

Prognostic value of pretreatment serum levels of lactate dehydrogenase in nonmetastatic nasopharyngeal carcinoma: single-site analysis of 601 patients in a highly endemic area

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Background: Numerous studies have generated promising but incomplete evidence for the prognostic value of pretreatment serum levels of lactate dehydrogenase (S-LDH) in nasopharyngeal carcinoma (NPC).

Methods: Pretreatment serum levels of S-LDH in 601 patients with NPC were measured before treatment, and their associations with overall survival and tumor-free survival were studied. Univariate and multivariate analysis of subgroups was used to evaluate the prognostic value of S-LDH in early-stage and late-stage NPC separately.

Results: Pretreatment S-LDH levels were significantly lower in T1+2 patients than in T3+4 patients, lower in N0+1 patients than in N2+3 ones, and lower in stage I + II patients than in III + IV ones. Multivariate analysis showed that among patients with late-stage NPC, high pretreatment S-LDH levels >225 U/L were an independent predictor of poor overall survival and tumor-free survival. Among patients with early-stage NPC, pretreatment S-LDH levels >171 U/L, which overlap with the normal range, were an independent predictor of shorter overall survival and tumor-free survival.

Conclusion: Pretreatment S-LDH levels may be a reliable biomarker for predicting the long-term prognosis of patients with early-stage or late-stage NPC.

Keywords: nasopharyngeal carcinoma, serum lactate dehydrogenase, prognosis, late stage, early stage

Introduction

Nasopharyngeal carcinoma (NPC) is common in southern China, with Guangdong and Guangxi provinces forming one of the largest endemic areas. The annual incidence of NPC in these areas is as high as 20–30/100,000,¹ accounting for as many as half the approximately 80,000 cases newly diagnosed annually around the world.² The primary treatment for NPC is radical radiotherapy with or without chemotherapy, and improvements in these approaches have led to a continuous increase in survival rate.³ Nevertheless, approximately 50% of NPC patients experience recurrence, especially those with late-stage disease at the time of initial treatment.^{3,4}

This makes accurate prognosis of NPC extremely important. The most common system used to predict NPC outcomes is the TNM classification.⁵ T refers to the size of the primary tumor and whether it has invaded nearby tissue; N, to regional lymph node involvement; and M, to distant metastasis. This classification scheme is imperfect, not only because it does not take into account the variability in survival and

response to chemotherapy among NPC patients with distant metastases, but also because patients in the same T class can still show substantial clinicopathological heterogeneity.^{6,7} This highlights the need for better prognostic indicators for NPC.

Serum levels of enzymes and signaling molecules have proven to be useful prognostic factors for various malignant tumors, facilitating the evaluation of disease development and prognosis.^{8–10} A previous study by Cheng et al showed that elevated serum lactate dehydrogenase (S-LDH) levels >410 U/L are associated with poor locoregional control of nonmetastatic, locally advanced NPC.^{11,12} Some other reports have suggested that elevated levels of S-LDH above the normal range predict poor prognosis in NPC.^{12–17} Jin et al reported that pretreatment S-LDH levels >245 U/L, which was the upper limit of the normal range in their study, were an independent prognostic factor for poor overall survival and progression-free survival in metastatic NPC.¹⁷ Li et al and Wang et al also showed that S-LDH levels >240 U/L, which was the upper limit of the normal range in their study, predicted poor prognosis in NPC without distant metastasis.^{10,15}

These studies make a strong case for the prognostic value of S-LDH levels, but the evidence is far from definitive. Three of these studies made their conclusions based on subsets of only 4.3%, 6.7%, or 8.3% of patients with S-LDH levels above the upper limit of the normal range, defined as 240 U/L or 245 U/L in their works,^{10,14,15} increasing the risk of selection bias and reporting bias. In addition, all patients from these three studies came from one medical center in Guangdong province, and whether S-LDH may affect the outcome of NPC in other endemic areas remained to be investigated. In fact, the finding by one Guangdong study that S-LDH levels are associated with tumor-free survival in NPC¹⁴ contrasts with a Turkish study that came to the opposite conclusion.¹³ New research from other endemic areas would extend our existing knowledge and make S-LDH a more reliable biomarker in predicting the prognosis of NPC.

While the literature gives an unclear picture of the prognostic value of S-LDH levels in metastatic or locally advanced NPC, it provides no information about the prognostic value in early-stage NPC. Identifying prognostic factors for these patients is particularly important because radical radiotherapy fails to work for 15%–30% of patients.¹⁸ This suggests that the prognosis can differ significantly among early-stage patients.

