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Original Article

The derived neutrophil-lymphocyte ratio and the neutrophil-lymphocyte ratio are related to poor prognosis in Hodgkin lymphoma patients

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Abstract: Introduction: The inflammatory and immune cells have an important impact on Hodgkin lymphoma (HL). The derived neutrophil-lymphocyte ratio (dNLR) has been confirmed to have a similar prognostic value as the neutrophil-lymphocyte ratio (NLR) in many kinds of tumors, but it has not been explored as a prognostic marker for Hodgkin lymphoma patients. Objective: The aim of the study is to evaluate the prognostic value of dNLR and NLR in HL. Methods: This retrospective study included 213 newly diagnosed HL patients from 2008 to 2019. Then, the prognostic significance of dNLR and NLR in these patients was evaluated. Meanwhile, subgroup analyses based on the Ann Arbor stage and histotype were also carried out. Finally, propensity score matching was used to reduce selection bias. Results: Patients with dNLR ≥ 2.1 showed shorter overall survival (OS) (P = 0.006). Also, patients with NLR ≥ 3.0 showed worse OS (P = 0.005) and progression-free survival (PFS) (P = 0.031). These results were also found in patients with early-stage and mixed cellularity subtype HL. Besides, high dNLR represented an independent prognostic marker for OS and high NLR remained an independent prognostic factor for OS and PFS on multivariable analysis. Conclusion: Elevated dNLR and NLR were related to worse survival in HL patients. For the first time, the dNLR has shown the potential to be a new prognostic factor for patients with HL.

Keywords: Neutrophil-lymphocyte ratio, Hodgkin lymphoma, prognosis, propensity score matching

Introduction

Hodgkin lymphoma (HL) is an uncommon B-cell lymphoid malignancy [1], and approximately 20% of HL patients continue to have the refractory or relapsed disease [2]. Importantly, HL has a special pathological feature; there are only about 1% of cancer cells and plenty of reactive cells, including neutrophils, eosinophils, macrophages (monocytes), fibroblasts, and T and B lymphocytes in the background [3]. Recently, several studies have found that these inflammatory and immune cells in the tumor microenvironment have an impact on the pathogenesis and prognosis of HL [4-8]. As already known, the inflammatory and immune cells in the tissue are significantly correlated with those in the peripheral blood because these tissue cells may be derived from the peripheral blood. Therefore, in recent years, accumulating studies have suggested that inflammation-related parameters have an influence on the prognosis of various tumors, including HL. For instance, the lymphocyte to monocyte ratio (LMR) and neutrophil-lymphocyte ratio (NLR) have revealed prognostic significance in HL [9-12].

Furthermore, a study firstly proposed that derived neutrophil-lymphocyte ratio (dNLR), comprising neutrophil count divided by leukocyte count-neutrophil count, had a similar prognostic value as NLR in many solid tumors [13]. Later, an increasing number of studies have discovered that dNLR could affect the prognosis of different lymphomas, including diffuse large B cell lymphoma (DLBCL), multiple myeloma (MM), extranodal Natural Killer/T-cell lymphoma (ENKTL), and angioimmunoblastic T-cell lymphoma (AITL) [14-19]. Nevertheless, for HL, the dNLR has not yet been evaluated. Also, the role of NLR in HL has not often been described [20-24].

Consequently, the present study aimed to assess the prognostic value of dNLR and NLR in

newly diagnosed HL patients and compare the difference between these ratios. Additionally, propensity score matching in the present study was applied to reduce the impact of confounding factors [25].

Methods

Patients

This was a retrospective analysis of a cohort of 213 consecutive patients with newly diagnosed HL at our center between January 2008 and June 2019. The inclusion criteria were pathologically confirmed HL, no previous therapy, no second malignancy or history of cancer, no immunosuppression, and availability of clinical data. Patients were excluded in case of missing pre-treatment data on the count of complete blood cells; no treatment for HL in our hospital; severe infection or abnormal function of important organs; and loss to follow up. The patients were treated by chemotherapy with or without radiation treatment. Meanwhile, treatment response was evaluated by using the standard guideline [26]. And the follow-up was carried out until December 2019. The clinical data and laboratory parameters, such as age, gender, Ann Arbor stage, histotype, B symptoms, International Prognostic Score (IPS), serum lactate dehydrogenase (LDH), white blood cell (WBC), absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) before therapy, were retrieved from the electronic medical records.

The dNLR was calculated as follows: dNLR = ANC/(WBC-ANC) [13]. Meanwhile, the NLR was computed as follows: NLR = ANC/ALC.

