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Original Article

Prognostic predictors of newly diagnosed Diffuse large B-cell lymphoma treated with R-THP-COP regimen

Yoshiaki Okano, Tatsuo Oyake, Sawako Kitamura, Kazuya Asano, Tsuyoshi Sato, Takahiro Maeta, Shinri Miyajima, Akihiro Otsu, Maki Nishiya, Ryousei Sasaki, Shugo Kowata, Yoji Ishida, Shigeki Ito

The prognostic value of models such as the international prognostic index (IPI) in patients with malignant lymphomas treated with a combination of rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisolone is well established. However, whether these prognostic models apply to patients treated with a combination of tetrahydropyranyl adriamycin, rituximab, cyclophosphamide, vincristine, and prednisolone (R-THP-COP) is unclear. This retrospective analysis included 101 patients with Diffuse large B-cell lymphoma (DLBCL) treated with R-THP-COP. The primary endpoint was overall survival (OS). The secondary endpoints were progression-free survival (PFS), complete response rate (CRR), and effectiveness of risk prediction in the IPI, revised international prognostic index (R-IPI), and National Comprehensive Cancer Network (NCCN)-IPI groups. OS and PFS at 5 years were 67% and 58.9%. CRR was 63.5%. The IPI, R-IPI, and NCCN-IPI predicted the outcomes of patients treated with R-THP-COP. According to the NCCN-IPI, OS and PFS could distinguish four risk groups. In conclusion, the NCCN-IPI is the most effective prognostic tool for identifying patients with poor prognosis, even those treated with R-THP-COP.

Keywords: pirarubicin, National Comprehensive Cancer Network-IPI, revised international prognostic index, international prognostic index, Diffuse large B-cell lymphoma

INTRODUCTION

Rituximab combined with doxorubicin (DOX), cyclophosphamide, vincristine, and prednisolone (R-CHOP) is the standard first-line treatment for Diffuse large B-cell lymphoma (DLBCL).[1] Tetrahydropyranyl adriamycin (pirarubicin, THP), less cardiotoxic than other anthracyclines, was developed for cancer patients and approved for treating lymphoma in Japan. Several studies have shown that THP-COP or R-THP-COP, in which DOX is replaced with THP, is a useful alternative regimen for minimizing the cardiac toxicity of DOX, especially in elderly patients.[2–10]

Although rituximab combined with anthracycline-containing regimens leads to a cure in over 60% of patients with DLBCL,[11] 30–40% of patients with DLBCL exhibiting primary refractory or relapsed disease are hardly salvaged, even with aggressive chemotherapy regimens and autologous stem-cell transplantation.[12] These patients urgently need more effective therapeutic options early in their disease course. Recently, autologous anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy[13] and a polatuzumab vedotin-containing regimen[14] have been highly effective as first-line therapies for high-risk patients with DLBCL. In line with the development of new agents for DLBCL, the prevention of treatment-related side effects of anthracyclines is becoming increasingly important. Long-term and irreversible cardiac toxicity due to anthracycline may frustrate patient outcomes and seriously limit therapeutic opportunities. In addition, cardiac toxicity is often undiagnosed in patients receiving first-line R-CHOP therapy. Thus, in the early phase of first-line treatment, it is critical to strictly identify patients for whom anthracycline-containing regimens are insufficient and to change early to alternative treatments, leading to better outcomes.

The prognosis of DLBCL has been predicted using the international prognostic index (IPI) in the pre-rituximab era[15] and the revised international prognostic index (R-IPI) in the rituximab era.[16] However, even in the R-IPI, the 4-year over-

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Division of Hematology and Oncology, Department of Internal Medicine, Iwate Medical University School of Medicine, Yahaba, Iwate, Japan
Corresponding author: Yoshiaki Okano, Hematology and Oncology, Department of Internal Medicine, School of Medicine, Iwate Medical University, 2-1-1 Idaidori, Yahaba-cho, Shiwa-gun, Iwate Prefecture, Japan. E-mail: yokano @iwate-med.ac.jp

all survival (OS) of patients in the high-risk group was 55%, and patients expected to have a poor prognosis were not distinguished. The enhanced National Comprehensive Cancer Network (NCCN)-IPI differs from the IPI by stratifying age and lactate dehydrogenase levels and recognizing the risk associated with particular extranodal sites of involvement.[11] The 5-year OS of NCCN-IPI-defined high-risk patients was 33 to 38% in cohorts, suggesting an improved selection of high-risk groups compared to the IPI.[17] However, because these prognostic factors have been analyzed in the cohort mainly treated with the CHOP or R-CHOP regimen, it is uncertain whether the IPI can be used as a prognostic tool for patients treated with the R-THP-COP regimen. This study retrospectively examined the efficacy and prognostic predictors of R-THP-COP in 101 patients with DLBCL treated at the Iwate Medical University Hospital.

