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Pretreatment Serum Lactate Dehydrogenase Level as an Independent Prognostic Factor of Nasopharyngeal Carcinoma in the Intensity-Modulated Radiation Therapy Era

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Background: The aims of this study were to analyze the prognostic value of baseline lactate dehydrogenase (LDH) among nasopharyngeal carcinoma (NPC) patients treated with intensity-modulated radiation therapy (IMRT), and to evaluate the potential application of LDH in monitoring treatment efficacy dynamically.

Material/Methods: From June 2005 to December 2010, 1188 patients with non-metastatic NPC who underwent IMRT with or without chemotherapy were reviewed. Univariate and multivariate analyses were performed to evaluate the predictive value of baseline LDH. Wilcoxon signed-rank test was used to analyze the difference between baseline and post-radiotherapy LDH, and to compare post-radiotherapy LDH with the LDH in cases of distant failure.

Results: Patients with elevated LDH had significant inferior survival rates, in terms of overall survival (70.0% *vs.* 83.2%, p=0.010), disease-specific survival (71.1% *vs.* 85.7%, p=0.002), and distant metastasis-free survival (71.1% *vs.* 83.4%, p=0.009), but not correlated with locoregional relapse-free survival (p=0.275) or progression-free survival (p=0.104). Subgroup analysis demonstrated that this predictive effect was more significant with advanced stage. Sixty-five post-radiotherapy LDH levels were available from the 90 patients with high LDH at initial diagnosis, and these levels fell in 65 patients, with 62 cases (95.4%) falling within the normal range. Of the 208 patients who experienced distant metastasis, 87 had an available LDH level at that time. Among them, 69 cases (79.3%) had an increased level compared with the post-radiotherapy LDH level.

Conclusions: Pretreatment LDH is a simple, cost-effective biomarker that could predict survival rates and might be used in individualized treatment. It is also a potential biomarker that might reflect tumor burden and be used to monitor therapy efficacy.

MeSH Keywords: Lactate Dehydrogenases • Nasopharyngeal Neoplasms • Prognosis • Radiotherapy, Intensity-Modulated • Treatment Outcome

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Background

Nasopharyngeal carcinoma (NPC) is a highly ethnic and regional malignant disease, predominantly occurring in southern China and Southeast Asia, with the incidence reported to be 25 to 50 per 100,000 people [1]. Radiotherapy is the only curative treatment modality for non-metastatic NPC, and the introduction of intensity-modulated radiation therapy (IMRT) has yield excellent locoregional control, as most studies reported that the 3-year locoregional control rate exceeded 90% [2–5]. Despite good locoregional control, 22–34% patients still experienced distant metastasis after treatment [2,5,6]. Distant metastasis has become the main cause of treatment failure. Therefore, estimating the prognosis accurately before treatment, especially the risk of distant metastasis, is crucial for the improvement of clinical management of NPC.

The current TNM staging system is insufficient for precisely predicting the prognosis of NPC, as patients in the same clinical stage often present with different treatment outcomes [7]. Increasing evidence has demonstrated that several significant biomarkers could be used in predicting the survival of NPC patients, such as Epstein-Barr virus DNA, Epstein-Barr virus microRNA, stanniocalcin 2, cyclooxygenase-2, epidermal growth factor receptor [8–11], and so on. However, none of them is detected in routine clinical exams, and testing for them will give rise to additional costs. There are still other problems, such as poor repeatability (i.e., Epstein-Barr virus DNA) and being time-consuming. Thus, it would make great sense if routine laboratory items could be used as indicators for predicting survival.

Lactate dehydrogenase (LDH) is an enzyme routinely detected in the pretreatment workup, and it has been identified as a prognostic factor in several malignancies, including renal cell, melanoma, gastric, prostate, breast, and lung cancers, as well as NPC [12–25]. For patients with NPC, conventional radiotherapy (CRT) and/or three-dimensional conformal radiotherapy (3D-CRT) were found to be the most commonly used radiation modalities, with only three reports based on IMRT, all derived from Sun Yat-sen University Cancer Center [23–25]. Besides, none of these reports analyzed the dynamic changes of LDH and its relationship with treatment efficacy. New research from other endemic areas is urgently needed to reduce the selection bias and reporting bias to make LDH a more reliable biomarker in predicting the prognosis of NPC in the IMRT era.