The study was performed in accordance with the standards of the Declaration of Helsinki and approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University.

Statistics analysis

OS was described from the time of diagnosis to the date of death for any reason or last follow-up. And the definition of PFS was from the date of diagnosis to the time of disease relapse, progression, death due to any cause, or last follow-up. Then, categorical variables were measured by the Chi-Square test. The optimal cut-off points of dNLR and NLR were determined using the receiver operative curve (ROC) and area under the curve (AUC). At the same time, the relationships of dNLR and NLR with OS and PFS were analyzed by utilizing Kaplan-Meier curves and measured by the log-rank test. Next, univariate and multivariable analyses were accomplished using the Cox regression model. Being a retrospective study, randomization was not performed. Accordingly, a propensity score matching study was performed to diminish the bias. Patients with higher dNLR and NLR were matched with those who had lower dNLR and NLR by propensity scores using the one-to-one caliper matching. After matching, the OS and PFS in matched pairs based on different groups were analyzed according to the Kaplan-Meier survival curves. All statistical analyses were performed with IBM-SPSS version 23.0. A two-sided P value < 0.05 was considered significant.

Results

Patient characteristics

A total of 213 patients with newly diagnosed HL were analyzed, and the detailed clinical features are described in **Table 1**. The median age at first treatment was 33 years (range, 14-82 years), and 61 (28.6%) patients were more than 45 years old. There were 85 (39.9%) female patients. Nodular sclerosis and mixed cellularity were the major subtypes, and the number of patients with these subtypes was 83 (39.0%) and 102 (47.9%), respectively. Also, 106 (49.8%) patients were in the early stage (Ann Arbor stage I/II) and 118 (55.4%) patients had ≥ 3 lymph node involvement. Regarding the IPS and B symptoms, 36 (16.9%) cases had high IPS (IPS ≥ 4) and 98 (46.0%) patients presented with B symptoms. Besides, an elevated level of LDH was found in 56 (27.2%, n = 206) patients, and there were 92 (43.4%) patients with depressed albumin level (< 40 g/L). Among the patients who completed at least two cycles of chemotherapy, 92 (49.7%) patients achieved complete remission, 71 (38.4%) patients exhibited partial remission, and 22 (11.9%) patients showed no remission. The median time of follow-up was 79 months (range, 2-143 months) in the study; 25 patients died due to any cause and 48 patients had disease recurrence or progression.

Table 1. Patient characteristics

Characteristic	N (%)
Age ≥ 45	61 (28.6)
Male	128 (60.1)
Histotype	
Nodular sclerosis	83 (39.0)
Mixed cellularity	102 (47.9)
Lymphocyte rich	8 (3.8)
Undifferentiated	20 (9.4)
Ann Arbor Stages	
I	27 (12.7)
II	79 (37.1)
III	47 (22.1)
IV	60 (28.2)
B symptoms	98 (46.0)
Bulky mass	11 (5.2)
Lymph node involved ≥ 3	118 (55.4)
Bone marrow involvement	33 (15.5)
IPS	
0/1	92 (43.2)
2/3	85 (39.9)
≥ 4	36 (16.9)
Treatment response (n = 185)	
CR	92 (49.7)
PR	71 (38.4)
SD+PD	22 (11.9)
Albumin < 40 g/L	92 (43.4)
Hemoglobin < 105 g/L	45 (21.1)
LDH ≥ 250 IU/L (n = 206)	56 (27.2)
ALC < 0.6 × 10^9/L	27 (12.7)
WBC ≥ 15 × 10^9/L	19 (8.9)
ANC > 1 × normal	81 (38.0)

IPS: International Prognostic Score; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; WBC: white blood cell; ANC: absolute neutrophil count.

Clinical indicators according to the different levels of dNLR and NLR

The ROC curve analysis was carried out to determine the cut-off values of dNLR and NLR. A dNLR value of 2.1 was related to an AUC of 0.6 (95% CI, 0.6-0.7, *P* = 0.002, **Figure 1A**) and the maximum combinative sensitivity and specificity (74% sensitivity and 53% specificity). Similarly, an NLR value of 3.0 was related to an AUC of 0.6 (95% CI, 0.6-0.7, *P* = 0.001, **Figure 1B**) and the maximum combinative sensitivity and specificity (76% sensitivity and 51% specificity).

