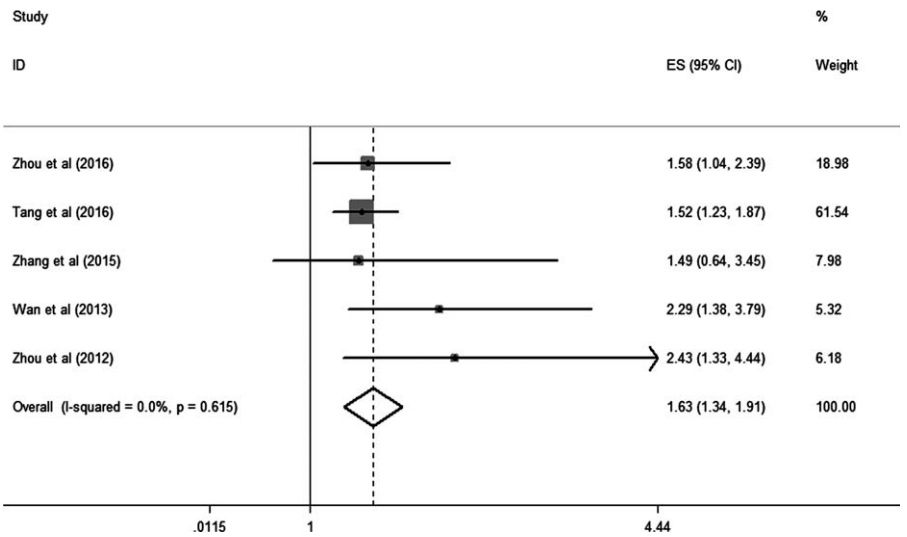

Figure 7. Forest plot illustrating HRs for DFS of high serum LDH level in nasopharyngeal carcinoma. DFS = disease-free survival, HR = hazard ratio, LDH = lactate dehydrogenase.

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