Int J Clin Exp Med 2016;9(11):20846-20855
www.ijcem.com /ISSN:1940-5901/IJCEM0030111

Original Article

Prognostic role of serum lactate dehydrogenase in nasopharyngeal carcinoma: a meta-analysis

Hongxia Li[1,2], Xuefei Feng[1], Wei Li[1], Ling Zhu[1], Jiang Zhu[1]

[1]Department of Otolaryngology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China; [2]Now Work in Department of Otolaryngology, West China-Guang'an Hospital, Sichuan University, Sichuan 638001, China

Received March 18, 2016; Accepted September 20, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Background: Recent studies have shown that serum lactate dehydrogenase (LDH) is a useful predictive factor in several cancers; however, the prognostic value of high pre-treatment serum LDH in patients with nasopharyngeal carcinoma (NPC) remains controversial. Objective: This meta-analysis was conducted to quantitatively assess the prognostic significance of serum LDH levels in nasopharyngeal carcinoma patients. Methods: Eligible studies were identified through systematic literature searches. The pooled hazard ratios (HR) or odds ratios (OR) with their corresponding 95% confidence intervals (95% CI) were used to estimate the effect sizes. A meta-analysis of fifteen studies (6,690 patients) was carried out to evaluate the association between high pre-treatment serum LDH and overall survival (OS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and local relapse free survival (LRFS) in NPC patients. Sensitivity and subgroup analyses were carried out. Results: Our analysis results showed that high pre-treatment serum LDH implied poor OS (HR: 0.29, 95% CI: 0.23-0.37, P < 0.00001), DMFS (HR: 0.30, 95% CI: 0.17-0.55, P < 0.0001), DFS (HR: 0.59, 95% CI: 0.47-0.74, P < 0.00001) and LRFS (HR: 0.48, 95% CI: 0.32-0.71, P=0.00003) of NPC. Subgroup analyses were performed in further investigations. When the patients were segregated according to treatment, country, and cut-off level, high levels of serum LDH were found to be significantly correlated with OS. Conclusion: This meta-analysis suggests serum LDH levels may be a useful biomarker to predict a poorer prognosis for patients with nasopharyngeal carcinoma.

Keywords: Nasopharyngeal carcinoma, LDH, prognosis, meta-analysis

Introduction

Nasopharyngeal carcinoma (NPC) is distinct from other head-and-neck cancers in its pathology, epidemiology, and clinical attributes. NPC has the highest propensity to metastasis to distant sites among head and neck cancers. Approximately 70% of NPC patients presented with stage III or IV disease at the initial diagnosis. About 17-54% of patients with NPC had failed treatment due to distant metastases [1, 2], and systemic disease remains the major cause of death among patients with NPC [3-5]. Though radiotherapy is the radical therapeutic regimen for non-disseminated NPC, the 5 year survival rate of patients with NPC has reached approximately 60-70% [6]. However, locoregional recurrence and distant metastasis after radiotherapy are still the main patterns of failure affecting the survival rate of patients with NPC, the current TNM staging system has limited power in individually determining patient outcomes [7, 8]. Thus, it is important to identify molecular predictive markers for the prognosis, which is helpful in the selection of therapeutic strategies and can further improve the survival for NPC patients.

To improve the long term survival rate and quality of life for patients, implementing individualized therapy is a critical step [9]. Nowadays, more and more novel biomarkers have been reported to have diagnostic and prognostic value in predicting tumourigenesis and tumour progression. For NPC, serum lactate dehydrogenase (LDH) was closely related to glycolysis and mitochondrial deficiency that is required for tumor maintenance [10]. High serum LDH level was found to correlate with a larger tumor burden, to be associated with the extent of locoregional control and/or distant metastasis events,