PATIENTS AND METHODS

Study design

The primary endpoint was overall survival (OS) in patients with DLBCL treated with the R-THP-COP regimen, and the secondary endpoints were progression-free survival (PFS) and complete response rate (CRR). In addition, we compared the effectiveness of risk prediction between the R-IPI and NCCN-IPI, particularly in identifying high-risk patients.

This study was a retrospective analysis of an unselected population of patients with DLBCL treated with R-THP-COP at Iwate Medical University Hospital between January 2011 and December 2018. Eligible patients were 18 years of age or older. All patients were newly diagnosed with CD20-positive DLBCL based on the pathological findings of biopsy specimens. We excluded HIV-positive patients with evidence of a secondary malignancy, an underlying indolent lymphoproliferative disorder, or a major coincident illness that precluded an attempt to cure the lymphoma. This study was approved by the Ethics Committee of Iwate Medical University Hospital (MH2020-028).

Staging included clinical examination, computed tomography (CT), fluorodeoxyglucose positron emission tomography (FDG-PET), bone marrow biopsy, and lumbar puncture. Cardiac function was evaluated using echocardiography before chemotherapy initiation. The patient response to treatment and the incidence of relapse were defined according to the International Workshop criteria for non-Hodgkin's lymphoma.[18] Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Toxicity Criteria ver.4.0. Following the completion of chemotherapy and confirmation of CR achievement, patients were evaluated periodically to monitor their disease status according to the NCCN guidelines.[18] The doses of the chemotherapeutic agents were adjusted according to the patient's age. Patients under 69 years received 3–8 cycles every 21 days of R-THP-COP (375 mg/m^2 rituximab on day 1, 50mg/m^2 pirarubicin on day 1, 750 mg/m^2 cyclophosphamide on day 1, 1.4 mg/m^2 vincristine on day 1, and 100 mg prednisolone on day 1–5). Patients aged 70–79 years received dose-reducing R-THP-COP (375 mg/m^2 rituximab on day 1, 40 mg/m^2 pirarubicin on day 1, 650 mg/m^2 cyclophosphamide on day 1, 1.0 mg/m^2 vincristine on day 1, and 100 mg prednisolone on day 1–5). Patients aged > 80 received dose-reducing R-THP-COP (375 mg/m^2 rituximab on day 1, 30 mg/m^2 pirarubicin on day 1, 400 mg/m^2 cyclophosphamide on day 1, 1.0 mg/m^2 vincristine on day 1, and 100 mg prednisolone on day 1–5). Granulocyte colony-stimulating factors were administered at the discretion of each physician.

STATISTICAL ANALYSIS

OS was calculated from the date of diagnosis until death due to any cause or last follow-up. PFS was calculated from the date of diagnosis to the date of disease progression or death. OS and PFS were estimated using the Kaplan-Meier method, and differences were compared using a log-rank test. Graph generation and statistical analyses were performed using EZR software.[19] Statistical significance was set at $P < 0.05$ significant.

RESULTS

Patients

In total, 101 patients were enrolled in this study. Patient characteristics at diagnosis are listed in Table 1. The median age was 64 years (range 19–86 years), and approximately 78.2% of the patients had advanced-stage disease (stage III or IV). According to the WHO classification system, 101 patients (100%) had DLBCL. According to the International Prognostic Index (IPI),[15] 27 (26.7%) patients had low risk, 15 (14.9%) patients had low-intermediate risk, 21 (20.8%) patients had high-intermediate risk, and 38 (37.6%) patients had high risk[15]. Additionally, the revised IPI, 7 (6.9%) patients had very good risk, 34 (33.7%) patients had good risk, and 60 (59.4%) patients had poor risk. According to the NCCN-IPI, 7 (6.9%) patients had low risk, 32 (31.6%) patients had low intermediate risk, 33 (32.8%) patients had high intermediate risk, and 29 (28.7%) patients had high risk. Ninety patients (89.1%) had good PS (grade 0–2), and 11 patients (10.9%) had poor PS (grade 3–4).

