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Neutrophil-to-lymphocyte ratio (NLR) fails to predict outcome of diffuse large B cell lymphoma

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ABSTRACT

Background: Neutrophil-to-lymphocyte ratio (NLR) has been recognized as a poor prognostic indicator in various solid tumors.
Methods: We retrospectively analyzed 530 patients with de novo DLBCL who were diagnosed from April 2002 to November 2017.
Results: The median age of patients was 69 (range, 20–95) years, and 59% were male. The optimal cutoff for NLR was 5.2. NLR (5.2) was not associated with overall and progression free survival.
Conclusion: Our study failed to reveal the predictive value of NLR and demonstrated that the NCCN-IPI might be the most powerful predictor in DLBCL.

1. Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). Approximately 60%–70% of newly diagnosed DLBCL patients are curable by rituximab [1]. Before the advent of rituximab, the international prognostic index (IPI) was the most powerful prognostic scale. However, its power has reduced [2] and it has been replaced with the National Comprehensive Cancer Network - International Prognostic Index (NCCN-IPI). Zhou et al. developed the NCCN-IPI to predict survival following rituximab treatment more accurately than the older IPI system [3]. However, some reports described results showing that the NCCN-IPI failed to accurately predict outcomes for elderly patients [4,5]. Thus, the predictive value of this scale is not sufficient.

Recently, neutrophil-to-lymphocyte ratio (NLR) has been recognized as a poor prognostic indicator in various solid tumors. NLR, calculated as the absolute neutrophil count (ANC) divided by the absolute lymphocyte count (ALC) within peripheral blood, has been shown to be correlated with prognosis in various malignancies [6–10].

NLR has been evaluated in DLBCL and appears prognostic in these patient populations [11–20]. Although reports that used NLR have since been published from various geographic regions, whether these results can be extrapolated to different ethnic populations is unclear. To date, there has been no large-scale report to evaluate this scale in Japan.

The purpose of the present study was to analyze whether NLR is associated with the outcome of patients with DLBCL.

2. Patients and methods

2.1. Patients

This retrospective analysis was conducted in two hematology centers, Kansai Medical University Hospital and Kansai Medical University Medical Center. A total of 530 patients diagnosed with DLBCL from April 2002 to November 2017 were enrolled in this study. Primary treatment included R-CHOP or R-CHOP-like regimens.

2.2. Statistics

Overall survival (OS) was calculated as the time from diagnosis until the time of death or the last clinical follow-up. Progression free survival (PFS) was defined as the time from diagnosis to the objective progression of disease. Survival curves were generated using the Kaplan–Meier method, and differences were evaluated using the log-rank test. Univariate and multivariate logistic regression were used to determine whether baseline characteristics were associated with outcome. We categorized two groups with a cut-off value of 5.2 according to the interquartile range (IQR). All statistical tests were two-sided, statistical

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Table 1
Patients' characteristics.

No. of patients(*n*)	530
Median age, range(y/o)	69(20–98)
Male sex(%)	314(59%)
PS ≥ 3	12(2%)
elevated LDH	287(54%)
B symptom(%)	78(15%)
bulky mass	35(7%)
BM involvement	54(10%)
extranodal sites ≥ 2	290(55%)
stage(*n*)	
I	126(23%)
II	93(18%)
III	93(18%)
IV	218(41%)
IPI(%)	
low	162(31%)
low-int	128(24%)
high-int	117(22%)
high	123(23%)
NCCN-IPI(%)	
low	49(9%)
low-int	250(48%)
high-int	224(42%)
high	7(1%)

PS: performance status.
LDH: lactate dehydrogenase.
BM: bone marrow.

significance was defined as $P < 0.05$, and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 2.13.0 (The R Foundation). Specifically, EZR is a modified version of R Commander (version 1.6–3) that adds statistical functions frequently used in biostatistics [21].

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Boards of Kansai Medical University.

3. Results

3.1. Patient characteristics

The clinical characteristics of the 530 patients (median age, 69 years; range, 20–98 years; 59% male) included in this study are shown in Table 1. A performance status (PS) of >3 was observed in 2% of patients, elevated lactate dehydrogenase (LDH) levels occurred in 54%, and B symptoms were detected in 15%. Bulky tumors were noted in 7% of patients, bone marrow involvement occurred in 10%, and extranodal sites ≥ 2 were observed in 55%. Tumor stage I was seen in 23% of patients, stage II in 18%, stage III in 18%, and stage IV in 41%. The IPI classified 31% of patients as being at low risk, 24% as low-intermediate (LI), 22% as high-intermediate (HI), and 23% as high risk. In comparison, the NCCN-IPI classified 9% of patients as being at low risk, 48% as LI, 42% as HI, and 1% as high risk. The median follow-up period was 35.8 months (range, 0.2–158.5 months).