In this retrospective study, a total of 1188 patients with non-metastatic NPC and an available baseline LDH level were included. The aim was to investigate the prognostic significance of LDH in NPC patients treated with IMRT in the endemic area. Moreover, the preliminary analysis was performed to evaluate the potential value of LDH changes in the judgment of treatment efficacy.

Material and Methods

Ethical statement

This study was approved by the institutional ethical committee of Fujian Provincial Cancer Hospital. Although patients' consents were not specifically obtained for this analysis, all information was retrospectively extracted in the context of compliance with the relevant regulations and protection of patients' privacy.

Patients' characteristics

We studied a consecutive cohort of 1188 patients diagnosed with NPC at our institution between June 2005 and December 2010. The inclusion criteria consisted of (1) histologically confirmed NPC; (2) radiologically no distant metastases; (3) magnetic resonance imaging (MRI) of the nasopharynx and the neck; (4) complete baseline blood biochemical records including LDH; and (5) treatment with IMRT. Those who had preexisting complications, such as concomitant malignant disease, active hepatobiliary and pancreatic disease, and congestive heart failure NYHA III–IV, were excluded. The median age was 46 years (range: 11 to 84 years). According to the histopathological criteria for NPC of the World Health Organization, most of the cases were defined as type III (1126, 94.8%), while there were a few type I (12, 1.0%) and type II (50, 4.2%) cases. Patients were re-staged according to the 7th American Joint Committee on Cancer (AJCC) staging system [26] and completed a pretreatment evaluation according to our institutional protocol [27]. Other clinical characteristics were listed in Table 1.

Measurement of LDH

Fasting blood samples for evaluation of serum LDH were obtained from each patient by a venous puncture to the median cubital vein using sterile needles and tubes, as a routine examination before treatment. Serum LDH was detected by an enzyme kinetics kit (produced by Roche Diagnostics, Germany), using a Modular PP model automated analyzer. The manufacturer-specified normal value was in the range of 80–190 IU/L.

Treatment

All patients underwent definitive radiotherapy, and specific assignments of the IMRT have been published previously [27]. Among the 1132 patients with stage II–IVb NPC, 1015 (89.6%) patients received platinum-based chemotherapy. To be more specific, 503 (44.4%) patients received concurrent chemotherapy with or without other types of chemotherapy, while 512 (45.2%) patients underwent neoadjuvant and/or adjuvant chemotherapy. The median chemotherapy cycle was three (range from zero to seven).

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Table 1. Association between baseline LDH level and clinicopathological parameters.

Parameters	Serum LDH level (IU/L)						
	N (%)		≤190 (%) (N=1098)		>190 (%) (N=90)		p-value
Age(y)							
≤50	752	(63.3)	696	(92.6)	56	(7.4)	0.825
>50	436	(36.7)	402	(92.2)	34	(7.8)	
Gender							
Male	897	(75.5)	828	(92.3)	69	(7.7)	0.790
Female	291	(24.5)	270	(92.8)	21	(7.2)	
Chemotherapy cycles							
<3	447	(37.4)	422	(94.4)	25	(5.6)	0.045
≥3	741	(62.6)	676	(91.2)	65	(8.8)	
T category							
T1	290	(24.4)	270	(93.1)	20	(6.9)	0.673
T2	223	(18.8)	208	(93.3)	15	(6.7)	
T3	441	(37.1)	408	(92.5)	33	(7.5)	
T4	234	(19.7)	212	(90.6)	22	(9.4)	
N category							
N0	169	(14.2)	162	(95.9)	7	(4.1)	<0.001
N1	669	(56.3)	633	(94.6)	36	(5.4)	
N2	289	(24.3)	256	(88.6)	33	(11.4)	
N3	61	(5.2)	47	(77.0)	14	(23.0)	
Clinical stage							
I	56	(4.7)	54	(96.4)	2	(3.6)	0.004
II	299	(25.2)	288	(96.3)	11	(3.7)	
III	427	(35.9)	394	(92.3)	33	(7.7)	
IVA-B	406	(34.2)	362	(89.2)	44	(10.8)	

LDH – lactate dehydrogenase; T – tumor; N – node.

