Original Research Article

Pretreatment Serum Lactate Dehydrogenase and Metastases Numbers as Potential Determinants of Anti-PD-1 Therapy Outcome in Nasopharyngeal Carcinoma

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Wael A. S. Ali, MD, PhD[1], Xinxin Huang, MD[2], Yuehan Wu, MD[3], Yuxiang Ma, MD, PhD[1], Hui Pan, MD, PhD[1], Jun Liao, MD[1], Zhang Yang, MD[3], Shaodong Hong, MD, PhD[1], Yunpeng Yang, MD, PhD[1], Yan Huang, MD, PhD[1], Yuanyuan Zhao, MD, PhD[1], Wenfeng Fang, MD, PhD[1], Hongyun Zhao, MD, PhD[3], and Li Zhang, MD, PhD[1]

Abstract

Background: We aimed to investigate the determinant factors of anti-PD-1 therapy outcome in nasopharyngeal carcinoma (NPC).

Methods: In this retrospective study, we included 64 patients with recurrent/metastatic NPC. The association of patients' characteristics, C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), and lactate dehydrogenase (LDH) with survival benefit of anti-PD-1 therapy were analyzed using Cox regression models and Kaplan-Meier analyses. Patients were divided based on the median value of CRP, NLR or LDH into different subgroups.

Results: At a median follow-up time of 11.4 months (range: 1-28 months), median progression-free survival (PFS) and overall survival (OS) were 1.9 months (95% CI, .18-3.6) and 15 months (95% CI, 10.9-19.1) months, respectively. Pretreatment metastases numbers was significant predictor of PFS (HR = 1.99; 95% CI 1.10-3.63; $P = .024$) and OS (HR = 2.77; 95% CI 1.36-5.61; $P = .005$). Baseline LDH level was independent predictor of OS (HR = 7.01; 95% CI 3.09-15.88; $P < .001$). Patients with LDH level >435 U/L at the baseline had significantly shorter PFS and OS compared to patients with LDH level ≤435 U/L (median PFS: 1.7 vs 3.5 months, $P = .040$; median OS: 3.7 vs 18.5 months, $P < .001$). Patients with non-durable clinical benefit (NDB) had significantly higher LDH level at the baseline compared to patients who achieved durable clinical benefit (DCB) ($P = .025$). Post-treatment levels of CRP, LDH, and NLR were decreased compared to baseline in patients with DCB ($P = .030$, $P = .088$, and $P = .066$, respectively), whereas, there was a significant increase in post-treatment level of LDH compared with baseline in patients with NDB ($P = .024$).

Conclusions: LDH level at the baseline was an independent predictor of OS and pretreatment metastases numbers was a significant predictor of PFS and OS.

[1]Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China
[2]Department of Endoscopy, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China
[3]Department of Clinical Research, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Corresponding Author:
Wael A. S. Ali, MD, Sun Yat-sen University Cancer Center, Department of Medical Oncology, 651 Dongfeng Road East, Guangzhou 510060, China.
Email: wael_alhammadi@hotmail.com

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Introduction

Nasopharyngeal carcinoma (NPC) is a commonly found malignancy of the head and neck characterized by distinctive geographic and racial distribution.[1] Currently, the treatment of patients with NPC is mainly dependent on radio- and chemotherapy.[2,3] The association of NPC with Epstein Bar Virus and high density of tumor infiltrated lymphocyte marks it an attractive target for immunotherapy.[4-7] In addition, recent advances in immune checkpoint inhibitors (ICIs) therapy across different cancer types generated interest in investigating anti-PD-1/PD-L1 in NPC.

Several phase I-II trials have demonstrated a promising clinical efficacy of anti-PD-1 therapy in pretreated NPC patients with advanced-stage.[8,9] Two single-arm phase II clinical trials evaluated the efficacy of nivolumab and pembrolizumab in pretreated patients with recurrent/metastatic NPC and demonstrated an objective response rate of 20.5% and 25.9%, respectively.[10,11] However, in recent phase II clinical trial, spartalizumab, a PD-1inhibitor did not improve PFS compared with chemotherapy.[12] In addition, in KEYNOTE-122 clinical trial, pembrolizumab did not improve OS compared with standard chemotherapy. These results have motivated investigations for predictive biomarkers that may help to increase the efficacy of ICIs in NPC.