To address these evidence gaps in the literature, we performed a retrospective study of S-LDH levels and prognosis

in a large patient cohort at our hospital, which is the only medical center focusing on NPC prophylaxis and treatment in Guangxi province. We tried to examine as large a cohort as possible in order to maximize the number of patients with elevated S-LDH levels, and we examined the associations of S-LDH levels with overall survival and tumor-free survival separately for early-stage and late-stage disease. Our aim was to provide clearer evidence for or against the value of pretreatment S-LDH levels for predicting long-term outcome of NPC patients in endemic areas.

Materials and methods

Patients

A retrospective study was performed on patients newly diagnosed with NPC who were treated in the radiotherapy department of the Affiliated Tumor Hospital of Guangxi Medical University in Guangxi, People's Republic of China. This study was approved by the ethics committee of Guangxi Medical University. All patients treated between July 2003 and March 2006 were considered for inclusion in this study. Inclusion criteria were as follows: histological diagnosis of type II or III NPC based on the World Health Organization typing system; examination of the nasopharynx, head, and neck by computed tomography or magnetic resonance imaging before radical treatment; blood collection for S-LDH measurements prior to the start of radiotherapy or chemotherapy; no evidence of distant metastasis or secondary carcinoma at diagnosis; treatment by complete radical radiotherapy with or without chemotherapy; and absence of any severe heart, lung, kidney, or liver problems that would prevent patients from receiving radiotherapy and chemotherapy.

All patients were evaluated based on medical history, physical examination, full blood count, baseline serum biochemistry, nasopharyngeal endoscope examination and nasopharyngeal tumor biopsy. Levels of serum immunoglobulin (Ig)A against the Epstein-Barr virus (EBV) capsid antigen (EBV-VCA-IgA) and early antigen (EBV-EA-IgA) were measured, as were levels of serum IgG against EBV early antigen (EBV-EA-IgG). All patients were classified according to the American Joint Committee on Cancer staging system (6th edition).¹⁹

Measurements of S-LDH

All blood samples were obtained through venipuncture before radical treatment. Levels of S-LDH were assayed based on an enzyme kinetics kit (Beijing Strong Biotechnologies, Beijing, People's Republic of China), according to the manufacturer's instructions. Measurements were carried out

on a 7170A automated analyzer (Hitachi Ltd, Tokyo, Japan). The manufacturer-specified normal range of S-LDH using this kit is 135–225 U/L.

Treatment

All patients received radical radiotherapy using conventional or three-dimensional conformal radiotherapy. The following cumulative doses were delivered to each region: nasopharyngeal region, 64–89 Gy; neck (N1, N2, or N3), 70–80 Gy; and neck without lymph node involvement (N0) as a preventive dosage, 50–64 Gy.

In addition to radiotherapy, certain patients also received induced, concurrent, or adjuvant chemotherapy, for which 5-fluorouracil (500–600 mg m⁻² per day, days 1–5) and cisplatin (20–30 mg m⁻² per day, days 1–3 or days 1–5) were administered. For induction chemotherapy, 5-fluorouracil and cisplatin were used for one or two cycles before radiotherapy. For concurrent chemotherapy, 5-fluorouracil and cisplatin were used every 4 weeks on day 1 and day 29 unless severe side effects occurred. For adjuvant chemotherapy, 5-fluorouracil and cisplatin were administered every 3 weeks for two to three cycles, unless severe side effects occurred.

Patient follow-up and outcomes

During the first 3 years after treatment, patients were followed up every 3–6 months in our hospital or at a local hospital. Beyond 3 years, follow-up checks were conducted at intervals ranging from every 3 months to each year. Data from follow-up checks conducted in local hospitals were collected by telephone.

Overall survival was defined as the interval between diagnosis and death or the last follow-up visit if the patient was still alive by the end of the study. Tumor-free survival was defined as the interval between initial diagnosis of NPC and diagnosis of tumor progression, death, or the last follow-up visit if the patient was still alive at the end of the study.

Statistical analysis

Data were analyzed statistically using Statistical Package for the Social Sciences version 15 software (SPSS Inc., Chicago, IL, USA). Overall survival and tumor-free survival were calculated using the Kaplan-Meier method. We dichotomized S-LDH levels as $>$ or ≤ 225 U/L (the upper limit of normal range in our study) when analyzing the entire patient cohort. In univariate and multivariate analyses of the entire cohort, T classification, N classification, and TNM stage were treated as continuous variables. Pretreatment S-LDH

(low or high), sex, age (≤ 50 or > 50 years), smoking history (yes or no), and chemotherapy (yes or no) were binary variables. Univariate analysis was used to study correlations of each of these variables with overall survival and tumor-free survival. Variables showing a correlation of $P < 0.10$ were then used in multivariate analysis based on the Cox proportional hazards regression model to identify combinations of prognostic factors that correlated with overall survival and tumor-free survival.