Follow-up and statistical analyses

Evaluation of treatment response and adverse reactions of patients was done weekly. Within the first two years after radiotherapy, follow-up was required every 3 months, and then every 3–6 months until the end of the study. Data were analyzed using SPSS version 19.0. The overall survival (OS), disease-specific survival (DSS), distant metastasis-free survival (DMFS), locoregional relapse-free survival (LRRFS), and progression-free survival (PFS) rates were defined as the date from the first diagnosis to death from any cause, death due to NPC, appearance of distant failure, locoregional failure, and disease progression, respectively. The chi-square test was used to compare categorical variables. Survivals were calculated using the Kaplan-Meier method, and the differences were compared by the log-rank test. Multivariate analysis was performed with Cox regression models to test independent significance of various potential prognostic factors. Wilcoxon signed-rank test was used to analyze the difference between baseline and post-radiotherapy LDH, and to compare post-radiotherapy LDH and those when distant failure occurred. LDH levels were grouped by the upper limit of normal value (ULN) as a cutoff. A two-sided p-value of ≤0.05 was deemed statistically significant.

Results

Serum LDH levels and patients' characteristics

The mean serum LDH level was 147.15 IU/L (range 71–586 IU/L). As detailed in Table 1, serum LDH level increased with advanced N category (p<0.001) and clinical stage (p=0.004).

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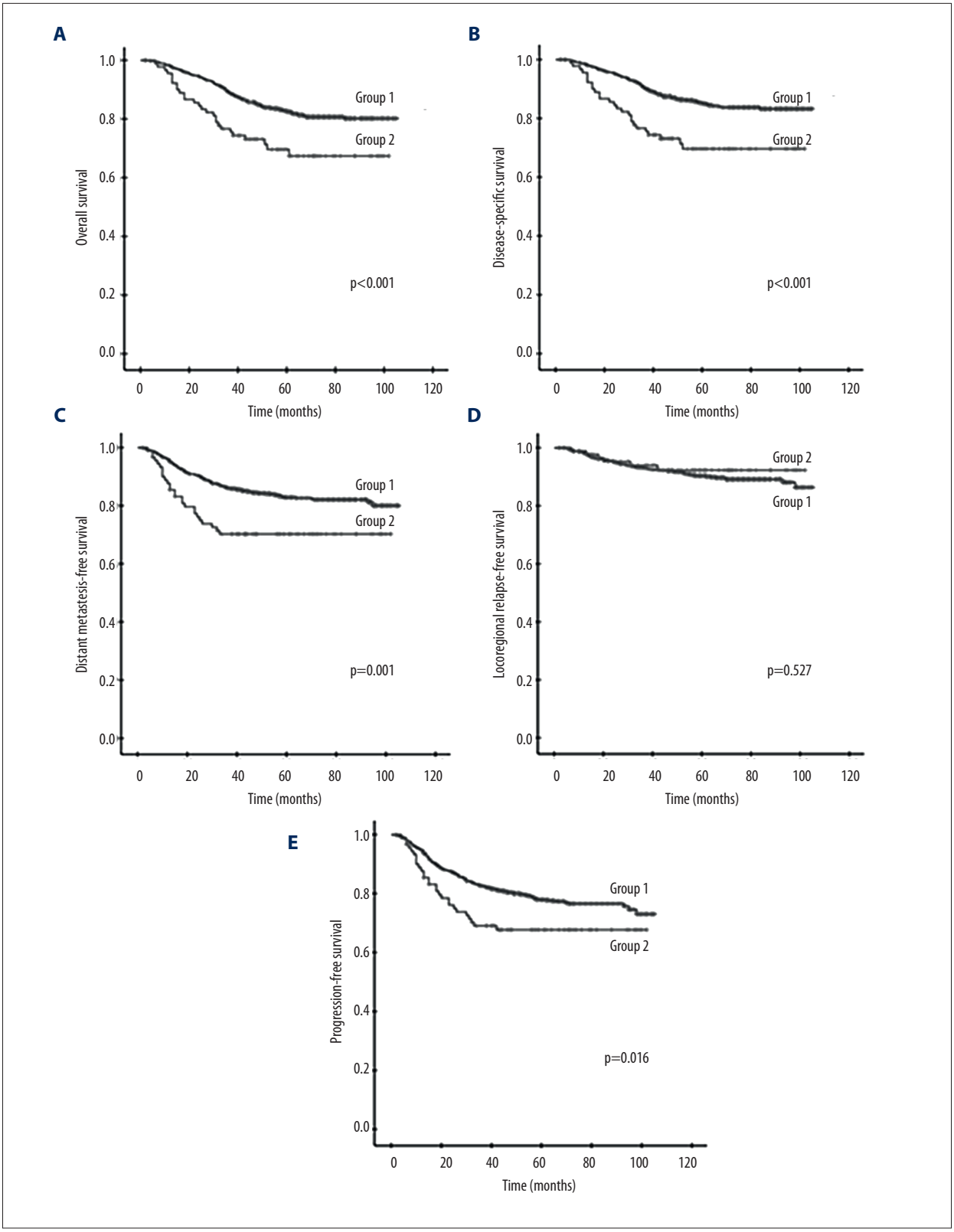