Several biomarkers have been investigated for immunotherapy outcome including expression of PD-L1 and tumor mutation burden (TMB), both may reflect a preexisting immune reaction that can be modulated by immunotherapy.[13,14] Although, the expression of PD-L1 in NPC was found to be high, especially in Epstein-Barre Virus (EBV) related carcinoma, its predictive value was not established.[11,15] In addition, the role of TMB as a predictive biomarker of ICIs in NPC remain unclear.[11,16] Therefore, predictive biomarkers for immunotherapy outcome in NPC still urgently needed.

Peripheral blood-based inflammatory and metabolite markers such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and lactate dehydrogenase (LDH) have shown prognostic value in patients treated with ICIs therapy.[17-19] In melanoma and non-small cell lung cancer patients treated with anti-PD-1, baseline LDH level was identified as an independent prognostic factor for treatment outcome.[20,21] However, the association between these biomarkers and anti-PD-1 treatment outcome in patients with NPC is still not clear. Here, we aimed to evaluate the association of NLR, CRP, and LDH with treatment outcome in NPC patient treated with anti-PD-1 therapy.

Methods

Patients

The present study was conducted according to the declaration of Helsinki and was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (approval number: B2021-445-01). This retrospective study included patients with advanced/metastatic NPC who received anti-PD-1 therapy in 2 controlled clinical trials at Sun Yat-sen University Cancer Center between January 2016 and November 2017.[10,22] Patient recruitment was based on predefined inclusion criteria: age more than 18 years; confirmed diagnosis of NPC with histology or cytology; metastatic or recurrence NPC; Eastern Cooperative Oncology Group performance (ECOG) of 0 or 1; disease progressed on standard chemotherapy. All patients' details are de-identified. The authors have completed the STROBE reporting checklist.[23]

Data Collection

Peripheral blood samples were obtained in all patients before starting treatment (within 1 week) and before every subsequent treatment cycle for complete blood tests. NLR was calculated as the absolute count of neutrophil divided by lymphocyte count. Baseline and 6-8 weeks post-treatment neutrophil, lymphocyte, LDH, CRP were obtained from patients' medical records. Patients baseline characteristics including gender, age, smoking history, performance status, metastases number, and weather patients received anti-PD-1 therapy as the second line or later were also collected.

Treatment and Response Assessment

Patients had received either camrelizumab monotherapy at an escalating dose of 1 mg/kg, 3 mg/kg, 10 mg/kg, and a bridging dose of 200 mg per 2 weeks, or nivolumab monotherapy of 3 mg/kg or 240 mg and 360 mg once every 2 and 3 weeks. Patients were followed up through visits to doctors' offices or via telephone calls. Evaluation of treatment response was assessed by radiological imaging according to RECIST criteria (version 1.1) and indicated as complete remission (CR), stable disease (SD), partial response (PR), or progressive disease (PD). Durable clinical benefit (DCB) was defined as PFS more than 6 months after the initial response, and non-durable clinical benefit (NDB) was considered if a patient had less than 6 months of PFS.

Statistical Analysis

Normally distributed numeric variables are indicated by the mean ± SD, categorical variables are indicated as percentages (%). Simple t-test or chi-square/fisher's exact test was applied for comparison of normally distributed numerical variables or categorical variables, respectively. Non-parametric test was used for comparison of non-normally distributed variables. Estimation of PFS and OS was extracted by the Kaplan-Meier analysis, and the differences were examined by a log-rank test. Patients with missing data of survival at the time of last follow up were considered as censored cases. Cox regression model were used to analyses the association of baseline variables with PFS and OS. Patient' gender, age, smoking history, ECOG, pretreatment metastases number, line of immunotherapy, LDH, CRP, and NLR were included in the multivariable regression model. A two-sided P-value < .05 were considered significant. All analysis was conducted by SPSS version 20 (IBM SPSS Statistics, RRID:SCR_019096) and GraphPad software version 8 (GraphPad Prism, RRID: SCR_002798) was used to draw figures.