We then repeated these analyses separately for patients with early-stage NPC (stage I + II) and those with late-stage NPC (stage III + IV). First we performed the analyses using the same cutoff value of 225 U/L to dichotomize S-LDH values as high or low, as we did for the entire cohort. Later, we performed the analyses for patients with early-stage NPC ($n=262$) using the mean S-LDH level of these cases as a cutoff value to define subgroups with high or low level of this marker. Differences in subgroup means were assessed for significance using the Student's *t*-test or the Mann-Whitney *U* test. Differences with a two-sided $P < 0.05$ were considered to be statistically significant.

Results

Patient characteristics

During the study period, 696 patients newly diagnosed with NPC were treated in the inpatient radiotherapy department of our hospital. Of the 693 patients for which pretreatment S-LDH measurements were available, 92 (13.3%) were excluded for the following reasons: 30 (4.3%) showed signs of distant metastasis, 29 (4.2%) did not receive complete radical treatment, 14 (2.0%) had received radiotherapy or chemotherapy before their S-LDH levels were measured, four (0.58%) had secondary malignant tumors at diagnosis, two (0.3%) were histologically diagnosed as type I NPC on the World Health Organization typing system, and 13 (1.9%) were lost to follow-up. The remaining 601 cases (86.7%) satisfied all inclusion criteria and were included in the analysis.

The ratio of males to females was 2.7:1, and the mean age was 44.3 (11–82) years. Pretreatment serum levels of EBV-VCA-IgA, EBV-EA-IgA, or EBV-EA-IgG were available for 583 patients (97%). Of these, 539 (89.7%) were positive for at least one of the three antibodies (Table 1). All patients received radical radiotherapy, and 338 (58.4%) also received induced, concurrent, or adjuvant chemotherapy. The median follow-up time was 51.5 (5–116) months. During follow-up, 216 patients (35.9%) experienced tumor progression after treatment, including those who developed

Table 1 Patient characteristics

Characteristic	n (%)	Pretreatment serum LDH (U/L, mean \pm SD)	P-value
Age (years)			
≤ 50	436 (74.1)	186.95 \pm 88.19	0.149
> 50	165 (25.9)	198.37 \pm 83.14	
Sex			
Male	440 (76.2)	188.98 \pm 69.92	0.683
Female	161 (23.8)	193.12 \pm 121.14	
Tumor classification			
T1+2	379 (62.0)	184.09 \pm 70.04	0.039
T3+4	222 (38.0)	201.06 \pm 109.10	
Lymph node classification			
N0+1	421 (70.1)	178.85 \pm 53.68	0.000
N2+3	180 (29.9)	216.91 \pm 131.72	
TNM stage (AJCC)			
I + II	262 (43.6)	171.27 \pm 47.86	0.000
III + IV	339 (56.4)	205.14 \pm 105.41	
Smoking history			
Yes	136 (24.1)	189.40 \pm 68.42	0.915
No	465 (75.9)	190.29 \pm 91.27	
Chemotherapy			
Yes	338 (58.4)	196.14 \pm 97.87	0.067
No	263 (41.6)	182.52 \pm 69.81	
EBV-related antibodies			
Negative	44 (7.3)	199.56 \pm 81.48	0.531
Positive	539 (89.7)	190.45 \pm 88.13	
NA	18 (3.0)		
Family history of NPC			
Yes	25	195.80 \pm 75.16	0.737
No	576	189.84 \pm 87.08	

Abbreviations: AJCC, American Joint Committee on Cancer; LDH, lactate dehydrogenase; EBV, Epstein-Barr virus; NA, not available; NPC, nasopharyngeal carcinoma; SD, standard deviation; TNM, tumor nodes metastasis-classification.

local or regional recurrence and those who developed distant metastasis. By the end of follow-up, 169 patients (28.1%) had died. All but two deaths were due to local recurrence or distant metastasis; the two exceptions were due to diseases unrelated to NPC.

Association between pretreatment S-LDH and tumor stage

The mean (\pm standard deviation) pretreatment S-LDH level across our entire cohort was 190.09 \pm 86.57 U/L. This level was elevated (>225 U/L) in 114 patients (18.8%). The S-LDH level was significantly higher in patients classified as T3+4 than in patients classified as T1+2 ($P=0.039$), and was higher in N2+3 patients than in N0+1 patients ($P<0.0001$; Table 1). The level was significantly higher in patients in stage III + IV than in patients in stage I + II ($P<0.0001$). S-LDH levels were not associated with sex, age, smoking

history, drinking history, chemotherapy, family history of NPC, or presence of anti-EBV antibodies.