Figure 1. Kaplan-Meier survival curves to compare the overall survival rates (**A**), disease-specific survival rates (**B**), distant metastasis-free survival rates (**C**), locoregional relapse-free survival rates (**D**), and progression-free survival rates (**E**) for patients grouped by pretreatment lactate dehydrogenase (LDH) level. Group 1: 71–190 IU/L; group 2: 191–586 IU/L.

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Table 2. Multivariate analysis of prognostic factors for the whole cohort.

Endpoint	Variable	B	p	Exp(B)	95%CI for exp(B)
Death	Age	0.970	<0.001	2.639	2.006–3.473
	Clinical stage	0.627	<0.001	1.872	1.559–2.248
	LDH	0.535	0.010	1.708	1.138–2.564
Disease related death	Age	0.808	<0.001	2.243	1.677–3.000
	Clinical stage	0.690	<0.001	1.995	1.633–2.436
	LDH	0.652	0.002	1.920	1.265–2.914
Distant failure	Age	0.320	0.023	1.377	1.045–1.815
	Clinical stage	0.547	<0.001	1.727	1.440–2.072
	LDH	0.551	0.009	1.736	1.149–2.623
Locoregional failure	Clinical stage	0.730	<0.001	2.074	1.599–2.692
Disease progression	Age	0.339	0.006	1.403	1.100–1.790
	Clinical stage	0.615	<0.001	1.851	1.576–2.173

CI – confidence interval; other abbreviations as in Table 1.

Besides, patients with high LDH were detected to undertake more chemotherapy cycles, and this might be due to the higher proportion of advanced cases in the high LDH group. However, LDH level failed to be significantly associated with age, gender, or T category (Table 1).

Survival and prognostic analysis

The median follow-up time for the whole cohort was 57 months (range 2–105 months), with the 5-year OS, DSS, DMFS, LRRFS, and PFS demonstrated to be 82.2%, 84.6%, 82.5%, 90.8%, and 77.5%, respectively. Univariate analysis showed that patients with an increased LDH level had significantly worse treatment outcomes, in terms of OS (70.0% *vs.* 83.2%, p<0.001), DSS (71.1% *vs.* 85.7%, p<0.001), DMFS (71.1% *vs.* 83.4%, p=0.001), and PFS (68.9% *vs.* 78.2%, p=0.016), while there was no significant difference in LRRFS (p=0.527) between different LDH statuses (Figure 1).

In the multivariate analysis, serum LDH level and other potential prognostic factors, including gender, age, chemotherapy cycles, and clinical stage, were taken into account by the Cox's proportional hazards regression. Data in Table 2 demonstrate that LDH level was an independent prognostic factor for OS (p=0.010), DSS (p=0.002), and DMFS (p=0.009), but was not significantly correlated with LRRFS (p=0.275) or PFS (p=0.104). Besides LDH, as detailed in Table 2, clinical stage was associated with all the endpoints we focused on, and age was correlated with OS, DSS, DMFS, and PFS, rather than LRRFS. However, neither gender nor chemotherapy cycles showed any significant association with the endpoints.

Subgroup analyses

Further analysis was done to separately evaluate the role of LDH among patients with early (stage I/II) and advanced stage (stage III-IVb) NPC. Multivariate statistical results suggested that LDH level remained an independent prognostic factor for OS (p=0.009), DSS (p=0.004), and DMFS (p=0.004) (Table 3) in the advanced stage. However, in the early stage, LDH lost its predictive role for OS (p=0.425), DSS (p=0.272), and DMFS (p=0.750).

Comparison of LDH levels between pretreatment and post-treatment

In order to explore whether LDH level was associated with tumor burden, post-treatment LDH level was determined in patients with elevated pretreatment LDH. Sixty-five out of the 90 patients (72.2%) were available for post-treatment LDH data, and our analysis demonstrated that LDH level decreased significantly after radiotherapy in all patients (Figure 2A, p<0.001). Of note, all post-treatment LDH levels decreased within the ULN except in the case of three individuals. After reviewing the medical records, we found that one patient had regional persistent disease at the end of the radiotherapy, which might raise the LDH level. However, the reason for the other two cases remained unknown, while the trend was still falling.