Results

Patients Characteristics

Patients' baseline characteristics are shown in Table 1. Our analysis included 64 constitutively collected patients who received ICIs therapy in controlled clinical trials. Fifty-one (79.7%) patients were male, 19 (29.7%) patients have smoking history and 23 (35.9%) patients with ECOG performance status of (0). Forty-seven patients (73.4%) had received ICIs therapy after failure of the second line therapy and 17 (26.6%) patients had more than 2 metastases site at the time of ICIs therapy initiation. Forty-two patients (65.6%) had received camrelizumab, 18 (28.1%) of patients received nivolumab, and 4 patients were treated with ipilimumab.

Table 1. Patients Baseline Characteristics.

Variables	Patients No (64)	%
Gender		
Male	51	79.7
Age (mean)	46.70 ± 11.40	
Smoking		
Yes	19	29.7
No	45	70.3
ECOG		
0	23	35.9
1	41	64.1
Line of immunotherapy		
≤2nd	17	26.6
>2nd	47	73.4
Pretreatment metastases		
≤2	47	73.4
>2	17	26.6
Immunotherapy agent*		
Nivolumab	18	28.1
Camrelizumab	42	65.6
Best overall response rate		
SD	16	25.0
PR	15	23.4
PD	33	51.6
Clinical benefit		
DCB	20	31.3
NDB	44	68.8

ECOG, eastern cooperative oncology group performance status; SD, stable disease; PR, partial response; PD, progressed disease; DCB, durable clinical benefit; NDB, non-durable clinical benefit; *4 patients treated with Ipilimumab.

Treatment Response

Overall, 16 (25%) patients had SD, 15 (23.4%) patients had partial response, and 33 (51.6%) patients with PD. Patients with PD had a significantly higher LDH level at the baseline compared with patients with PR or SD as shown in Figure 1A (P = .021, mean value: 598.24 ± 834.34 U/L, 243.47 ± 104.90 U/L, 279.06 ± 144.98 U/L, respectively). Furthermore, in patients with NDB, LDH level at the baseline was significantly higher than in patients who achieved DCB (P = .025, mean value 513.22 ± 736.31 U/L vs 263.97 ± 144.14 U/L) as shown in Figure 2A. However, there were no significant difference in baseline NLR or CRP based on treatment response or clinical benefit (all P > .05), (Figures 1 and 2B and C). There was a significant decrease in post-treatment CRP levels in patients who achieved DCB (P = .030). Similarly, these patients also showed decrease in LDH level and NLR compared with baseline (P = .088 and P = .066, respectively), whereas patients with NDB had a significant increase in LDH (P = .024). However, there were no significant change in post treatment CRP or NLR compared with baseline in patients with NDB (Figures 3 and 4).

PFS

During the median follow-up time of 11.4 months (range: 1–28), median PFS was 1.9 months (95% CI, .18-3.6). Fifty-seven (89%) patient had progressed disease during the follow up. Patients were classified based on the mean values of baseline CRP (35 mg/L), LDH (435 U/L), and NLR.[5] PFS was significantly longer in patients with low LDH (≤435 U/L) (3.5 months; 95% CI, 1.7-5.3) compared to those with high LDH levels (>435 U/L) (1.7 months; 95% CI, 1.2-2.1; P = .040). However, there were no significant difference in PFS in case of CRP or NLR (all P > .05) (Figure 5). In univariable Cox regression analysis of PFS predictors that included patient' gender, age, smoking history, ECOG, pretreatment metastases number, line of immunotherapy, LDH, CRP, and NLR. LDH (HR = 2.06;