Clinical features of all patients stratified by dNLR and NLR are described in **Table 2**. The groups with dNLR ≥ 2.1 and NLR ≥ 3.0 had more number of patients who were less than 45 years old, were female, and had nodular sclerosis. Besides, patients with dNLR of 2.1 or higher were inclined to present with more lymph node involvement (P = 0.003), advanced-stage (P = 0.012), high IPS (P = 0.027), elevated serum LDH (P = 0.011), and hypoalbuminemia (P = 0.000). However, the two groups of dNLR showed no difference in treatment response (P = 0.858). Further, with respect to NLR, a NLR of 3.0 or higher was associated with more lymph node involvement (P = 0.007), higher serum LDH (P = 0.017), hypoalbuminemia (P = 0.000), and anemia (P = 0.000). In the same way, there were no differences between the two groups with different NLR levels in terms of the Ann Arbor stage (P = 0.172), IPS (P = 0.059), and treatment response (P = 0.128).

Clinical features stratified by dNLR and NLR after propensity score matching

After accomplishing propensity score matching, the correlation between clinical characteristics and different levels of dNLR and NLR is presented in **Table 3**. There were 47 matched pairs of dNLR and 44 matched pairs of NLR. In the matched cohort, the difference in factors, such as gender, age, Ann Arbor stage, IPS, lymph node involvement, albumin, and hemoglobin, between the two groups had no statistical significance (all, P > 0.05). Therefore, some main primary factors were balanced in these patients.

Prognostic significance of the dNLR and NLR

Kaplan-Meier survival analysis of the 5-year OS showed that patients with high dNLR had a worse prognosis than those with low dNLR (5-yr OS, 83.0% in the high dNLR group vs. 97.9% in the low dNLR group, P = 0.006, **Figure 2A**). Nevertheless, there was no difference in the 5-year PFS between the two groups with different levels of dNLR (P = 0.148, **Figure 2B**). Regarding the NLR, the survival curves revealed that 5-year OS and 5-year PFS in the high NLR group were significantly lower than those in the low NLR group (5-yr OS, 82.9% in the high NLR group vs. 98.0% in the low NLR group, P = 0.005; and 5-yr PFS, 70.8% in the high NLR group vs. 86.4% in the low NLR group, P = 0.031, **Figure 2C** and **2D**). Currently, the IPS is

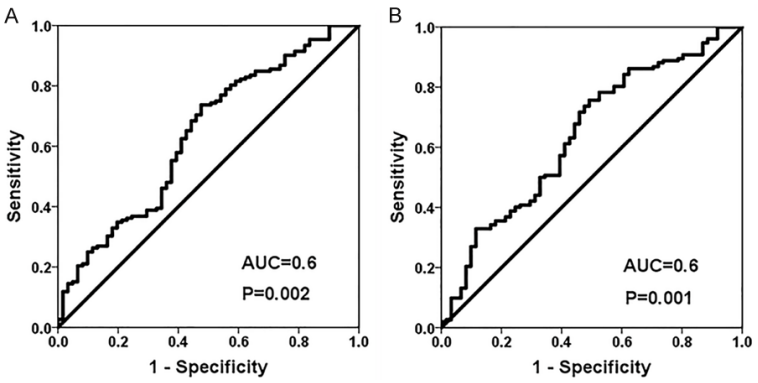

Figure 1. ROC curves for optimal cut off points of dNLR (A) and NLR (B). dNLR, derived neutrophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; AUC, area under the curve; ROC, receiver operating characteristics.