Post-treatment and subsequent metastatic LDH change

At the end of the follow-up, subsequent distant metastasis occurred in 208 patients. Further analysis of LDH level was performed among those with available post-treatment LDH (a total

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Table 3. Multivariate analysis of prognostic factors for patients with stage III–IV.

Endpoint	Variable	B	p	Exp(B)	95%CI for exp(B)
Death	Age	1.029	<0.001	2.798	2.060–3.801
	Clinical stage	0.606	<0.001	1.832	1.363–2.464
	LDH	0.562	0.009	1.754	1.148–2.679
Disease related death	Age	0.920	<0.001	2.510	1.834–3.436
	Clinical stage	0.622	<0.001	1.863	1.363–2.545
	LDH	0.639	0.004	1.894	1.226–2.927
Distant failure	Age	0.432	0.005	1.540	1.142–2.076
	Clinical stage	0.420	0.006	1.522	1.127–2.055
	LDH	0.615	0.004	1.849	1.210–2.826

Abbreviation as in Table 2.

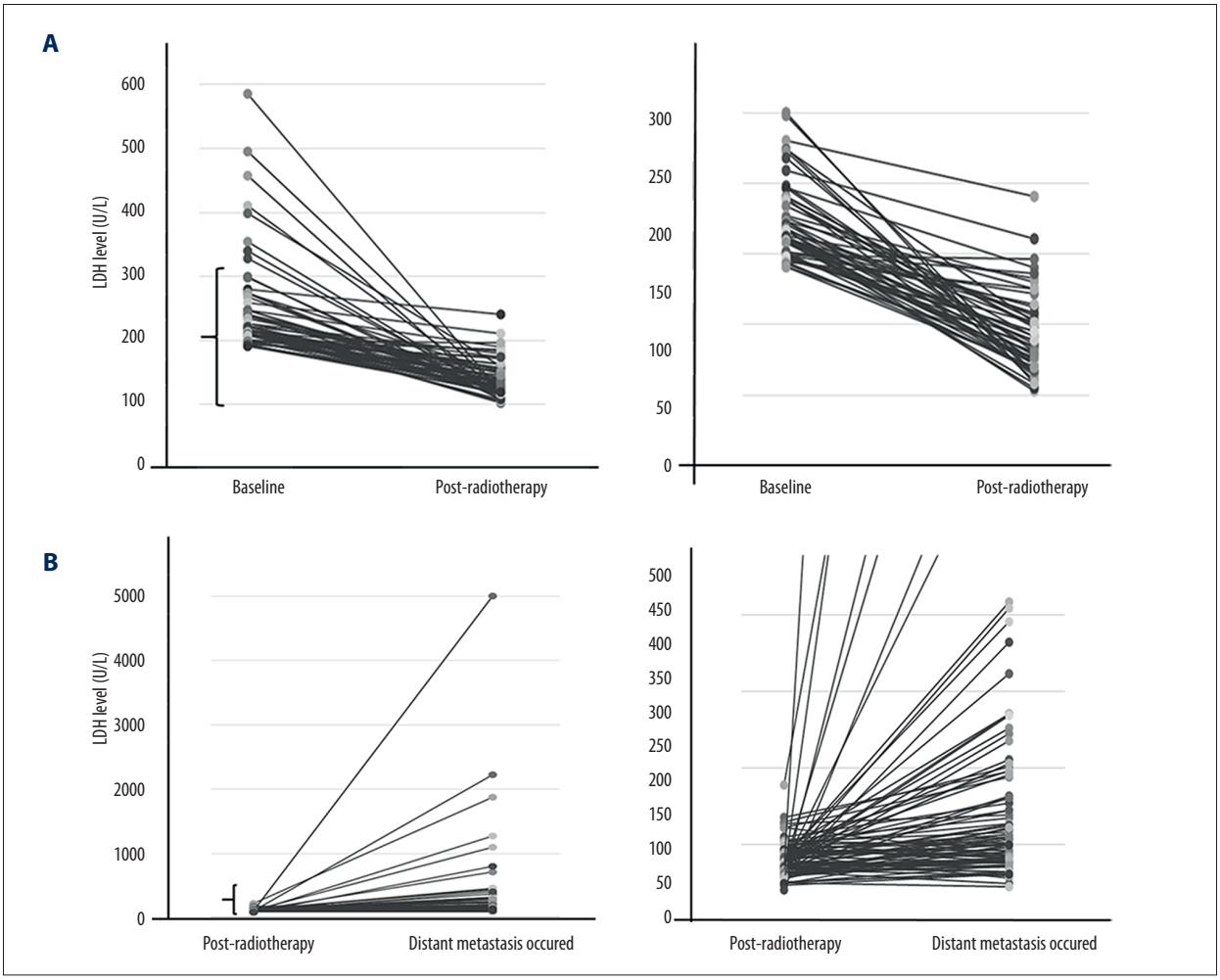

Figure 2. Comparison of baseline and post-radiotherapy lactate dehydrogenase (LDH) levels (**A**) and comparison of post-radiotherapy LDH levels and those in cases when distant metastasis occurred (**B**) were estimated as described above. The Wilcoxon signed-rank test was used to compare the differences (**A**: p<0.001; **B**: p<0.001). Each line represents one individual patient. Right-hand panels highlight the LDH level for cases with less than 300 IU/L (**A**) and 500 IU/L (**B**).

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of 87 patients). When compared with the post-treatment LDH level, the LDH level in 69 of those patients was raised, and the Wilcoxon signed-rank test showed statistical significance between these two groups (p<0.001) (Figure 2B). However, there were still 18 cases that failed to show the upward trend, with 13 of them decreasing less than 10 IU/L. Careful examination of the clinical reports revealed that three of the remaining five patients suffered from mild liver damage and one had regional persistent disease at the end of the radiotherapy, which might cause higher post-treatment LDH that would conceal the lifting tendency. Nevertheless, the cause for the falling trend of another case remained unclear.

Discussion

With the progress of NPC management, the predictor of prognosis has been brought into focus. Identification and distinction of patients with high risk of metastasis may contribute to perfecting the TNM stage and optimizing the therapy strategy. The current research found that pretherapeutic serum LDH level could be considered as a useful indicator to predict NPC survival in the IMRT era, especially in the advanced stage. High LDH level was significantly associated with OS, DSS, and DMFS, but not LRRFS or PFS. Moreover, further following up of the LDH level revealed that it fell after radiotherapy among all patients who possessed high pretreatment LDH. When subsequent metastasis occurred, the LDH level tended to become elevated compared with the post-treatment level. Our study is of particular importance in that we further confirmed the prognostic value of LDH among NPC patients receiving the new radiotherapy method in the endemic area, especially in cases of distant failure. Another interesting finding was that LDH might reflect the tumor burden and be of possible application in monitoring treatment efficacy, which sheds new light in the design of future trials.