The median NLR was 3.3 (IQR, 2.0–5.2); based on the IQR, patients were divided in four categories (category 1, 0–1.9; category 2, 2.0–3.1; category 3, 3.2–5.1; category 4, 5.2 or higher). Patients with a NLR of 5.2 or higher were more likely to have a positive correlation with poor outcome (data not shown).

3.2. Survival according to NLR

The median OS of the patients with an NLR of ≤5.2 was 152.9 months, whereas, an NLR of >5.2 was not reached ($P = 0.066$) (Fig. 1a). The median PFS of the patients with an NLR of ≤5.2 was 75.2 months, whereas, an NLR of >5.2 was 59.4 months ($P = 0.088$) (Fig. 1b).

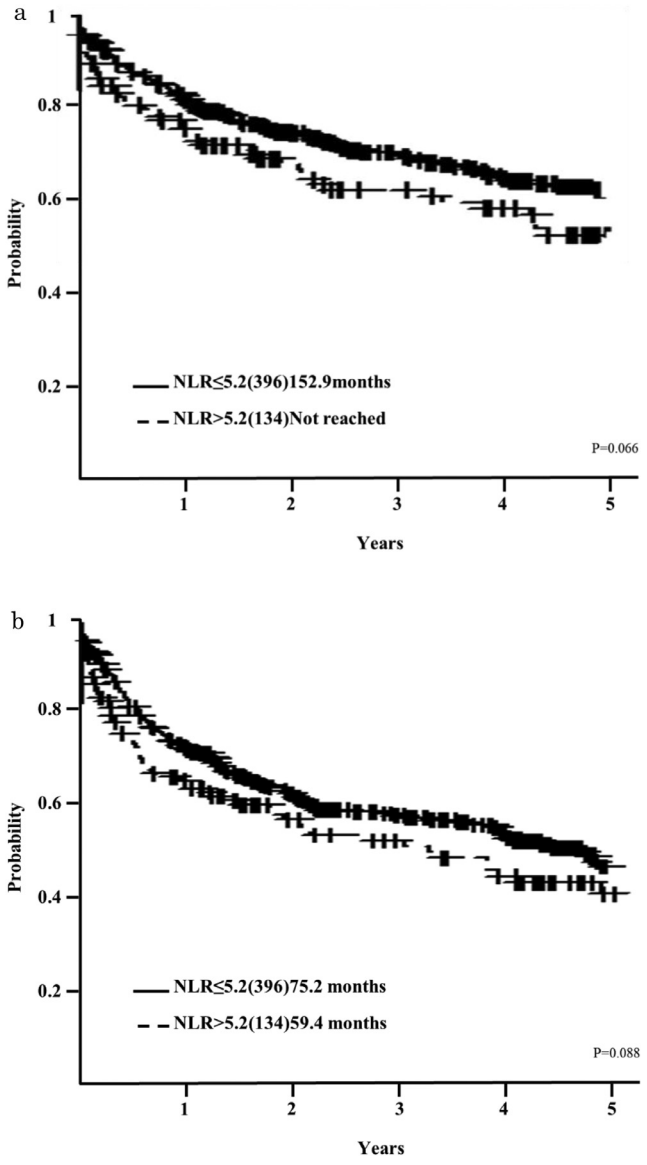

Fig. 1. Survival according to NLR. (a) Overall survival. (b) Progression free survival.

3.3. Prognostic factors

Univariate analysis was performed to identify risk factors associated with survival. Age over 70 years, male sex, PS ≥3, stage ≥3, elevated LDH, presence of B symptoms, extranodal sites ≥2, and NLR ≤5.2 were analyzed (Table 2). Age, PS ≥3, stage ≥3, and elevated LDH remained as significant factors affecting survival in multivariate analysis, whereas other factors were eliminated by backward stepwise selection.

4. Discussion

Previous reports have suggested that NLR is associated with worse survival in DLBCL [11–20]. A meta-analysis that combined nine studies including over 2000 patients was recently published [19]. The results showed that NLR was correlated with poor OS as well as worse PFS. In the study, seven studies were from Asian countries except Japan. Thus,

Table 2
Univariate and multivariate analysis.