being widely used for predicting the prognosis of advanced-stage HL patients, but there is a need for a prognostic factor in early-stage HL patients. Also, mixed cellularity and nodular sclerosis are the major subtypes of HL [27]. Therefore, the prognostic roles of dNLR and NLR were analyzed in the subgroups based on the stage and the histotype. **Figure 3A** shows that dNLR ≥ 2.1 was a significant factor for worse 5-year OS in early-stage patients (P = 0.020). However, early-stage patients with dNLR ≥ 2.1 revealed similar 5-year PFS as those with dNLR < 2.1 (P = 0.171) (**Figure 3B**). Moreover, **Figure 3C** and **3D** reveal that NLR ≥ 3.0 was a factor for shorter 5-year OS and 5-year PFS in early-stage patients (P = 0.029, P = 0.020, respectively). Additionally, mixed cellularity subtype patients with dNLR ≥ 2.1 had a shorter 5-year OS (P = 0.027), but they did not differ significantly in PFS (P = 0.050, **Figure 4A** and **4B**). NLR ≥ 3.0 also indicated poorer survival in terms of both 5-year OS (P = 0.016) and 5-year PFS (P = 0.030, **Figure 4C** and **4D**) in patients with the mixed cellularity subtype. However, in the advanced-stage and nodular sclerosis subgroup, patients with different levels of dNLR and NLR showed no obvious difference in the 5-year OS and PFS. After propensity score matching, the survival analysis presented similar results. For instance, patients with dNLR ≥ 2.1 had a worse 5-year OS (P = 0.014, **Figure 5A**) and a similar 5-year PFS (P = 0.714, **Figure 5B**). Also, patients with NLR ≥ 3.0 had a shorter 5-year OS (P = 0.001, **Figure 5C**) and 5-year PFS (P = 0.015, **Figure 5D**) than those with NLR < 3.0. Subsequently, univariate Cox proportional analysis identified that a worse 5-year OS was significantly correlated with high dNLR (HR = 9.9, P = 0.025) and NLR (HR = 10.2, P = 0.024), but a worse 5-year PFS was significantly associated with high NLR (HR = 2.3, P = 0.037) (**Table 4**). Furthermore, a better 5-year PFS was statistically significantly correlated with early-stage disease and remission status (**Table 4**). Due to the relation between NLR and dNLR, the corresponding multivariate analyses needed to be performed separately to avoid collinearity. Therefore, in the dNLR model, multivariate analysis adjusted for dNLR more than 2.1, age less than 45 years, early-stage, and hypoalbuminemia revealed that a high dNLR was an independent prognostic marker for 5-year OS (HR = 10.1, P = 0.028) (**Table 5**). Further, in the NLR model, multivariate analysis revealed that a high NLR was an independent prognostic marker for 5-year OS (HR = 10.4, P = 0.025) and 5-year PFS (HR = 2.3, P = 0.046) (**Table 5**).

Discussion

This is the first retrospective research to investigate the prognostic meaning of dNLR in HL patients. In the current study, dNLR and NLR had a similar impact on 5-year OS; their higher values were related to worse OS in univariate and multivariable analyses. Nevertheless, only NLR was associated with 5-year PFS, and the dNLR did not exert any influence on the PFS.

Generally, inflammation in the tumor microenvironment, such as inflammatory cells and inflammatory mediators, can promote the proliferation of tumor cells, angiogenesis, and restrain immune responses [28]. As already known, neutrophils are inflammatory cells that respond to any infection first. Previous studies have reported that normal neutrophils could suppress the function of T lymphocytes. Similarly, activated neutrophils also exhibited the properties of T-cell function suppression via increasing the value of arginase 1 [29, 30]. In addition, neutrophils were able to induce angiogenesis by providing and expressing matrix metalloproteinase 9 and vascular endothelial growth factors [31]. Increasing evidence has

Table 2. Clinical characteristics according to the different levels of dNLR, NLR

	dNLR < 2.1 (n = 71)	dNLR ≥ 2.1 (n = 142)	*P*-value	NLR < 3.0 (n = 69)	NLR ≥ 3.0 (n = 144)	*P*-value
Age			0.001*			0.000*
< 45	56.3%	78.9%		55.1%	79.2%	
≥ 45	43.7%	21.1%		44.9%	20.8%	
Sex			0.013*			0.011*
Male	71.8%	54.2%		72.5%	54.2%	
Female	28.2%	45.8%		27.5%	45.8%	
Histotype			0.009*			0.000*
Nodular sclerosis	30.4%	51.2%		24.1%	53.4%	
Mixed cellularity	69.6%	48.8%		75.9%	46.6%	
Ann Arbor Stages			0.012*			0.172
Early	62.0%	43.7%		56.5%	46.5%	
Advanced	38.0%	56.3%		43.5%	53.5%	
Lymph node involved			0.003*			0.007*
≥ 3	40.8%	62.7%		42.0%	61.8%	
< 3	59.2%	37.3%		38.0%	38.2%	
IPS			0.027*			0.059
0/1	53.5%	38.0%		53.6%	38.2%	
2/3	38.0%	40.8%		36.2%	41.7%	
≥ 4	8.5%	21.1%		10.1%	20.1%	
Treatment response			0.858			0.128
CR+PR	88.7%	87.8%		93.3%	85.6%	
SD+PD	11.3%	12.2%		6.7%	14.4%	
LDH IU/L			0.011*			0.017*
≥ 250	15.7%	32.4%		16.2%	31.9%	
< 250	84.3%	67.6%		83.8%	68.1%	
Albumin g/L			0.000*			0.000*
≥ 40	80.3%	44.3%		78.3%	45.8%	
< 40	19.7%	55.7%		21.7%	54.2%	
Hemoglobin g/L			0.000*			0.000*
≥ 105	94.3%	71.8%		94.1%	72.2%	
< 105	5.7%	28.2%		5.9%	27.8%	

dNLR: derived neutrophil-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; IPS: International Prognostic Score; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; LDH: lactate dehydrogenase. *Significantly different.