Elevated S-LDH levels (>225 U/L), overall survival, and tumor-free survival in entire cohort

Univariate analysis conducted with data from all 601 patients identified the following factors as significantly correlated with overall survival: pretreatment S-LDH level ($P<0.0001$), age ($P=0.005$), T classification ($P<0.0001$), and N classification ($P=0.002$). In contrast, the following factors showed no significant association with overall survival: sex ($P=0.210$), smoking history ($P=0.075$), drinking history ($P=0.275$), family history of NPC ($P=0.588$), and chemotherapy ($P=0.888$).

Univariate analysis also identified the following factors as significantly correlated with tumor-free survival: pretreatment S-LDH level ($P=0.002$), age ($P=0.002$), sex ($P=0.04$), smoking history ($P=0.017$), T classification ($P=0.005$), and N classification ($P=0.000$). In contrast, drinking history ($P=0.093$), family history of NPC ($P=0.860$), and chemotherapy ($P=0.151$) showed no significant association with tumor-free survival.

Multivariate analysis identified several demographic and clinical variables as independent prognostic factors for poor overall survival (Table 2): high pretreatment S-LDH level (hazard ratio [HR] 1.724, 95% confidence interval [CI] 1.221–2.434), age (HR 1.547, 95% CI 1.125–2.127), T classification (HR 1.362, 95% CI 1.160–2.559), and N classification (HR 1.243, 95% CI 1.071–1.442). The analysis also identified the following independent factors for poor tumor-free survival: high pretreatment S-LDH level (HR 1.482, 95% CI 1.084–2.028), age (HR 1.487,

Table 2 Cox multivariate analysis to identify prognostic factors in 601 patients with nasopharyngeal carcinoma using a cutoff of 225 U/L to define low and high S-LDH levels

Prognostic factor	P-value	HR	95% CI for HR
Overall survival			
Pretreatment S-LDH	0.002	1.724	1.221–2.434
Age	0.007	1.547	1.125–2.127
T classification	0.001	1.362	1.160–1.599
N classification	0.004	1.243	1.071–1.442
Tumor-free survival			
Pretreatment S-LDH	0.014	1.482	1.084–2.028
Age	0.006	1.487	1.121–1.973
T classification	0.004	1.228	1.067–1.415
N classification	0.014	1.825	1.127–2.955

Abbreviations: HR, hazard ratio; CI, confidence interval; S-LDH, serum lactate dehydrogenase.

95% CI 1.121–1.973), T classification (HR 1.228, 95% CI 1.067–2.415), and N classification (HR 1.825, 95% CI 1.127–2.955). In contrast, no significant association of tumor-free survival was observed with sex (HR 1.181, 95% CI 0.839–1.663) or smoking history (HR 1.242, 95%

CI 0.903–1.709). Consistent with these results, analysis using the log-rank test showed that patients with high pretreatment S-LDH levels had worse overall survival and tumor-free survival than patients with low levels (Figure 1).