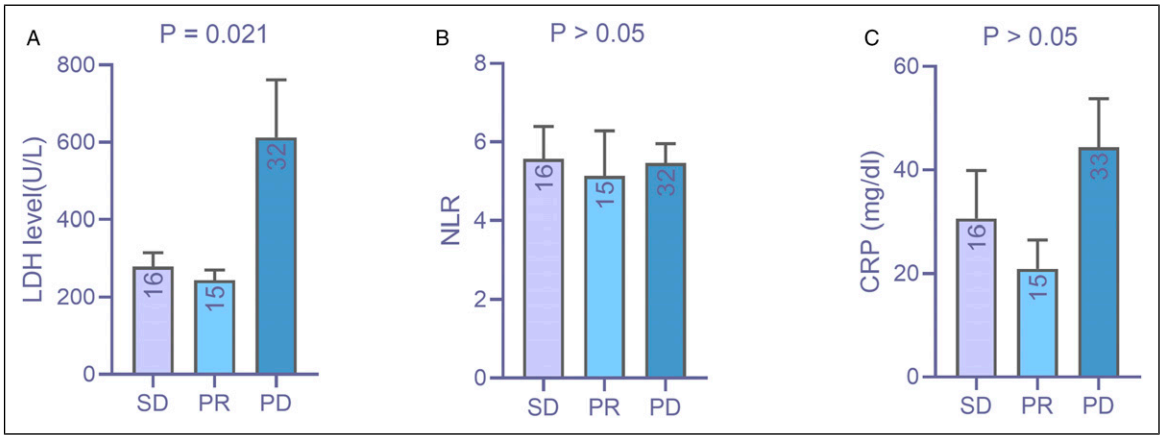

Figure 1. Baseline LDH, CRP, NLR levels and treatment response. Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; SD, stable disease; PR, partial response; PD, progressed disease; DCB, durable clinical benefit; NDB, non-durable clinical benefit.

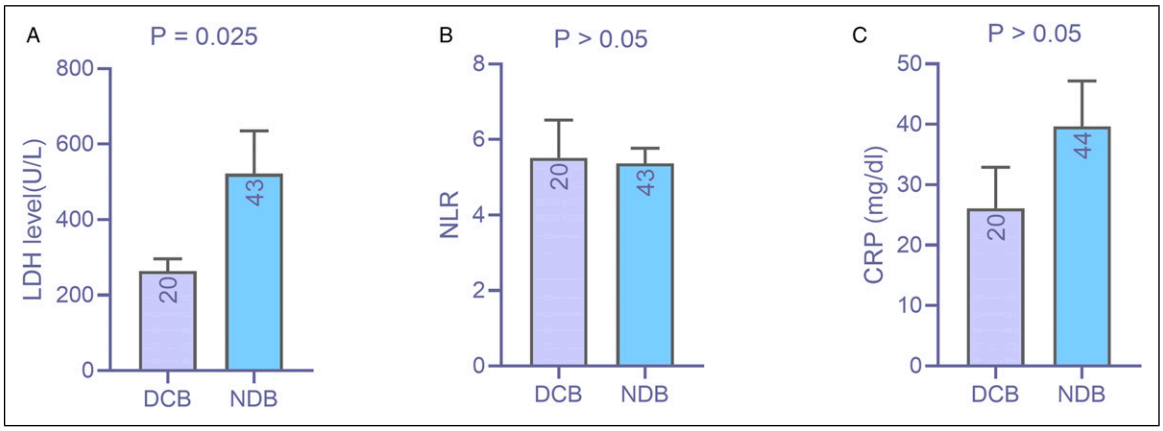

Figure 2. Baseline LDH, CRP, NLR levels and clinical benefit. Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; SD, stable disease; PR, partial response; PD, progressed disease; DCB, durable clinical benefit; NDB, non-durable clinical benefit.