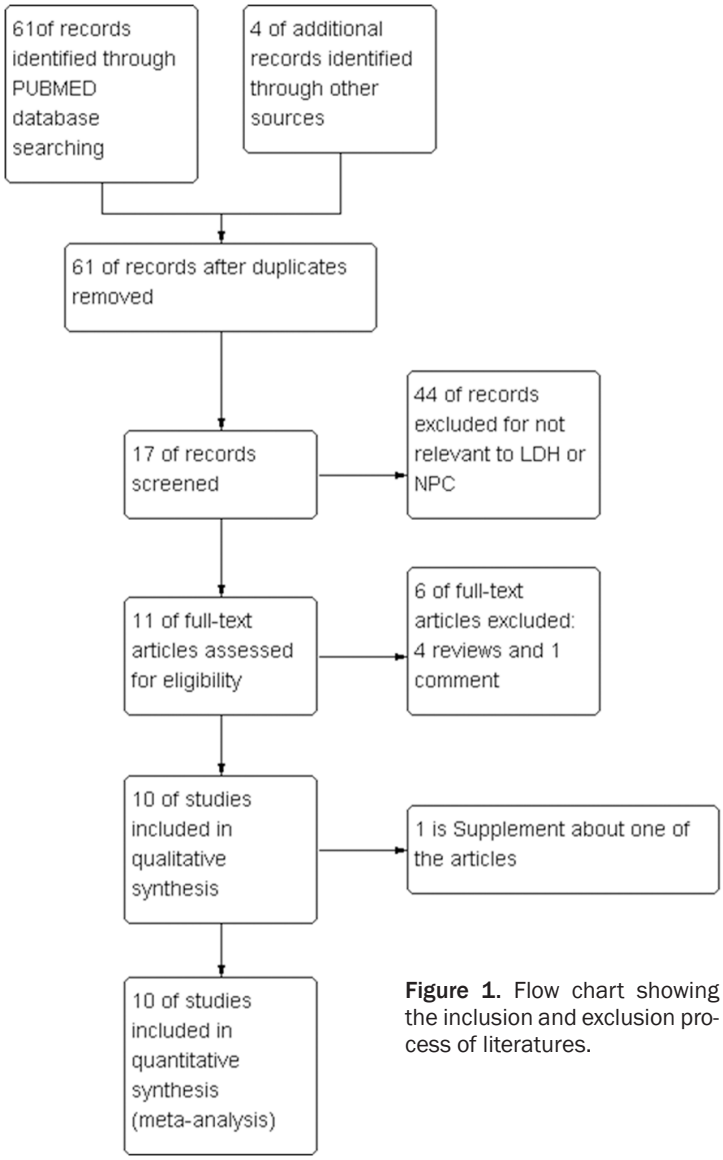

Figure 1. Flow chart showing the inclusion and exclusion process of literatures.

and to predict a poor prognosis. High serum LDH level was an independent unfavorable risk factor for overall survival (OS), but not for disease-free survival (DFS) [11]. Some other reports have suggested that elevated levels of serum LDH above the normal range predict poor prognosis in NPC [12-16]. However, another cohort study reported that elevated pretreatment LDH predicted an inferior survival not only for OS, but also for DFS and distant metastasis-free survival (DMFS) [13].

Due to the inconsistent results, the prognostic value of LDH in NPC remains unsure. Therefore, it is necessary to perform a meta-analysis to comprehensively and systematically understand the prognostic value of pre-treatment serum LDH in NPC.

Materials and methods

Searching strategy

A systematic literature search was conducted to identify studies eligible for the present meta-analysis in Medline, PubMed, Web of Science, China National Knowledge Internet, VIP database, Wanfang database, and Embase to identify studies that assessed the prognostic value of serum LDH for NPC. The search terms included the keywords variably combined by "LDH" or "lactate dehydrogenase", "prognosis" or "prognostic", "nasopharyngeal carcinoma", "nasopharyngeal cancer" or NPC. The reference lists of all retrieved articles were also screened for relevant additional articles.

Inclusion/exclusion criteria

Studies eligible for this meta-analysis should meet the following criteria: (1) patients were pathologically diagnosed as NPC; (2) the pre-treatment serum LDH was measured; (3) case-control studies; (4) the size of the sample, odds ratios (OR) and their 95% confidence intervals (CI) should also be offered; (5) Those publications that presented data allowing such outcomes to be derived were also selected; (6) full-text articles published; (7) for duplicate articles based on the identical or overlapping patient population, only the most recent and/or complete one was used in the meta-analysis. Duplicate articles reporting different endpoints (i.e., OS or DSS) were also included. Accordingly, the following exclusion criteria were also used: (1) review, letter, case report, or nonhuman research; (2) insufficient data to extract the hazard ratio (HR) and the 95% confidence interval (95% CI).

Assessment of risk of bias in included studies

With the guidance of Cochrane handbook (5.1.0), we assessed the risk of bias by using the following criteria: adequate reliability determined random sequence generation, allocation

Table 1. Baseline characteristics of the studies in the meta-analysis

Author	Year	Sample Size (M/F)	Median follow-up peroid (months)	Treatment	Endpoint	HR (95% CI)	Cut-off level (IU/L)	TNM stage (I-II/III-IV)
Guan-Qun Zhou	2011	465 (353/112)	44.7	CT/CRT	OS, DFS, DMFS, LRFS	Reported in text	165	159/306
Xiangbo Wan	2013	400 (312/88)	60	IC/CCRT IC/RT	OS/DFS/LRFS/RRFS/DMFS	Reported in text	245	0/400
Guo Li	2012	533 (396/137)	84	RT/CRT	OS/DMFS/LRFS	Reported in text	240	229/304
SelahattinTuren	2007	61 (48/13)	46	NCT + RT NCT + CCRT	OS/DFS	Reported in text	460	0/61
Lei Zheng	2014	234 (202/32)	22	CT/CRT	OS	Reported in text	245	N/A
Chuangzhen Chen	2013	345 (256/89)	80	CCRT	OS/DMFS	Reported in text	240	N/A
Lu Xue Guan	2000	42 (32/10)	40	RT	DMFS	Reported in text	240	22/20
Gong Kuiyu	2015	2665 (2032/633)	36	RT/CRT/CCRT	OS/LRFS/DMFS	Reported in text	245	984/1258
Chuang-Chi Liaw	1997	118 (N/A)	36	CT/RT	OS	Reported in text	140	N/A
Yun-Ming Tian	2013	85 (7/78)	36	CT/CTR	OS	Reported in text	245	35/50