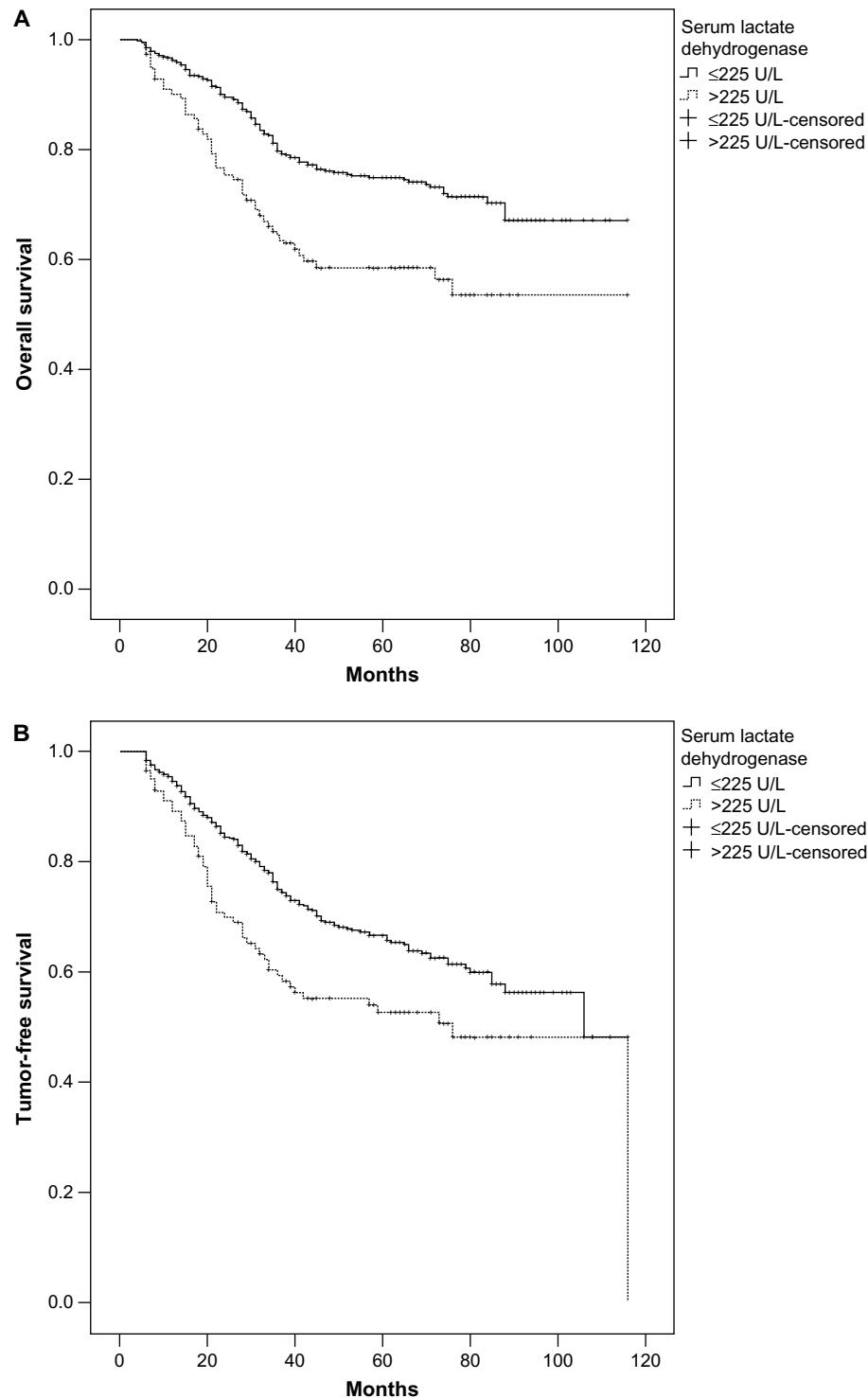


Figure 1 Survival analysis of 601 patients with nasopharyngeal carcinoma stratified by pretreatment serum levels of lactate dehydrogenase (\leq or >225 U/L). **Notes:** (A) Overall survival ($P<0.0001$). (B) Tumor-free survival ($P=0.002$).

S-LDH levels, overall survival, and tumor-free survival in early-stage and late-stage NPC

First we conducted multivariate analysis separately for early-stage and late-stage NPC using the same cutoff value for high S-LDH level (>225 U/L) as we had used for the entire patient cohort. This analysis identified S-LDH levels >225 U/L in patients in stage III + IV to be an independent prognostic factor for both overall survival (HR 1.693, 95% CI 1.139–2.517) and tumor-free survival (HR 1.533, 95% CI 1.068–2.201; Table 3). However, these elevated levels were not a prognostic factor in patients with stage I + II NPC for either overall survival (HR 1.748, 95% CI 0.803–3.805) or tumor-free survival (HR 1.525, 95% CI 0.775–3.003; Table 3).

The mean (\pm standard deviation) pretreatment S-LDH level of cases with stage I + II was 171.27 \pm 47.86 U/L, so next we repeated the multivariate analysis using 171 U/L as a cutoff value to classify early-stage patients as high or low S-LDH. The results identified two independent prognostic factors for overall survival: high pretreatment S-LDH levels (HR 1.945, 95% CI 1.123–3.367) and age (HR 1.799, 95% CI 1.031–3.137). The same variables were also independent prognostic factors for tumor-free survival: S-LDH, HR 1.866, 95% CI 1.182–2.944; and age, HR 2.170, 95% CI 1.371–3.434 (Table 4).

Analysis using the log-rank test and a cutoff value of 171 U/L showed that 5-year overall survival was significantly higher in patients in stage I + II when their pretreatment S-LDH levels were \leq 171 U/L than when they were >171 U/L (85.0% versus 71.4%; $P=0.005$; Figure 2A). Similar results were obtained for 5-year tumor-free survival (78.7% versus 61.8%; $P=0.002$; Figure 2B).

Discussion

Studies have suggested that pretreatment S-LDH levels in patients with nonmetastatic NPC may be a useful prognostic indicator, but the relatively small numbers of patients involved and other methodological issues make the evidence

less than definitive. In this retrospective study, we analyzed a larger number of patients and provide potentially more convincing evidence that elevated S-LDH levels are associated with poor overall survival and tumor-free survival. We also performed subgroup analyses showing that the prognostic value of S-LDH applies to both early-phase and late-phase NPC. To our knowledge, this is the first report of S-LDH as a prognostic indicator for early-phase NPC, which is challenging to treat because of the heterogeneous response to radical radiotherapy.¹⁸

Lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactate in hypoxic conditions, and it functions in numerous cell types in the human body.¹⁷ The enzyme also plays an important role in tumor initiation and maintenance,^{20,21} since its ability to function in anaerobic metabolism helps cancer cells grow even after their rapid proliferation leads to low-oxygen conditions in the tumor microenvironment.²² Under these conditions, tumor cells characteristically show rapid anaerobic glycolysis,²³ a process in which LDH plays a central role.²⁴ Not surprisingly, then, various malignant tumors have been reported to express higher levels of LDH isoforms than healthy cells, and S-LDH levels in these patients are higher than in healthy controls.^{9,10,25} The elevated S-LDH may reflect, at least in part, release of the enzyme from malignant cells.^{16,26} These findings suggest that S-LDH levels may reflect tumor burden and therefore correlate with disease progression.¹⁵

Consistent with this idea, we found pretreatment S-LDH level to be significantly higher in T3+4 than in T1+2 patients, higher in N2+3 than in N0+1 patients, and higher in stage III + IV than in stage I + II patients. Nevertheless, in our cohort of 601 cases, which is large for this type of study, only 18.8% of patients had S-LDH levels >225 U/L. This suggests that S-LDH, although it does appear to correlate with disease progression, is unlikely to have sufficient sensitivity as a clinical marker for NPC diagnosis and screening.

Instead, the usefulness of S-LDH may lie in its prognostic value. Pretreatment S-LDH values have proven effective at predicting prognosis in various malignancies, including

Table 3 Cox multivariate analysis to identify the prognostic value of pretreatment S-LDH levels in patients with early-stage or late-stage nasopharyngeal carcinoma based on a cutoff of 225 U/L to define low or high S-LDH

Pretreatment S-LDH	Stage I + II (AJCC)			Stage III + IV (AJCC)		
	P-value	HR	95% CI for HR	P-value	HR	95% CI for HR
OS	0.160	1.748	0.803–3.805	0.009	1.693	1.139–2.517
TFS	0.222	1.525	0.775–3.003	0.021	1.533	1.068–2.201

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; OS, overall survival; S-LDH, serum lactate dehydrogenase; TFS, tumor-free survival.

Table 4 Cox multivariate analysis to identify prognostic factors in 262 patients with stage I + II nasopharyngeal carcinoma using a cutoff of 171 U/L to define low and high S-LDH levels

Prognostic factor	P-value	HR	95% CI for HR
Overall survival			
Pretreatment S-LDH	0.018	1.945	1.123–3.367
Age	0.039	1.799	1.031–3.137
Tumor-free survival			
Pretreatment S-LDH	0.007	1.866	1.182–2.944
Age	0.001	2.170	1.371–3.434

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; S-LDH, serum lactate dehydrogenase.

lung cancer, malignant melanoma, and non-Hodgkin's lymphoma.^{9,27–29} Three reports have further suggested that these levels have prognostic value in NPC.^{10,14,15} These studies, which were based on the experience of a medical center in an endemic area (Guangdong province), only involved less than 9% of the patients who had elevated S-LDH levels higher than the upper limit of normal range (defined as 240 U/L or 245 U/L). This might increase the risk of selection bias or reporting bias, and the prognostic value of S-LDH should be further assessed by more studies with more NPC cases from other endemic areas. Our study was carried out in a new endemic area (Guangxi province) among patients at a different medical center, and our analyses involved 18.8% of our entire patient cohort (114/601) and 25% of our enrolled patients with stage III + IV NPC (84/339) who had elevated S-LDH levels higher than the upper limit of normal range (225 U/L in our work). Therefore, the present study extends the literature substantially by increasing the number of endemic areas, medical centers, and patients that have been analyzed. Our finding that elevated S-LDH levels (>225 U/L) are associated with reduced overall survival (HR 1.724) and tumor-free survival (HR 1.482) is consistent with the previous studies mentioned above.

Studies are needed to investigate how LDH affects the prognosis of patients with NPC, although the literature has provided several interesting leads. Elevated expression of LDH-5, one of the major LDH isoforms, is associated with an absence of lymphocytic infiltration at the invading tumor edge, markedly higher expression of vascular endothelial growth factor, and vascular density in tumor tissue;^{25,30,31} all three of these factors are associated with poor NPC outcome.^{32–34} Intriguingly, LDH-5 levels are directly associated with S-LDH levels.³⁵ Elevated S-LDH levels have also been linked to upregulation of hypoxia-inducible factor 1-alpha, which may contribute to resistance of NPC to chemotherapy and radiotherapy, leading to reduced overall survival

and tumor-free survival.^{15,36,37} Indeed, S-LDH is considered a strong marker of resistance to radiotherapy in certain malignant tumors, including head and neck cancers.^{38,39}