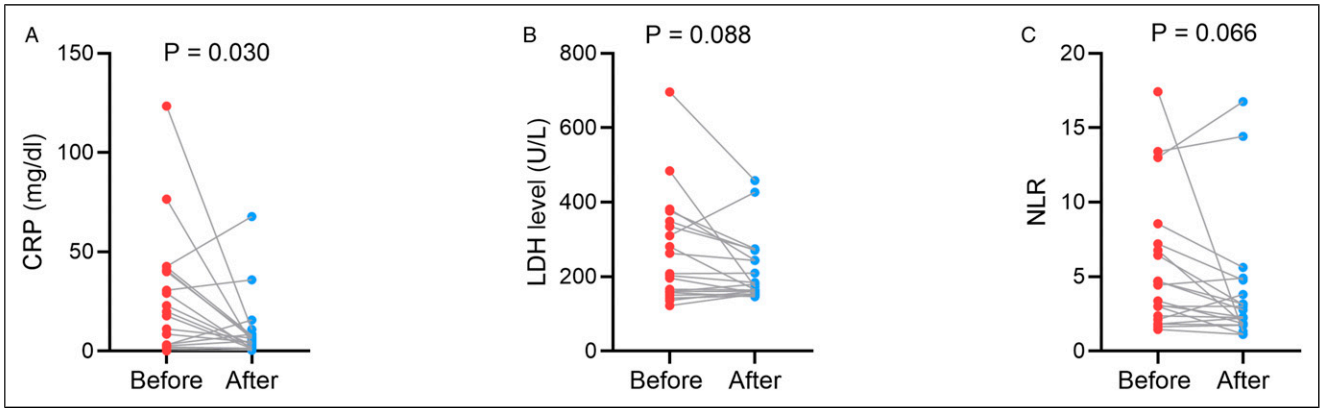

Figure 3. Post-treatment changes of CRP, LDH and NLR compared with baseline in patients with durable response. Abbreviations: CRP, C-reactive proteins; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio.

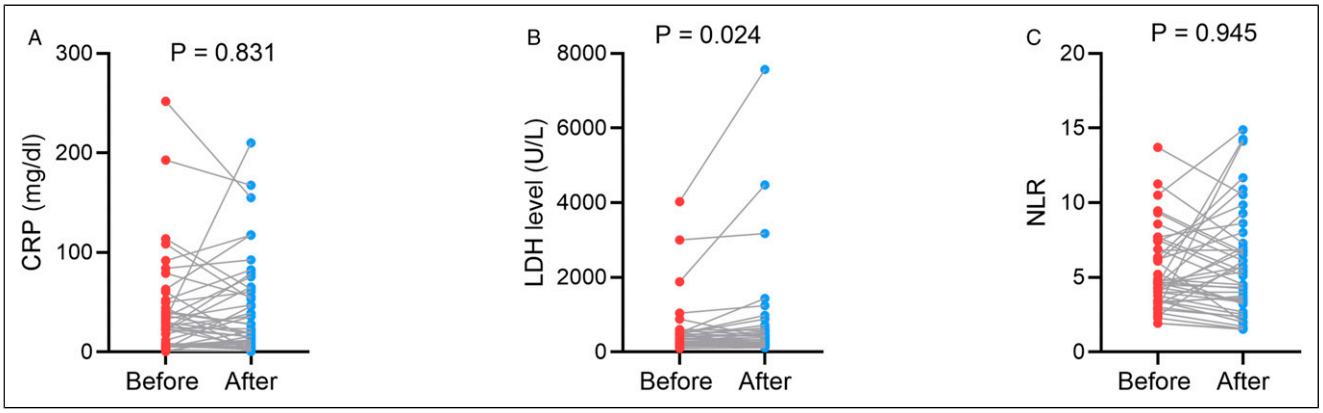

Figure 4. Post-treatment changes of CRP, LDH and NLR compared with baseline in patients with non-durable response. Abbreviations: CRP, C-reactive proteins; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio.