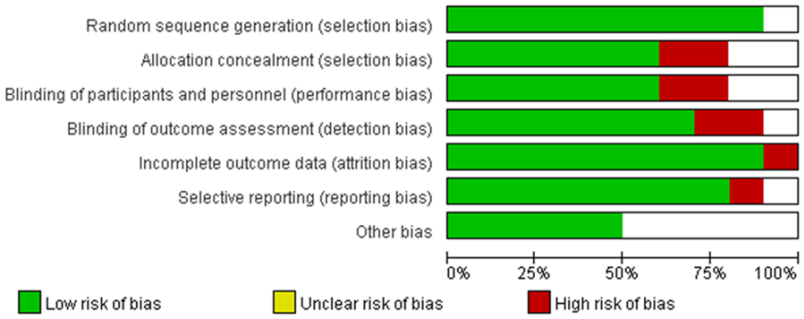

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

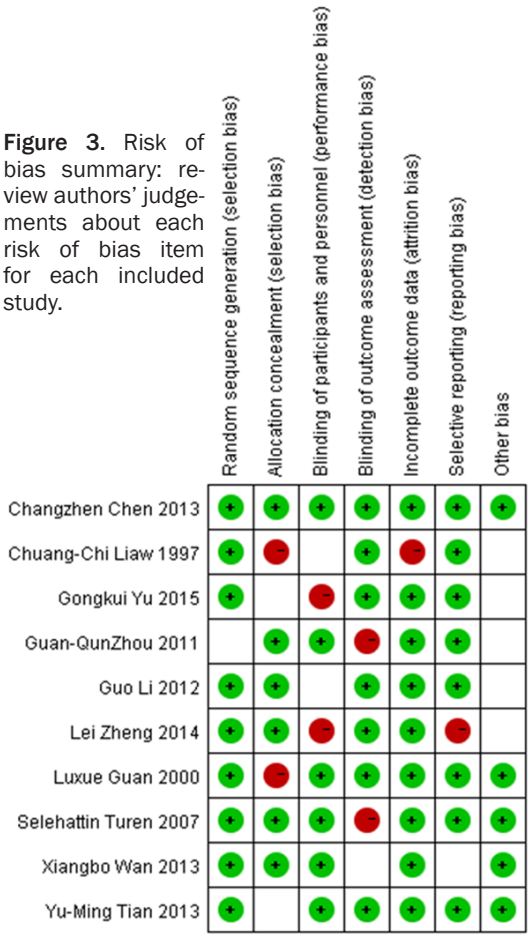

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

concealment, binding of participants and personnel, binding of outcome assessment, incomplete outcome data, selecting reporting and other bias. High risk, low risk, or unclear were used to evaluate the risk of bias.

Data extraction and quality assessment

Data were extracted independently by two reviewers. The extracted data included "authors", "sample size", "publication year", "country", "median age", "treatment information", cut-off value, HRs with their 95% CI for OS or DFS, disappointments between two reviewers were settled through discussion.

Statistical analysis

Review Manager (RevMan) 5.0 (The Cochrane Collaboration, Oxford, England) was used in the meta-analysis. Firstly, we used the fixed effects model to incorporate data from each study; A significant heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$ [17]. Then performed the heterogeneity test for *P* values and I^2 index to estimate the degree of heterogeneity in literature. If $P > 0.05$ and $I^2 < 50\%$, we considered that the analysis had the homogeneity. If $P < 0.05$, and $I^2 > 50\%$, we considered that the analysis had heterogeneity; If heterogeneity was significant, we used the random effect model. Otherwise, we used the fixed effect model; then the sensitivity analysis was needed to assess potential sources of the heterogeneity. Sensitivity analyses were conducted to assess the strength of our findings by excluding one study at a time. Funnel plot was used to evaluate publication bias. If the number included in the study is too few, we tried to use fail-safe number fail-safe number 0.5 (Nfs0.5). The greater the Nfs0.5, indicating that publication bias is smaller, the result of meta-analysis is the more stable.

Results

After the careful screening process, 10 studies met our inclusion criteria and were selected for our final meta-analysis [11, 13-15, 18-23]. Including 6,690 patients with NPC, were included in the meta-analysis. The inclusion and exclusion process of the studies is shown in **Figure 1**. Among the 10 studies, seven were performed in China [13, 14, 18-21, 23], one in Korea [11], and one in America [22], one in Taiwan [15]; eight studies reported data on the effect of serum LDH level on OS [11, 13-15, 18, 20-23], four on DMFS [13, 14, 19, 22], three on DFS [11, 13, 14], and four on LRFS [13, 14, 18, 21]. The basic feature description of the studies was summarized in **Table 1**.