Given that the literature has focused only on late-stage NPC, we sought to examine whether the prognostic factors may differ between early-stage and late-stage disease. We found that, among patients with stage III + IV NPC, S-LDH levels >225 U/L are an independent prognostic factor for 5-year overall survival and 5-year tumor-free survival, consistent with previous work.¹⁵ Among patients with stage I + II NPC, however, S-LDH levels lost their prognostic power. We attributed this result to two possibilities: our subgroup of stage I + II patients with S-LDH >225 U/L contained only 30 patients (5.0% of the entire cohort), suggesting a lack of statistical power; and/or the cutoff value of 225 U/L for defining high S-LDH may be inappropriate for early-stage patients, because this cutoff value was determined in healthy individuals and may not be appropriate for patients with NPC.¹⁴ Therefore, we chose the mean S-LDH level of early-stage patients as the cutoff value to define subgroups with low and high S-LDH levels, using the method mentioned in the study by Verstovsek et al.⁴⁰ Repeating the multivariate analysis using this cutoff of 171 U/L showed elevated S-LDH levels to be an independent prognostic factor for poor overall survival and tumor-free survival in early-stage NPC. Consistent with this result, we found that early-stage patients with S-LDH levels of 172–225 U/L had significantly shorter overall survival and tumor-free survival than did early-stage patients with S-LDH ≤171 U/L (data not shown).

The fact that redefining the cutoff value for S-LDH made such a difference in the multivariate analysis suggests that the widely used TNM staging system may be inadequate for evaluating tumor burden and disease progression in early-stage NPC. It also suggests that relatively high S-LDH levels that are still below the upper limit of normal (225 U/L in the present study) may be useful for predicting the prognosis of patients with early-stage disease.

Radiotherapy fails in 15%–30% of patients with early-stage NPC,¹⁸ for reasons that remain unclear. We report here that early-stage patients with S-LDH levels >171 U/L had poorer overall survival and tumor-free survival than did early-stage patients with S-LDH levels ≤171 U/L. Since higher S-LDH levels have been associated with tumor resistance to radiotherapy,^{38,39} we speculate that the relatively high treatment failure rate is due to radioresistance, and that elevated S-LDH contributes to this resistance. If this is true, then measuring S-LDH levels may help clinicians predict the effectiveness of radiotherapy for early-stage NPC