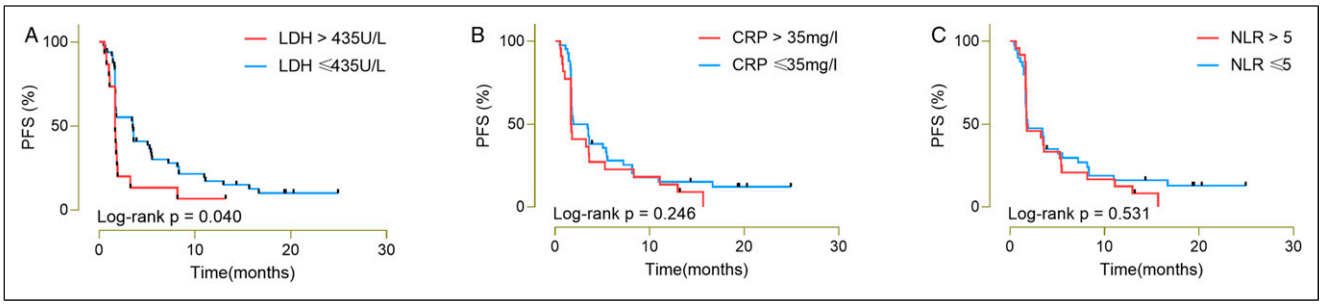

Figure 5. Kaplan Meier estimates of progression-free survival (PFS) according to the mean value of baseline CRP, LDH and NLR.

Table 2. Univariable and Multivariable Analysis of PFS Predictor Factors.

	Univariable		Multivariable	
Variable	HR (95% CI)	*P*	HR (95% CI)	*p*
Gender				
Male vs Female	2.01 (.85-4.78)	.113		
Age				
>48 vs ≤ 48	1.25 (.66-2.37)	.492		
Smoking				
Yes vs No	.55 (.27-1.13)	.104		
ECOG				
1 vs 0	1.50 (.74-3.01)	.260		
Immunotherapy treatment line				
>2nd vs ≤ 2nd	1.15 (.58-2.26)	.692		
Pretreatment metastases				
>2 vs ≤ 2	2.75 (1.33-5.69)	.006	1.99 (1.10-3.63)	.024
LDH				
>435 U/L vs ≤ 435 U/L	2.06 (1.02-4.19)	.045	1.82 (.97-3.38)	.060
CRP				
>35 vs ≤ 35	1.06 (.49-2.29)	.875		
NLR				
>5 vs ≤ 5	1.23 (.59-2.53)	.580		

LDH, lactate dehydrogenase; ECOG, eastern cooperative oncology group performance status; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

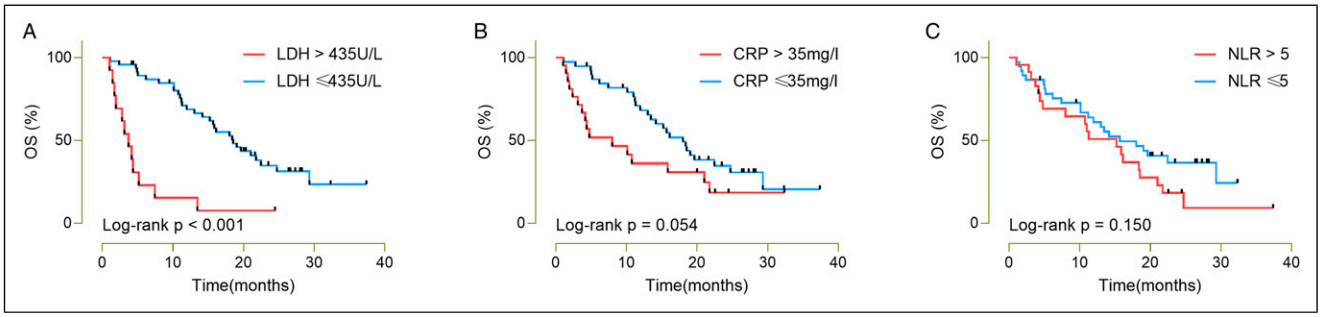

Figure 6. Kaplan Meier estimates of overall survival (OS) according to the mean value of baseline CRP, LDH and NLR.