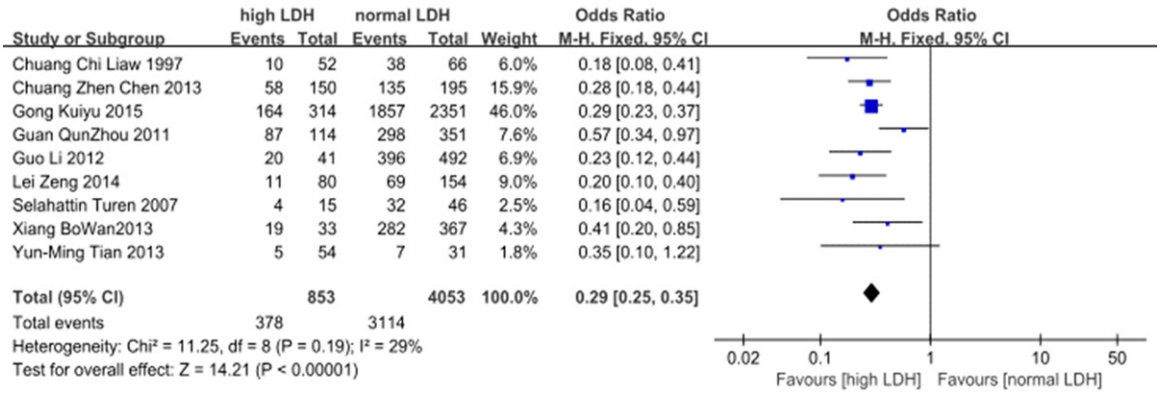

Figure 4. Meta-analysis of the association between LDH and overall survival (OS) of patients with NPC. Results are presented as individual and pooled hazard ratio (HR), and 95% confidence interval (CI).

Table 2. Subgroup analyses of pooled HRs for increased serum LDH and OS in NPC

Analysis	No. of studies	Pooled hazard ratio (95% CI)	I^2 statistic (%)	*P*-value for heterogeneity	Analytical model
Therapeutic method					
CT + CRT	5	0.29 [0.24, 0.35]	0	0.71	REM
CCRT	4	0.29 [0.24, 0.36]	0	0.64	FEM
LDH cut-off value					
245 U/L	5	0.32 [0.26, 0.39]	48	0.10	REM
Non-245 U/L	4	0.24 [0.17, 0.33]	0	0.71	FEM
Country					
China	7	0.30 [0.22, 0.41]	42	0.11	REM
non-China	2	0.26 [0.17, 0.40]	0	0.42	FEM

*Risk of bias of eligible studies in **Figures 2** and **3***

Of 10 studies, all satisfied the criteria of complete outcome data, while one RCT didn't correspond with the item of selective reports. Only three reported adequate reliability determined random sequence generation, allocation concealment, binding of participants and personnel, and binding of outcome assessment. There was no other bias found in these 10 studies.

Pre-treatment serum LDH and OS in NPC patients

There were 9 studies with a total of 4906 patients included in final analysis to assess the effect of serum LDH levels on OS. Combined data showed that high serum LDH were significantly correlated with poor OS with a pooled HR estimate of 0.29 [95% CI: 0.25-0.35, P < 0.00001] without strong evidence on the presence of heterogeneity (I^2=29%, P=0.19) by fixed-effects model (**Figure 4**). Meta-regression analysis and subgroup analysis according to country, treatment, and cut-off value were also performed (**Table 2**). The results suggested that all of relevant stratified factors did not have a significant correlation with heterogeneity, and did not alter the significant prognostic impact of high serum LDH levels.

Pre-treatment serum LDH and DMFS in NPC patients

A total of 4 studies including 1,252 patients were used to assess the association of serum LDH levels with DMFS in NPC patients. As shown in (**Figure 5**), the pooled HR was 0.30 (95% CI 0.17-0.55) by random-effects model for the existence of a significant heterogeneity (I^2=66%, P=0.003), which suggested high serum LDH level was associated with poorer distant metastasis-free survival in NPC patients.

Pre-treatment serum LDH and DFS in NPC patients

Figure 6 shows the forest plot for the association between high pretreatment serum LDH and DFS in NPC patients. Four of the studies reported data on high pretreatment serum LDH and DFS in NPC. The combined data suggested that elevated pre-treatment serum LDH levels were significantly correlated with DFS with a pooled HR estimate of 0.59 (95% CI: 0.47-0.74, P < 0.00001), and the statistical tests did not support heterogeneity in the data (I^2=0%, P= 0.67). The results suggested high serum LDH