revealed that neutrophils in the tumor microenvironment have various important effects on different tumors [32]. However, it is not easy and time-efficient to analyze the tumor microenvironment in daily clinical work and general practice. Hence, the correlative parameters in the peripheral blood should be explored because they can be detected easily and quickly.

In recent years, mounting researches have considered that NLR is a meaningful and simple parameter to reflect both inflammation (neutrophils) and immunity (lymphocytes) associated with the prognosis in patients with malignancy, including hematological malignancies [33, 34]. Regarding HL, only a small number of articles have investigated the prognostic role of NLR in patients. In 2012, a study first analyzed the prognostic meaning of NLR in 312 patients with HL; they found that high NLR (≥ 4.3) was associated with worse OS, but it was not related to event-free survival (EFS). Meanwhile, in the advanced stage subgroup, a high NLR was also found to be only correlated with a lower OS

Table 3. Correlation between clinical features and dNLR, NLR after propensity score matching

	dNLR < 2.1 (n = 47)	dNLR ≥ 2.1 (n = 47)	*P*-value	NLR < 3.0 (n = 44)	NLR ≥ 3.0 (n = 44)	*P*-value
Age			0.671			0.862
< 45	59.6%	63.8%		63.6%	61.4%	
≥ 45	40.4%	36.2%		36.4%	38.6%	
Gender			0.652			0.488
Male	72.3%	68.1%		72.7%	65.9%	
Female	27.7%	31.9%		27.3%	34.1%	
Ann Arbor Stages			0.298			0.669
Early	51.1%	61.7%		50.0%	54.5%	
Advanced	48.9%	38.3%		50.0%	45.5%	
Lymph node involved			1.000			0.669
≥ 3	53.2%	53.2%		54.5%	50.0%	
< 3	46.8%	46.8%		45.5%	50.0%	
Albumin g/L			0.472			0.808
≥ 40	72.3%	78.7%		75.0%	72.7%	
< 40	27.7%	21.3%		25.0%	27.3%	
Hemoglobin g/L			1.000			0.694
≥ 105	91.5%	91.5%		90.9%	93.2%	
< 105	8.5%	8.5%		9.1%	6.8%	
IPS			0.907			0.899
0/1	48.9%	53.2%		50.0%	54.5%	
2/3	40.4%	36.2%		38.6%	34.1%	
≥ 4	10.6%	10.6%		11.4%	11.4%	

dNLR: derived neutrophil-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; IPS: International Prognostic Score.

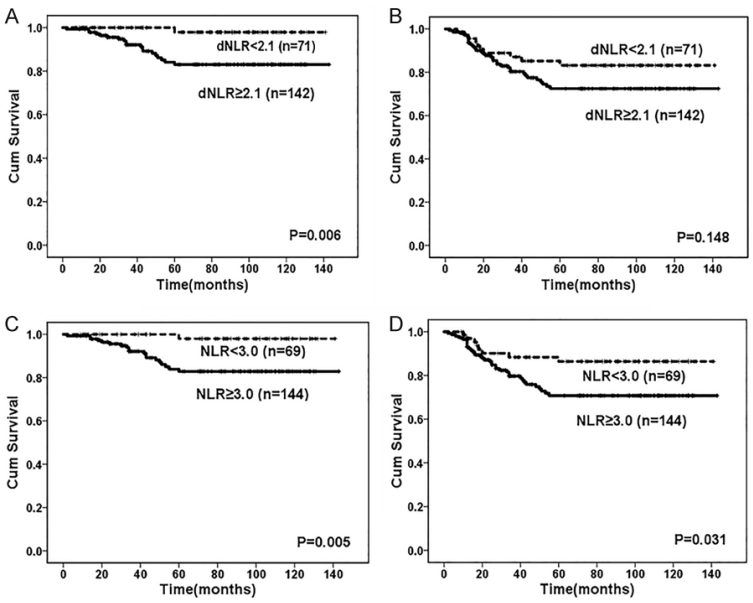

Figure 2. Kaplan-Meier curves of 5-year overall survival and 5-year progression-free survival in the newly diagnosed HL patients by pre-treatment dNLR, NLR. A: 5-year OS for different dNLR; B: 5-year PFS for different dNLR; C: 5-year OS for different NLR; D: 5-year PFS for different NLR. OS, overall survival; PFS, progression-free survival; HL, Hodgkin lymphoma; dNLR, derived neutrophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio.