Table 3. Univariable and Multivariable Analysis of OS Predictor Factors.

	Univariable		Multivariable	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender				
Male vs Female	.91 (.37-2.27)	.842		
Age				
>48 vs ≤ 48	2.50 (1.20-5.17)	.014	1.65 (.87-3.13)	.122
Smoking				
Yes vs No	.48 (.21-1.08)	.077	.48 (.22-1.04)	.064
ECOG				
1 vs 0	1.45 (.59-3.57)	.420		
Immunotherapy treatment line				
>2nd vs ≤ 2nd	1.59 (.73-3.47)	.241		
Pretreatment metastases				
>2 vs ≤ 2	3.13 (1.28-7.65)	.012	2.77 (1.36-5.61)	.005
LDH				
>435 U/L vs ≤ 435 U/L	6.71 (2.64-17.03)	<.001	7.01 (3.09-15.88)	<.001
CRP				
>35 vs ≤ 35	1.68 (.67-4.17)	.265		
NLR				
>5 vs ≤ 5	1.72 (.74–3.99)	.206		

LDH, lactate dehydrogenase; ECOG, eastern cooperative oncology group performance status; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

95% CI, 1.02-4.19; $P = .045$) and pretreatment metastases number (HR = 2.75; 95% CI, 1.33-5.69; $P = .006$) were identified as a significant predictor of PFS. In addition, LDH level was identified as predictor factor with marginal statistical *P*-value (HR = 1.82; 95% CI, .97-3.38; $P = .060$), and pretreatment metastases number (HR = 1.99; 95% CI, 1.10-3.63; P = .024) was identified as independent predictor of PFS, these results are shown in Table 2.

OS

The overall median OS was 15 months (95% CI, 10.9-19.1). There were 18 (28%) patients alive at the last date of follow up. OS was significantly longer in patients with low LDH (18.5 months; 95% CI, 14.5-22.6) compared to those with high LDH (3.7 months; 95% CI, 2.1-5.3; $P < .001$). Patients with low CRP (≤35 mg/L) had longer OS than those with high CRP (>35 mg/L) (18 months vs 8 months; $P = .054$). However, no significant difference in OS between patients with low NLR and high NLR (15.7 months vs 15.2 months; $P = .150$) (Figure 6). Univariable analysis results showed that patient' age (HR = 2.50; 95% CI, 1.20-5.17; $P = .014$), pretreatment metastases (HR = 3.13; 95% CI, 1.28-7.65, $P = .012$), and LDH (HR = 6.71; 95% CI, 2.64-17.03, $P < .001$) were significantly associated with OS benefit. In addition, pretreatment metastases (HR = 2.77; 95% CI, 1.36-5.61; $P = .005$) and LDH (HR = 7.01; 95% CI 3.09-15.88; $P < .001$) were identified as significant independent predictors of OS (Table 3). It's worth mentioning that, patients with post

treatment (6-8 weeks) levels of LDH ≤435 U/L, CRP ≤35 mg/L, or NLR ≤5 had significantly longer PFS and OS (Supplementary Figures 1 and 2).

Discussion

In the present study, we evaluated the association of CRP, NLR, and LDH with anti-PD-1 therapy outcome in patients with advanced NPC. We found that baseline levels of LDH was significantly higher in patients with PD and NDB. Post-treatment levels of CRP, LDH and NLR were significantly decreased or tended to decrease in patients who achieved DCB compared with baseline, whereas, only post-treatment levels of LDH was significantly higher in patients with NDB. Pretreatment metastases numbers were significantly associated with worse PFS and OS. In addition, baseline levels of LDH was identified as an independent predictor of OS benefit.