Variables	Hazard ratio	95%CI	*p*
Univariate analysis			
Age ≥ 70	1.63	1.19 – 2.25	0.002
Male	1.15	0.83 – 1.59	0.405
PS ≥ 3	12.9	7.01 – 23.74	2.22E – 16
stage ≥ 3	2.11	1.48 – 3.01	3.58E – 05
elevated LDH	2.07	1.48 – 2.89	2.00E – 05
B symptoms	1.98	1.35 – 2.91	5.21E – 04
extranodal sites ≥ 2	1.88	1.34 – 2.62	2.28E – 04
NLR ≤ 5.2	1.38	0.98–1.94	6.73E – 02
Multivariate analysis			
Age ≥ 70	1.49	1.07–2.07	1.74E – 02
PS ≥ 3	8.22	4.36–15.47	6.90E – 11
stage ≥ 3	1.73	1.20–2.50	3.63E – 03
elevated LDH	1.74	1.24–2.46	1.57E – 03

PS: performance status.
LDH: lactate dehydrogenase.
NLR: neutrophil-to-lymphocyte ratio.

the true value of NLR in Japanese DLBCL patients is not clear.

Our study failed to reveal statistical differences in both OS and PFS. However, patients with an NLR of ≤5.2 tended to show a better prognosis for both OS and PFS. We assumed the cut-off value might affect the results. In previous studies, cut-offs were uniform and separated in each study, but the methods cut-off selection remained unclear. Thus, we needed to verify the adaptive cut-off value by prospective studies.

NLR is an easy-to-measure tool but the precise mechanism that explains the poor prognosis of cancer patients who have high blood NLRs has not been clearly elucidated.

Lymphocytes have a crucial role in innate cellular immunity and are important in destroying residual malignant cells [22]. It is widely believed that tumor-infiltrating lymphocytes (TILs) are associated with better clinical outcomes in cancer [23]. On the contrary, neutrophils might reflect the presence of tumor-associated macrophages and circulating monocytes, which contribute to host antitumor immunity and promote tumor angiogenesis [24,25]. From our hypothesis, NLR might be a good index that reflects the balance between inflammation and immunoreaction in cancer. However, lymphoma is a cancer of lymphocytes whereupon host innate immunity has been destroyed, and TIL number might be decreased in lymphoma patients. Thus, we assumed that it might be difficult for NLR to reflect the outcome of lymphoid malignancies.

Although we tried to identify another predictive scale besides the NCCN-IPI, our study revealed that the NCCN-IPI has the most powerful predictive value. In multivariate analysis, age, PS ≥3, stage ≥3, and elevated LDH, which are included in the NCCN-IPI, remained as significant factors affecting survival.

This study had some limitations, including its retrospective design and the inclusion of only two study sites. Furthermore, no genetic analysis using techniques such as fluorescence in situ hybridization (FISH) and immunostaining was performed. Genetic analysis is carried out in clinical settings, and its relevance to prognosis has been established. However, FISH is not covered by insurance in Japan, and there are disparities in the immunostaining results between facilities. Thus, these evaluations are not routinely performed in clinical practice in Japan. As we described above, the cut-off value of NLR is unknown. In this study, we use the IQR obtained in a prior cohort study [20]. However, the methods of selecting NLR cutoffs remain unclear.

In conclusion, we failed to demonstrate the predictive value of NLR and revealed that the NCCN-IPI might be the most powerful predictor of DLBCL following rituximab treatment. A prospective study is required to evaluate NLR in lymphoid malignancies.

CRediT authorship contribution statement

Yoshiko Azuma: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Aya Nakaya:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Shinya Fujita:** Conceptualization, Data curation, Formal analysis. **Atsushi Satake:** Conceptualization, Data curation, Formal analysis. **Takahisa Nakanishi:** Conceptualization, Data curation, Formal analysis. **Yukie Tsubokura:** Conceptualization, Data curation, Formal analysis. **Ryo Saito:** Conceptualization, Data curation, Formal analysis. **Akiko Konishi:** Conceptualization, Data curation, Formal analysis. **Masaaki Hotta:** Conceptualization, Data curation, Formal analysis. **Hideaki Yoshimura:** Conceptualization, Data curation, Formal analysis. **Kazuyoshi Ishii:** Conceptualization, Data curation, Formal analysis. **Tomoki Ito:** Conceptualization, Data curation, Formal analysis. **Shosaku Nomura:** Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare no competing financial interest in relation to the work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2019.100173.

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