[24]. Moreover, in 2017, a study analyzed the significance of NLR in 990 patients with the nodular sclerosis subtype. Patients with high NLR (≥ 6.0) had a lower OS and PFS. The results were obtained in both early and advanced-stage patients [23]. Besides, an analysis including 338 early-stage HL patients revealed that a high NLR (≥ 6.4) was only related to worse freedom from progression (FFP) on the univariate analysis [21]. Later, two reports revealed that both early and advanced-stage patients with high NLR (≥ 6.0) had a lower PFS [20], and patients with high NLR (≥ 4.3) had worse OS and PFS [22]. Similarly, in the present study, it was demonstrated that patients with high NLR (≥ 3.0)

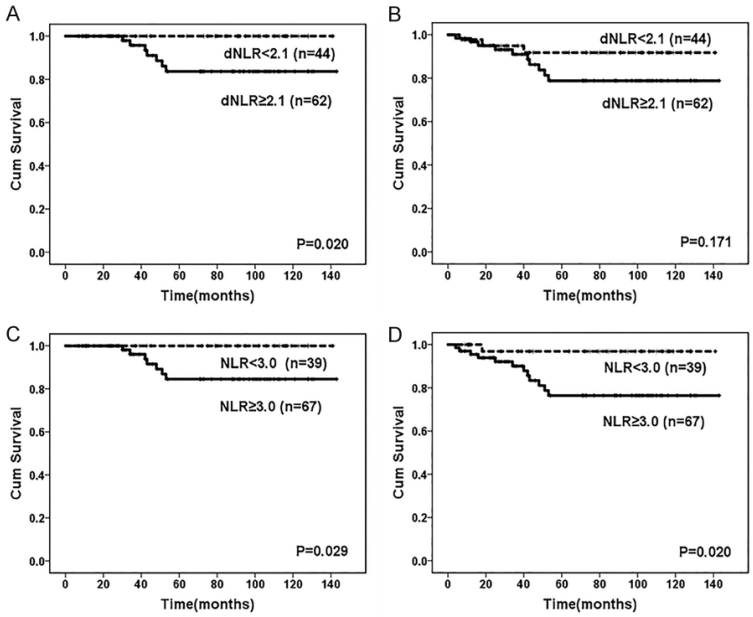

Figure 3. 5-Year overall survival and 5-year progression-free survival in the subgroup with early-stage (I+II) disease based on pre-treatment dNLR, NLR. A: 5-year OS for different dNLR; B: 5-year PFS for different dNLR; C: 5-year OS for different NLR; D: 5-year PFS for different NLR. dNLR, derived neutrophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

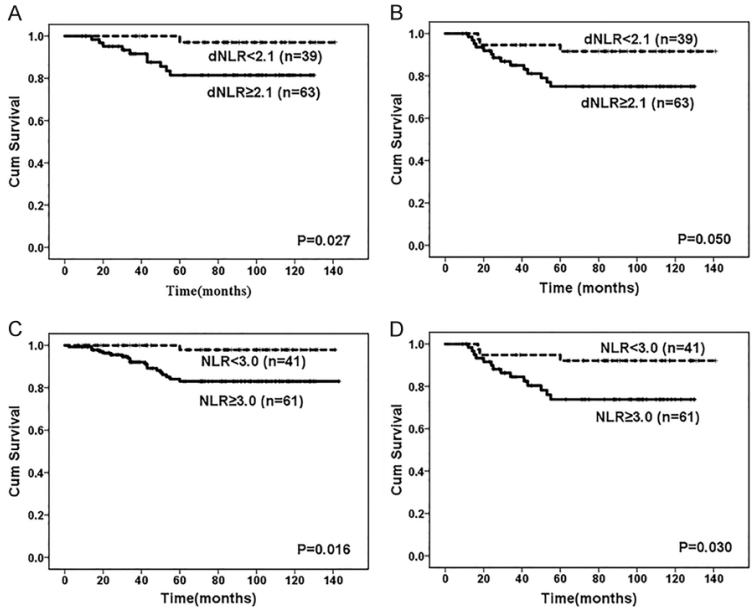

Figure 4. 5-Year overall survival and 5-year progression-free survival in the subgroup with mixed cellularity subtype based on pre-treatment dNLR, NLR. A: 5-year OS for different dNLR; B: 5-year PFS for different dNLR; C: 5-year OS for different NLR; D: 5-year PFS for different NLR. dNLR, derived neutrophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