Several papers in the literature have evaluated the prognostic significance of LDH in non-metastatic NPC patients. Early in 1993, a Japanese study by Chatani and his colleagues [15] first analyzed a consecutive cohort of 89 non-metastatic NPC patients. A proportion of patients (25.8%, 23/89) presented a high LDH level, and their results showed that LDH level could significantly influence 5-year survival in terms of OS (26% *vs.* 63%, p=0.0008), RRFS (p=0.0002), and DMFS (p=0.006). Another study by Turkish investigators also reported the relationship between LDH and OS in 61 patients with stage III-IV NPC (AJCC 1997 staging system). Among them, 24.6% (15/61) were detected to have an elevated LDH level (>460 IU/L), and as a result, LDH level was found to correlate with poor 4-year OS (28.5% *vs.* 68.7%, p=0.01) [16]. Because of the small number of samples and the fact that both Turkey and Japan were non-endemic areas, the conclusion was not so informative for the endemic areas. The earliest study from endemic areas was performed in Taiwan in 1997, in which 118 cases with stage IV NPC (International Union for Cancer Control [UICC] stage) were analyzed to evaluate the predictive role of LDH. It was found that patients with abnormal LDH status of more than 140 IU/L (44.1%, 52/118) had significantly shorter median OS time (10 *vs.* 53 months, p=0.008) [17]. The significant relationship between LDH and prognosis was confirmed by another two institutions from Taiwan [18,19]. More recently, Wan et al. [20] from Sun Yat-Sen Cancer Center concluded that patients with a high LDH level had worse 5-year OS (56.9% *vs.* 76.8%, p=0.004), DFS (45.4% *vs.* 64.7%, p=0.001), LRFS (76.1% *vs.* 89.6%, p=0.019), and DMFS (54.3% *vs.* 72.2%, p=0.001). In their study, 400 patients with stage III–IVa (1992 NPC staging system of China) were enrolled, with 8.25% cases (33/400) showing abnormal LDH (>245 IU/L). Li et al. [21] from the same institution also indicated the prognostic value of LDH in 533 patients with a positive rate of LDH (>240 IU/L) as 8.3% (44/533), but only 5-year OS was found to be significant (75% *vs.* 57%, p=0.033). Researchers from Guangxi, another endemic area in China, also very recently published their results based on 601 non-metastatic NPC patients, in which significantly lower OS (p=0.002) and tumor-free survival (TFS) (p=0.014) were found in patients who presented with an LDH level higher than 225 IU/L (18.8%, 114/601) [22].