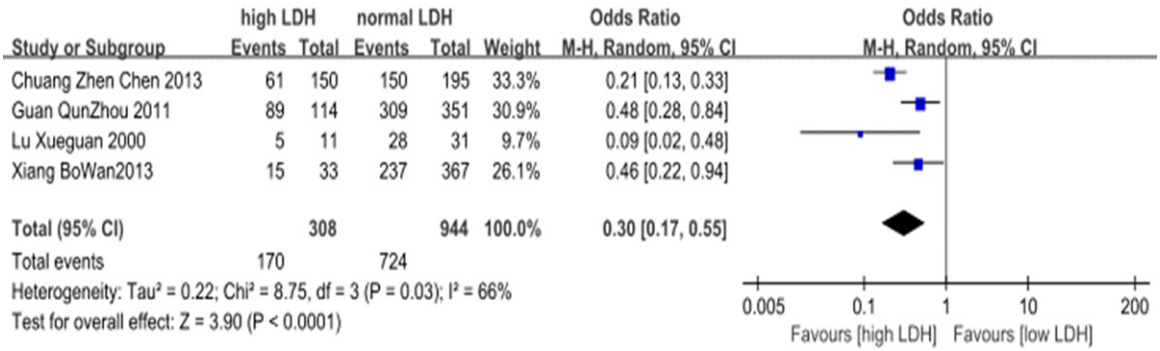

Figure 5. Meta-analysis of the association between LDH and DMFS of patients with NPC. Results are presented as individual and pooled hazard ratio (HR), and 95% CI.

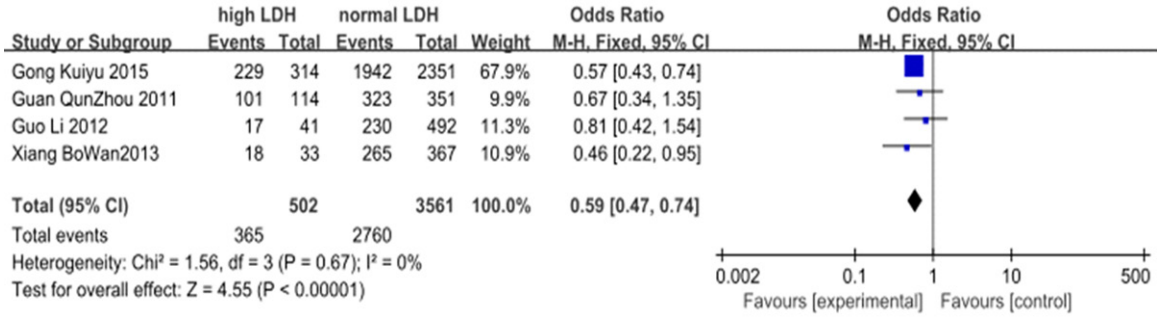

Figure 6. Meta-analysis of the association between LDH and DFS of patients with NPC. Results are presented as individual and pooled hazard ratio (HR), and 95% CI.

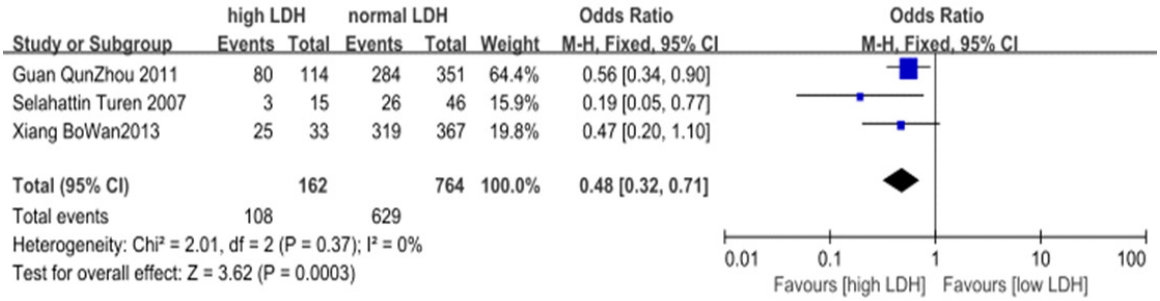

Figure 7. Meta-analysis of the association between LDH and LRFS of patients with NPC. Results are presented as individual and pooled hazard ratio (HR), and 95% CI.

level was associated with poorer disease-free survival in NPC patients.

Pre-treatment serum LDH and LRFS in NPC patients

The main results of this meta-analysis were showed in **Figure 7**.

The pooled HR and 95% CI about LRFS for all three results were 0.48 (95% CI 0.32-0.71; P=0.0003), indicating that LDH level predicts a poorer local relapse-free survival in NPC patients. Few heterogeneity was observed (P=0.37, I^2=0%).

Sensitivity analysis

Sensitivity analyses were performed by considering only the studies with sample size ≥ 100 and excluding the study with the largest effect size. The summary HRs of the eligible studies was not altered similarly to the overall effect of the meta-analysis (**Table 3**).