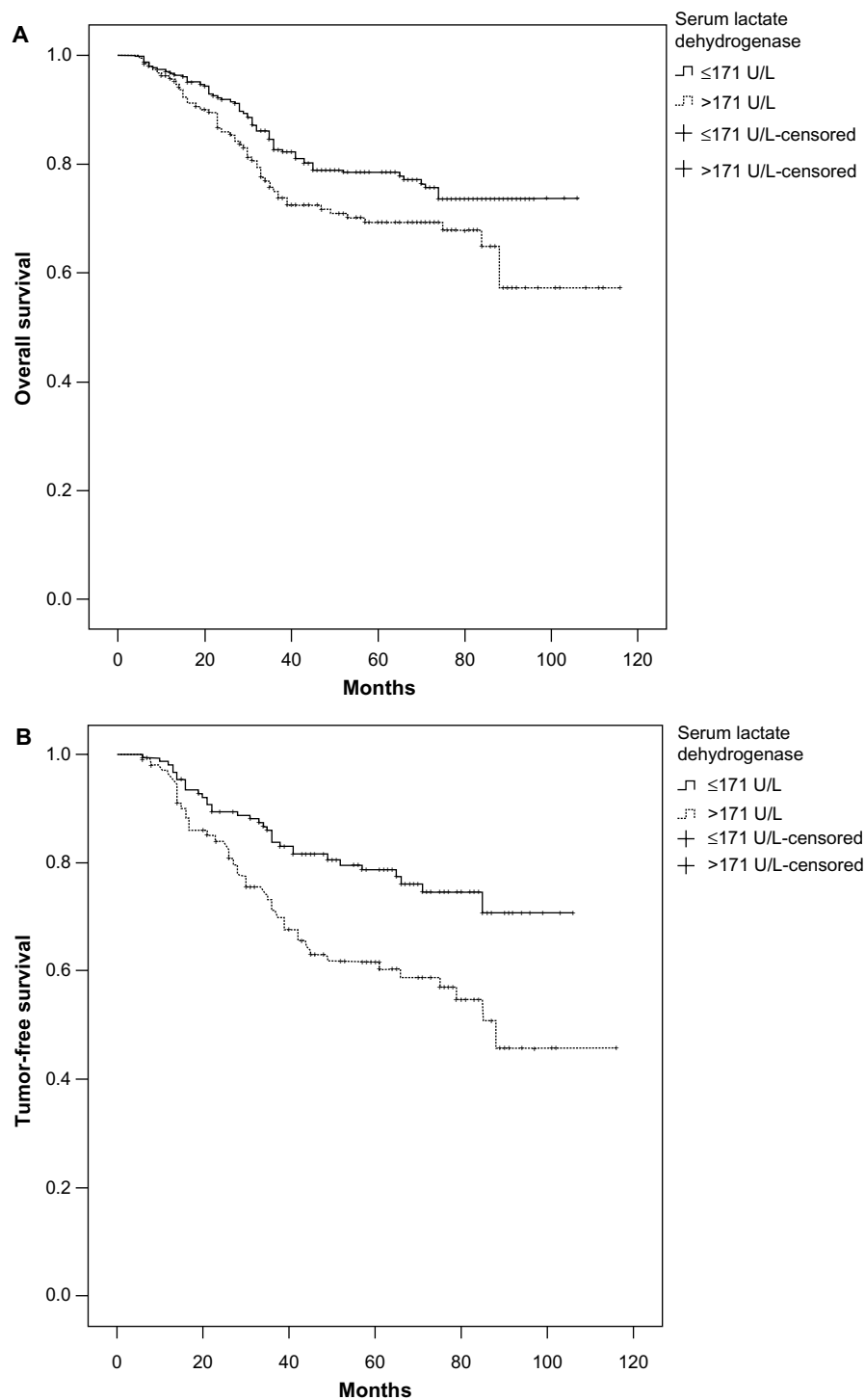


Figure 2 Survival analysis of 262 patients with stage I + II nasopharyngeal carcinoma stratified by pretreatment serum levels of lactate dehydrogenase (\leq or >171 U/L). **Notes:** (A) Overall survival ($P=0.005$). (B) Tumor-free survival ($P=0.002$).

patients and decide whether additional treatment modalities are appropriate.

Our data also show that levels of S-LDH in patients who were positive for EBV-specific antibodies (EBV-VCA-IgA, EBV-EA-IgA, EBV-EA-IgG), were not significantly different

from those of patients who were negative (Table 1). This result suggests that EBV status may not be significantly associated with the level of S-LDH in NPC. However, previous studies have indicated a positive correlation of circulating LDH with plasma EBV DNA in EBV-positive lymphomas, raising

the speculation that high EBV burden might contribute to elevated S-LDH in EBV-positive tumors including NPC.^{41,42} Indeed, it has been well documented that EBV plays a central role in the initiation and progression of NPC, and some EBV proteins, such as EBV latent membrane protein 1 and EBV nuclear antigen 1, could enhance the expression or induce the synthesis of hypoxia-inducible factor 1-alpha,^{43,44} which elevates LDH activity and might transcriptionally upregulate 5-LDH.^{15,39} In our study, the insignificant effect of EBV status on S-LDH may be attributed to the low proportion (44/601) of cases who had negative EBV-specific antibodies. Further investigations involving more such cases are needed to obtain exact information about the relationship between S-LDH and EBV burden in NPC.

It is noteworthy that chemotherapy may not have significant prognostic value predicting the outcome of NPC, as shown by the results of our univariate analysis, which are inconsistent with previous studies.⁴⁵⁻⁴⁷ This indicates that the chemotherapy regimens used in our study, which were similar to those in previous studies,^{45,48,49} could not significantly improve the overall survival and tumor-free survival of this tumor when compared with radiotherapy alone. Two factors may be associated with the insignificant prognostic value of chemotherapy in our study. First, a considerably high proportion (43.6%) of patients in our cohort had early-stage disease. These patients have been reported to have better locoregional control rates and fewer events of distant metastasis, and thus may obtain less benefit from chemotherapy.⁵⁰ The inclusion of patients with early-stage might weaken, at least in part, the contribution of chemotherapy in predicting overall survival and tumor-free survival in NPC.⁵⁰ Second, of the patients with late-stage NPC in our cohort, about 47% (159/339) had locally advanced staging (T3-4N0-1M0). Previous studies have suggested that chemotherapy could not significantly reduce the risk of death in patients with T3-4N0-1M0 NPC or the rate of local recurrence and distant metastasis in those with T3-4N0 M0 disease,^{51,52} suggesting that patients with T3-4N0-1M0 disease might also obtain less benefit from chemotherapy. Inclusion of patients with locally advanced-stage NPC might have reduced the beneficial effects of chemotherapy and thus weakened the effect of chemotherapy as a prognostic indicator for NPC in our study.

Conclusion

Elevated S-LDH levels before treatment are an independent prognostic factor for poor outcomes in NPC patients without distant metastasis, especially in the late stages of the disease.

In addition, S-LDH levels that are higher but still within normal range are significantly associated with a poor prognosis in early stages of the disease.

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Disclosure

The authors report no conflicts of interest in this work.

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