had a shortened OS and PFS compared to those with low NLR (< 3.0). Specifically speaking, patients in the early-stage and mixed cellularity subtype groups with high NLR also had lower OS and PFS. Therefore, consistent with previous studies, an increased NLR, which was considered as a marker of inflammation and immunity, had prognostic significance in HL patients. Meanwhile, to our knowledge, the prognostic value of NLR in the mixed cellularity subtype was reported first in the study. However, the results of the present study also showed some difference from those of previous studies. For instance, the cut-off values of NLR were different in these researches, and some studies showed that there was no significant difference in PFS between the two groups. To our knowledge, the reasons for this occurrence may be that they were retrospective analyses, which could have some bias. Also, there was a difference in parameters, such as the number of patients, treatment plans, and patient features, among these researches.

Additionally, the absolute lymphocyte count is not routinely recorded in clinical trials. To solve the problem, the dNLR, which is calculated using the WBC and ANC, has been considered to be an indicator of prognosis in diverse cancer patients, and it had similar significance to NLR [13]. Furthermore, the leukocyte-neutrophil count in the peripheral blood mainly reflects the count of lymphocytes and monocytes, but the ratio of lymphocytes to monocytes is about 6:1 in normal persons and about 3:1 in tumor patients [35]; thus, it can be a similar indicator to NLR for reflecting inflammation and immunity of cancer, and the possible impact of mono-

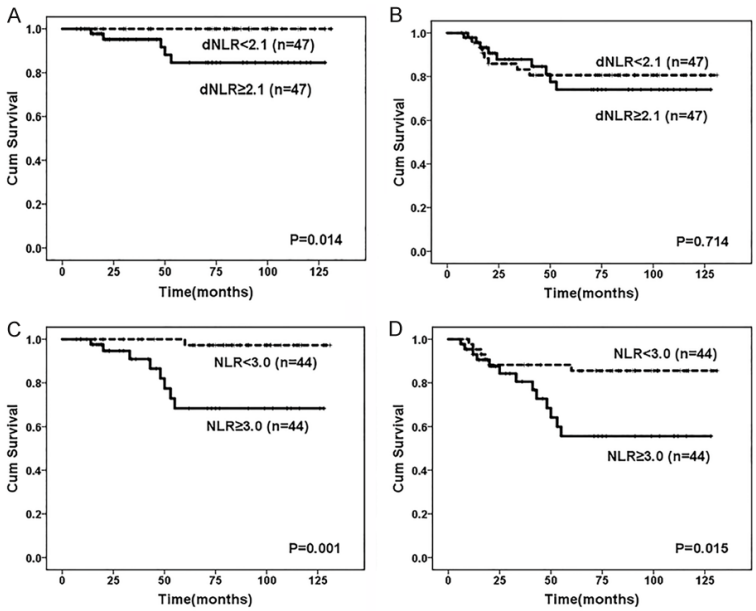

Figure 5. Kaplan-Meier curves of 5-year overall survival and 5-year progression-free survival regarding dNLR, NLR after propensity score matching. A: 5-year OS for different dNLR; B: 5-year PFS for different dNLR; C: 5-year OS for different NLR; D: 5-year PFS for different NLR. dNLR, derived neutrophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

cytes is negligible. Therefore, dNLR has been suggested as a replacement for NLR due to its expedience in patients with lack of a lymphocyte count. Recently, a growing number of studies have focused on the prognostic meaning of dNLR in patients with various tumors, including lymphoma. For example, in 290 newly diagnosed DLBCL patients, those with a dNLR of ≥ 4.0 exhibited a shortened OS, and dNLR of ≥ 1.8 was associated with worse disease free survival (DFS) [14]. Meanwhile, for refractory or relapsed DLBCL, a study also reported that patients with a high dNLR (≥ 3.5) had poor OS and PFS [15]. Besides, ENKTL patients [16] with dNLR ≥ 3.6 and AITL patients [17] with dNLR ≥ 2.2 also showed shorter OS and PFS, respectively. However, the prognostic role of dNLR in HL has not yet been defined. In the current study, cHL patients with a high dNLR (≥ 2.1) had a poor OS, while they had a similar PFS. Patients in the early stage with high dNLR only had worse OS. Therefore, as observed, the prognostic meaning of dNLR in the present study has some difference from that in other researches. Various lymphomas may have different pathogenesis and prognosis. Also, there might be many kinds of bias in these different studies. However, because the prognostic value of dNLR in HL patients was analyzed for the first time in this study, more studies are needed to answer these questions.