Table 3. The results of sensitivity analyses

Analysis	No. of studies	Pooled hazard ratio (95% CI)	I^2 statistic (%)	*P*-value for heterogeneity	Analytical model
OS					
Exclusion of study with the largest effect size	7	0.27 [0.23, 0.33]	0	0.66	FEM
Sample size > 100	7	0.30 [0.25, 0.35]	42	0.11	FEM
DMFS					
Exclusion of study with the largest effect size	3	0.25 [0.12, 0.51]	59	0.09	REM
Sample size > 100	3	0.35 [0.19, 0.63]	70	0.04	REM
DFS					
Exclusion of study with the largest effect size	2	0.35 [0.17, 0.70]	15	0.28	FEM
Sample size > 100	2	0.54 [0.35, 0.81]	0	0.74	FEM
LRFS					
Exclusion of study with the largest effect size	3	0.57 [0.45, 0.72]	0	0.76	FEM
Sample size > 100	4	0.59 [0.47, 0.74]	0	0.67	FEM

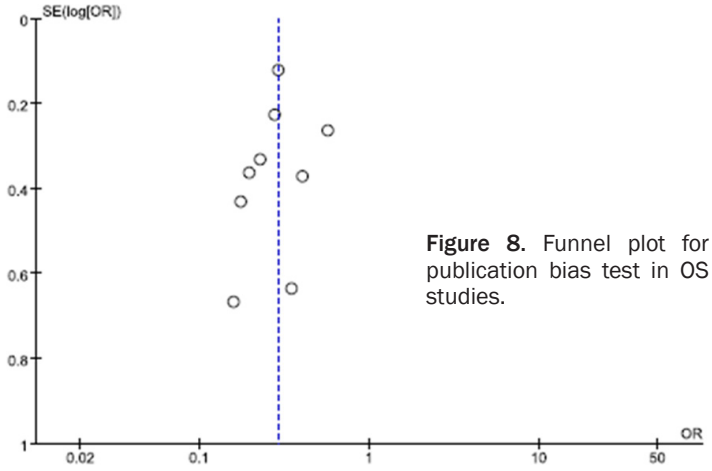

Figure 8. Funnel plot for publication bias test in OS studies.

Publication bias

Publication bias estimate was mainly used to evaluate there liability of meta-analysis results, especially for those showing statistical significance. It suggested evidence for publication bias in OS studies by unnel plot (**Figure 8**). Funnel plots were not created for assessment of possible publication biases in DMFS, DFS, LRFS studies, because it is useless when the number of included studies is limited. Instead, we tried to use fail-safe number, which is defined as the number of negative results that could reverse the significant finding, for the evaluation of the reliability of meta-analysis. The Nfs0.05 for data in **Figures 5**-**7**, were 142, 22 and 37, respectively, suggesting that the publication biases may not have a remarkable influence on the results of the meta analyses.

Discussion

NPC has the highest propensity to metastasis to distant sites among head and neck cancers. Although palliative chemotherapy has been demonstrated as the most effective way with high objective response rates, recurrence frequently occurs after chemotherapy ceases. However, the application of radiotherapy of the primary tumor remains controversial because of their short life expectancy and radiation-induced complications [24, 25]. LDH as a pathophysiological marker has been studied in relation to several opportunistic infections, including infection by Pneumocystis cariniipneumonia (PCP), tuberculous and bacterial pneumonia [26]. The transformation of normal cells into malignant cells often leads to abnormal serum enzyme synthesis, even before changes in tumor morphology [27]. Therefore, enzyme studies have recently received widespread attention. Fantin reported that lactate dehydrogenase (LDH) was closely related to glycolysis and mitochondrial deficiency that is required for tumor maintenance [28].

Elevated serum lactate dehydrogenase (LDH) levels were identified as a negative prognostic indicator for many solid tumors, including non-Hodgkin's lymphoma [29], germ cell tumors [30], small-cell lung cancer [31], and others. An effective pretreatment prognostic marker can-

not only give information for prediction of survival, but can help clinicians make decisions on treatment selection.

Considered as a valuable tool in biomarker validation, a meta-analysis was carried out to study the predictive value of high pretreatment serum LDH on the prognosis of NPC patients. In this meta-analysis, preliminary combined HRs showed that the increased CRP level in nasopharyngeal carcinoma patients indicated a significant association with poorer OS (HR 0.24, 95% CI 0.17-0.36) without apparent heterogeneity (I^2=34%, P=0.51). In the subgroup analyses, with data stratified by country and treatment, every subgroup showed significant HRs and 95% CI. These results indicated that no matter what country or treatment, the patients were in the high levels of serum LDH could significantly predict the poor OS in patients with NPC. In addition, when stratified by cut-off value, the results were also significant no matter what cut-off level was used: 245 U/L (0.32 [0.26, 0.39], I^2=48%) or non-245 U/L (0.24 [0.17, 0.35], I^2=0). The results of sensitivity analyses by sequential omission of individual studies one at a time suggested the significant association was highly unlikely due to chance.

In this study, we also evaluated the association of serum LDH with DMFS, DFS and LRFS on NPC patients. The summary HRs and 95% CI of DMFS, DFS and LRFS suggested that high pretreatment serum LDH levels indicated a poor prognosis for NPC patients. Because less included literature, therefore we cannot do subgroup analysis. Through sensitivity analysis by considering only the studies with sample size ≥ 100 and excluding the study with the largest effect size, the summary HRs and 95% CI suggested the significant association was highly unlikely due to chance without apparent heterogeneity.