All studies described above were based on CRT and/or 3D-CRT, except that reported by Li et al. [21] in which only 3.2% of patients underwent IMRT. The only three studies that referred to IMRT were all from Sun Yat-sen University Cancer Center and confirmed the prognostic value of LDH in NPC [23–25]. Zhou et4al. [23] first analyzed 465 non-metastatic NPC cases treated by IMRT in 2012. The study involved 6.67% of patients (31/465) with high LDH (>245 IU/L) and demonstrated that high LDH was an unfavorable prognostic factor for OS, DFS, and DMFS (p<0.001, 0.004, and 0.003, respectively), rather than LRFS. These results were confirmed in their two subsequent reports, in which LDH was used as a significant parameter in their prediction-score system established for DMFS (p=0.002) [24], but not for LRRFS in the other study [25]. The present series, which included the largest cohort of NPC patients so far, also indicated worse treatment outcomes among patients with a high LDH level, in terms of OS, DSS, and DMFS, which was consistent with other reports in the literature [15–24]. As for local and regional control, LDH level failed to show any significance. This was consistent with those two IMRT studies [23,25] and some other reports based on non-IMRT technique [18,19,21]. However, two of the studies mentioned above showed a significant relationship between LDH status and local and/or regional control [15,20]. The superior locoregional control of IMRT was considered as one of the most important reasons that the influence of LDH on LRRFS might be concealed.

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Another interesting point of the current study was that the post-treatment LDH level decreased in all patients with elevated baseline LDH, and the LDH level increased when subsequent distant metastasis occurred. This suggests that LDH may be used as a biomarker to monitor the treatment efficacy dynamically and to detect distant micrometastasis before radiographic changes or clinical symptoms are presented. Furthermore, LDH was also found to be positively correlated with tumor burden, as the positive rate of LDH increased with more advanced N category and clinical stage (Table 1). Another supportive fact was that among the majority of studies with a larger percentage of advanced patients (stage III–IV) or those that only focused on advanced patients, the positive rate of LDH was apparently higher than that in our study (18.8–44.1% *vs.* 7.6%) [15–17,22], except in only one reported by Wan et al. [20].

The reasons for LDH being involved in the prognosis of cancer have not been clearly demonstrated. It is generally considered that LDH level may reflect the extent of hypoxia, since it catalyzes the transformation of pyruvate to lactate in hypoxic conditions. With a large amount of lactate produced, upregulation of the LDH level ensures the efficiency of the activity [12,23]. However, further physiologic and biochemical studies will have been requested to clarify the specific mechanism.

Several limitations of our study have to be described here. First of all, since it was a retrospective design, further prospective randomized control clinical trials should be conducted. Secondly, all patients were from the same medical center, and the single-center samples might increase the risk of selection bias. Finally, owing to the long study period and lack of therapeutic guidelines at that time, chemotherapy was not strictly standard. Further well-designed prospective studies with multicenter collaboration are warranted.

Conclusions

NPC patients who possessed high pretreatment serum LDH had significant worse treatment outcomes, especially those with advanced stage disease. Additionally, serum LDH was found to be significantly correlated with tumor burden among NPC patients, and dynamic tracing of LDH might be able to monitor therapy efficacy. Thus, it should be considered when determining the TMN stage, treatment, and post-treatment strategies, to provide support for individualized therapy. However, our study cannot be considered definitive, and more reports on the role of LDH in NPC prognosis are urgently needed from prospective clinical trials.

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