Several lines of evidence indicated the significant association between inflammation and tumor initiation, growth, and metastases.[24,25] Neutrophils as a major player of acute inflammation are recruited by different cytokines/chemokine or growth factors to the tumor microenvironment where they exert their protumor or antitumor functions.[26,27] In NSCLC and melanoma, increased NLR showed a significant association with poor ICIs therapy outcome.[17,28-30] Although high NLR has been associated with poor prognosis and an inferior chemo-radiotherapy outcome in NPC patients in some studies, others have not found such association.[31-36] In our present study, there were no significant association between baseline NLR and response or survival benefit of anti-PD-1 therapy. Another inflammation mediator, CRP, is considered as an indicator of acute inflammation and has been associated with treatment response of conventional and ICIs therapy across several tumor type.[37-41] Recent studies demonstrated a significant impact of CRP on differentiation and function of adaptive immune cells.[42-44] In the present study, although post-treatment level of CRP was significantly decreased in patients who achieved DCB, there were no significant change in CRP levels in patients with NDB compared with baseline levels. In addition, baseline CRP was not significantly associated with survival benefit. The heterogeneity of immune microenvironment across different tumor types, and the relatively small patient population included in our analysis might account for this discrepancy.[45-47] Large-scale prospective studies are needed to address the role of these inflammation mediators in NPC patients.

High levels of LDH in peripheral blood are associated with poor prognosis across different tumor types.[48] Recent studies showed that LDH as a metabolic enzyme contribute to the conversion of pyruvate to lactate, which, consequently, supports tumor growth and progression and may be involved in regulating cancer cell apoptosis.[49] LDH facilitate lactate accumulation in the tumor microenvironment, which may lead to the apoptosis of tumor infiltrated lymphocytes or alter their functions as well as supporting the accumulation and differentiation of immunosuppressive lymphocytes.[50,51] A recent study by Watson et al[52] demonstrated that T-regulatory (Treg) cells use lactic acid as an alternative metabolic source to fuel and maintain their suppressive capacity against the effect of glucose. In our analysis, baseline levels of LDH were significantly associated with treatment response and clinical benefit. Furthermore, baseline LDH was identified as a significant predictor of OS. In patients with NSCLC who received anti-PD-1 therapy, high level of LDH at the baseline was significantly associated with poor PFS and OS.[53] In addition, high level of LDH was significantly associated with OS in patients with melanoma receiving nivolumab therapy.[54] Several studies have indicated the prognostic value of LDH in patients with NPC treated with conventional therapy.[55,56] However, the data regarding the impact of pretreatment level of LDH in patients with NPC receiving ICIs still limited. Our study has some limitations. First, this study was a retrospective study; however, the patient population included in our analysis was enrolled in a controlled clinical trial, which has reduced the bias of patients' selection. Another limitation of our current study is that no calculation and justification for sample size were performed. The relatively small number of patients in our analysis may have constrained us from drawing a comprehensive conclusion of the prognostic value of LDH. Additional large-scale prospective studies are needed to further clarify the role of LDH in ICI therapy in patients with NPC.

Conclusion

Our current study indicated the association between pretreatment level of LDH and treatment outcome of anti-PD-1 therapy in patients with NPC. In light of the recent studies on the negative effect of lactic acid on anti-tumor immunity, it seems that LDH may play a causative role in immunotherapy failure. Therefore, measuring the serum LDH levels before initiating ICI therapy might serve as a simple indicator of treatment outcome. In addition, targeting the activity of LDH enzymes may help to reduce the resistance of the tumor to ICIs and maximize their effects.

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Author Contributions

(I) Conception and design: WA and YX; (II) Administrative support: HY and ZL; (III) Provision of study materials or patients: WA, YX, HY, and ZL; (IV) Collection and assembly of data: WA,

YH, and YZ; (V) Data analysis and interpretation: WA and YX; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Data Availability

The data sharing statement available in data sharing statement form.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (approval number: B2021-445-01), and individual consent for this retrospective analysis was waived.

ORCID iDs

Wael A. S. Ali https://orcid.org/0000-0002-1142-3135
Jun Liao https://orcid.org/0000-0002-2017-5065

Supplemental Material

Supplemental material for this article is available online.

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