Importantly, as far as we know, the current study firstly applied propensity score matching to evaluate the prognostic importance of dNLR and NLR in HL patients. This method is often applied to lower confounding and selection bias in retrospective analyses [36]. In the current research, some clinical features showed differences between the two groups; thus, the two groups might be imbalanced and these characteristics might be confounders that could affect the result of prognosis. After implementing the matching, there were no discrepancies between the two groups with different levels of dNLR and NLR. In the matched cohort, the Kaplan-Meier analysis also indicated that dNLR and NLR were related to OS, and only NLR was associated with PFS. Therefore, the findings of our study may be comparatively more believable than those of other studies, which is crucial for lowering the selection and confounding bias in the retrospective analysis.

Nevertheless, this research has some limitations. This was a retrospective analysis in a single-center; thus, the number of cases in the study was limited. Moreover, although the method of propensity score matching was applied to reduce the bias, a few factors, which were not collected, could have a prognostic value. Also, fewer cases were included in the matched cohort. Therefore, the results after propensity score matching may not represent those of a study including all patients accurately. To confirm these results, further researches, including prospective studies and multi-center larger population cohorts, are needed. Moreover, more clinical variables should be collected when the propensity score matching is performed.

Disclosure of conflict of interest

None.

Table 4. Univariate analysis of variables for OS and PFS

Variables	5-Year OS			5-Year PFS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
dNLR ≥ 2.1	9.9	1.3-74.2	0.025*	1.7	0.8-3.4	0.154
NLR ≥ 3.0	10.2	1.4-76.1	0.024*	2.3	1.1-4.9	0.037*
Age < 45	0.8	0.3-2.0	0.654	0.9	0.5-1.7	0.762
Male	1.5	0.6-3.9	0.407	1.1	0.6-2.0	0.773
Stage (Early)	0.6	0.2-1.4	0.228	0.4	0.2-0.8	0.006*
B symptoms (-)	0.8	0.3-1.8	0.526	0.9	0.5-1.5	0.590
IPS < 4	0.8	0.3-2.4	0.677	0.8	0.4-1.6	0.467
Histotype (NS vs. MC)	1.2	0.5-2.9	0.747	0.6	0.3-1.2	0.146
Lymph node Involved ≥ 3	1.0	0.4-2.4	0.951	1.1	0.6-1.9	0.879
Treatment response (CR+PR)	0.4	0.1-1.5	0.193	0.2	0.1-0.4	0.000*
Albumin < 40 g/L	2.4	1.0-6.0	0.066	1.5	0.8-2.8	0.165
Hemoglobin < 105 g/L	1.3	0.5-3.5	0.662	1.5	0.8-2.9	0.221
LDH < 250 IU/L	0.8	0.3-2.0	0.601	1.4	0.7-3.0	0.350

OS: overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; dNLR: derived neutrophil-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; IPS: International Prognostic Score; NS: Nodular sclerosis; MC: Mixed cellularity; CR: complete response; PR: partial response; LDH: lactate dehydrogenase. *Significantly different.

Table 5. Multivariate analysis of variables for OS and PFS according to dNLR, NLR

	Variables	5-Year OS			5-Year PFS		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
dNLR	dNLR ≥ 2.1	10.1	1.3-76.7	0.028*	1.5	0.7-3.3	0.304
	Age < 45	0.6	0.2-1.6	0.299	0.9	0.5-1.8	0.755
	Stage (Early)	0.9	0.3-2.4	0.816	0.4	0.2-0.9	0.022*
	Albumin < 40 g/L	1.5	0.5-4.1	0.463	1.0	0.5-2.0	0.997
NLR	NLR ≥ 3.0	10.4	1.3-80.8	0.025*	2.3	1.0-5.2	0.046*
	Age < 45	0.6	0.2-1.6	0.300	0.8	0.4-1.6	0.560
	Stage (Early)	0.8	0.3-2.2	0.675	0.4	0.2-0.9	0.017*
	Albumin < 40 g/L	1.5	0.5-4.1	0.462	0.9	0.5-1.7	0.729

OS: overall survival; PFS: progression-free survival; dNLR: derived neutrophil-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; HR: hazard ratio; CI: confidence interval. *Significantly different.

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