The underlying molecular mechanism by which LDH can be correlated with a prognosis of cancer remains unclear. According to the recent studies, the glycolytic pathway of LDH in tumour cells can be the major factor. First, the growth and metastasis of an aggressive tumor requires more intense anaerobic glycolysis to produce energy, which may result in an elevated level of LDH, a key enzyme in the anaerobic glycolysis pathway. In addition, increased LDH levels result in low extracellular pH due to lactic acid production. This, combined with unregulated activity of the hypoxia inducible factor (HIF) pathway, which regulates gene expression and tumor angiogenesis, may trigger activation of pathways that control tumor growth and aggressiveness [32-35]. In the present study, elevated levels of LDH correlated with a worse prognosis, and the hypoxic status of the NPC cells present may have been a contributing factor.

Although we assessed comprehensively the prognostic significance of pre-treatment LDH in NPC, some limitations in our meta-analysis should be discussed. First, the number of included studies was limited. Secondly, potential language and risk bias may exist in this systematic review, because positive study results were more often published than negative ones. In addition, although we tried to identify all relevant information, some missing data were still unavoidable. Moreover, more large-scale, high-quality studies are therefore needed to update our assessment and to give more convincing evidence in the future.

In conclusion, our meta-analysis revealed that high levels of serum LDH were significantly associated with poor OS, DMFS, DFS and LRFS in patients with NPC. We conclude that pretreatment serum CRP is considered to be a promising prognostic factor for nasopharyngeal cancer patients, and serve as a useful bio-maker for NPC.

Acknowledgements

This work was supported in part by grant-in-aid from National clinical key discipline construction project (No. 2012-649), And Chongqing Yuzhong science and technology projects (No. 20150110).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jiang Zhu, Department of Otolaryngology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China. Tel: 01186-13668052903; E-mail: zhujiang2903@163.com

References

[1] Liu MT, Hsieh CY, Chang TH, Lin JP, Huang CC and Wang AY. Prognostic factors affecting the

outcome of nasopharyngeal carcinoma. Jpn J Clin Oncol 2003; 33: 501-508.
[2] Chiesa F and De Paoli F. Distant metastases from nasopharyngeal cancer. ORL J Otorhinolaryngol Relat Spec 2001; 63: 214-216.
[3] Leung SF, Teo PM, Shiu WW, Tsao SY and Leung TW. Clinical features and management of distant metastases of nasopharyngeal carcinoma. J Otolaryngol 1991; 20: 27-29.
[4] Tao Y, Bidault F, Bosq J and Bourhis J. Distant metastasis of undifferentiated carcinoma of nasopharyngeal type. Onkologie 2008; 31: 574-575.
[5] Gunn GB, Villa RD, Sedler RR, Hardwicke F, Fornari GA and Mark RJ. Nasopharyngeal carcinoma metastasis to the pituitary gland: a case report and literature review. J Neurooncol 2004; 68: 87-90.
[6] Li ZQ, Xia YF, Liu Q, Yi W, Liu XF, Han F, Luo W and Lu TX. Radiotherapy-related typing in 842 patients in canton with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006; 66: 1011-1016.
[7] Hong MH, Mai HQ, Min HQ, Ma J, Zhang EP and Cui NJ. A comparison of the Chinese 1992 and fifth-edition International Union Against Cancer staging systems for staging nasopharyngeal carcinoma. Cancer 2000; 89: 242-247.
[8] Wan XB, Zhao Y, Fan XJ, Cai HM, Zhang Y, Chen MY, Xu J, Wu XY, Li HB, Zeng YX, Hong MH and Liu Q. Molecular prognostic prediction for locally advanced nasopharyngeal carcinoma by support vector machine integrated approach. PLoS One 2012; 7: e31989.
[9] Leung TW, Tung SY, Sze WK, Wong FC, Yuen KK, Lui CM, Lo SH, Ng TY and O SK. Treatment results of 1070 patients with nasopharyngeal carcinoma: an analysis of survival and failure patterns. Head Neck 2005; 27: 555-565.
[10] Fantin VR, St-Pierre J and Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell 2006; 9: 425-434.
[11] Turen S, Ozyar E, Altundag K, Gullu I and Atahan IL. Serum lactate dehydrogenase level is a prognostic factor in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy. Cancer Invest 2007; 25: 315-321.
[12] Cheng SH, Jian JJ, Tsai SY, Chan KY, Yen LK, Chu NM, Tan TD, Tsou MH and Huang AT. Prognostic features and treatment outcome in locoregionally advanced nasopharyngeal carcinoma following concurrent chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 1998; 41: 755-762.
[13] Zhou GQ, Tang LL, Mao YP, Chen L, Li WF, Sun Y, Liu LZ, Li L, Lin AH and Ma J. Baseline serum lactate dehydrogenase levels for patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma: a predictor of poor prognosis and subsequent liver metastasis. Int J Radiat Oncol Biol Phys 2012; 82: e359-365.
[14] Wan XB, Wei L, Li H, Dong M, Lin Q, Ma XK, Huang PY, Wen JY, Li X, Chen J, Ruan DY, Lin ZX, Chen ZH, Liu Q, Wu XY and Hong MH. High pretreatment serum lactate dehydrogenase level correlates with disease relapse and predicts an inferior outcome in locally advanced nasopharyngeal carcinoma. Eur J Cancer 2013; 49: 2356-2364.
[15] Liaw CC, Wang CH, Huang JS, Kiu MC, Chen JS and Chang HK. Serum lactate dehydrogenase level in patients with nasopharyngeal carcinoma. Acta Oncol 1997; 36: 159-164.
[16] Jin Y, Ye X, Shao L, Lin BC, He CX, Zhang BB and Zhang YP. Serum lactic dehydrogenase strongly predicts survival in metastatic nasopharyngeal carcinoma treated with palliative chemotherapy. Eur J Cancer 2013; 49: 1619-1626.
[17] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta analyses. BMJ 2003; 327: 557-560.
[18] Li G, Gao J, Tao YL, Xu BQ, Tu ZW, Liu ZG, Zeng MS and Xia YF. Increased pretreatment levels of serum LDH and ALP as poor prognostic factors for nasopharyngeal carcinoma. Chin J Cancer 2012; 31: 197-206.
[19] Lu XG ZY, Feng Y. The Relationship Between Serum LDH and Distant Metastasis of Nasopharyngeal Carcinoma. Int J Learned Journal of Suzhou Med Col 2000; 20.
[20] Zeng L, Tian YM, Huang Y, Sun XM, Wang FH, Deng XW, Han F and Lu TX. Retrospective analysis of 234 nasopharyngeal carcinoma patients with distant metastasis at initial diagnosis: therapeutic approaches and prognostic factors. PLoS One 2014; 9: e108070.
[21] KY G. Analysis of LDH in Radiotherapy-related typing of nasopharyngeal carcinoma. Int J Chin J Radiat Oncol 2015; 24: 55-59.
[22] Chen C, Chen S, Le QT, Chen J, Chen Z, Li D, Zhou M and Li D. Prognostic model for distant metastasis in locally advanced nasopharyngeal carcinoma after concurrent chemoradiotherapy. Head Neck 2015; 37: 209-214.
[23] Tian YM, Zeng L, Wang FH, Liu S, Guan Y, Lu TX and Han F. Prognostic factors in nasopharyngeal carcinoma with synchronous liver metastasis: a retrospective study for the management of treatment. Radiat Oncol 2013; 8: 272.
[24] Setton J, Wolden S, Caria N and Lee N. Definitive treatment of metastatic nasopharyngeal carcinoma: Report of 5 cases with review of literature. Head Neck 2012; 34: 753-757.

[25] Yeh SA, Tang Y, Lui CC and Huang EY. Treatment outcomes of patients with AJCC stage IVC nasopharyngeal carcinoma: benefits of primary radiotherapy. Jpn J Clin Oncol 2006; 36: 132-136.
[26] Sevinc A SR, Fadillioglu E. The utility of lactate dehydrogenase isozyme pattern in the diagnostic evaluation of malignant and non-malignant ascites. J Natl Med Assoc 2005; 97: 79-84.
[27] Cascante M, Centelles JJ, Veech RL, Lee WN and Boros LG. Role of thiamin (vitamin B-1) and transketolase in tumor cell proliferation. Nutr Cancer 2000; 36: 150-154.
[28] Fantin VR, St-Pierre J and Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell 2006; 9: 425-434.
[29] A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329: 987-994.
[30] Shamash J, Oliver RT, Gallagher CJ, Newland AC, Lister TA, Kelsey S, Gupta RK and O'Doherty CA. Pre-induction LDH as a prognostic factor for outcome of high dose chemotherapy (HDCT) for germ cell tumours relapsing or refractory to conventional chemotherapy. Br J Cancer 2000; 82: 2022-2023.
[31] Byhardt RW, Hartz A, Libnoch JA, Hansen R and Cox JD. Prognostic influence of TNM staging and LDH levels in small cell carcinoma of the lung (SCCL). Int J Radiat Oncol Biol Phys 1986; 12: 771-777.
[32] Stubbs M, McSheehy PM, Griffiths JR and Bashford CL. Causes and consequences of tumour acidity and implications for treatment. Mol Med Today 2000; 6: 15-19.
[33] Colgan SM, Mukherjee S and Major P. Hypoxia-induced lactate dehydrogenase expression and tumor angiogenesis. Clin Colorectal Cancer 2007; 6: 442-446.
[34] Harris AL. Hypoxia--a key regulatory factor in tumour growth. Nat Rev Cancer 2002; 2: 38-47.
[35] Maxwell PH. The HIF pathway in cancer. Semin Cell Dev Biol 2005; 16: 523-530.