Efficacy and survival according to risk stratification

The OS at 5 years was 67% (Fig. 1A), the PFS at 5 years was 58.9% (Fig. 1B), and the CRR was 63.5% (Table 2). The OS and PFS according to IPI are shown in Figs. 1C and 1D. The relative dose intensity (RDI) was 86%. The IPI could stratify the survival curve into only two groups, with the 5-year OS ranging from 40.4% to 91.7% ($P < 0.001$) and the 5-year PFS ranging from 36.0% to 83.3% ($P < 0.001$). The survival curves for the low- and low-intermediate risk and high- and high-intermediate risk groups were similar. Outcomes according to R-IPI are shown in Figs. 1E and 1F. The R-IPI could separate the three prognostic groups with 5-year OS ranging from 45.7% to 100% ($P < 0.001$) and

Table 1. Patient Characteristics

		No. of patient	%
Total No.		101	
Age (years)	Median	64 (19–86)	
Sex	Male/Female	49/52	48.5/51.5
PS (ECOG)	0/1/2/3/4	45/35/10/6/5	44.6/34.6/9.9/5.9/5
Clinical Stage (Ann Arbor)	I/II/III/IV	9/13/8/71	8.9/12.9/7.9/70.3
B symptoms		34	33.7
Extranodal involvement	≤ 1	54	53.5
	≥ 2	47	46.5
Site of extranodal involvement	Bone marrow	25	24.7
	Liver	12	11.8
	Gastrointestinal tract	24	23.7
	Lung	5	5
	Central nervous system	6	5.9
	Other extranodal site	19	18.8
LDH	Normal	37	36.6
	> ULN - 2×ULN	35	34.7
	> 2 - 3×ULN	9	8.9
	> 3×ULN	20	19.8
Histology (WHO classification)			
DLBCL		101	100
IPI			
Low		27	26.7
Low-intermediate		15	14.9
High-intermediate		21	20.8
High		38	37.6
R-IPI			
very good		7	6.9
good		34	33.7
poor		60	59.4
NCCN-IPI			
Low		7	6.9
Low-intermediate		32	31.6
High-intermediate		33	32.8
High		29	28.7
Auto-SCT		15	14.7
Relapse		4	3.9
Refractory		2	1.9
Up front		9	8.9

PS: performance status, IPI: international prognostic index, R-IPI: revised IPI, LDH: lactate dehydrogenase, DLBCL: diffuse large B cell lymphoma, Auto-SCT: autologous hematopoietic stem cell transplantation, ULN: upper limit of normal

5-year PFS ranging from 40.6% to 100% ($P < 0.001$). The estimated 5-year OS of patients classified as high risk according to the IPI and R-IPI was 40.4% and 45.7%, respectively, suggesting that the IPI and R-IPI are limited in selecting patients expected to have poor outcomes. In contrast, OS and PFS, according to the NCCN-IPI, could distinguish four risk groups, with 3-year OS ranging from 30.3% to 100% ($P < 0.001$) and 3-year PFS ranging from 20.6% to 100% ($P < 0.001$) (Figs. 1G, 1H). The 3-year OS of patients stratified as high risk according to the NCCN-IPI was 30.3%. These results indicate that the NCCN-IPI is the most effective prognostic tool and is excellent for identifying poor prognosis groups. The efficacy of the R-THP-COP regimen in this study was inferior to that previously reported.[7,8] This was because more patients with high-risk and poor conditions were included in our study than in previous reports.

TOXICITIES

The adverse events (AEs) observed are listed in Table 3. The rates of hematological toxicity with grade 3 or 4 neutropenia, anemia, and thrombocytopenia were 83.3%, 31.6%, and 17.7%, respectively. G-CSF was administered to almost all the patients. Grade 2–4 non-hematologic AEs occurred at the following rates: febrile neutropenia (31.6%), sepsis (3.9%), pneumonia (4.8%), and diarrhea (5.8%). Electrocardiogram (ECG) was monitored in every course; no patient showed abnormal changes, and no cardiac events, including arrhythmia, cardiac failure, or ischemic heart disease, were observed during every course of treatment.

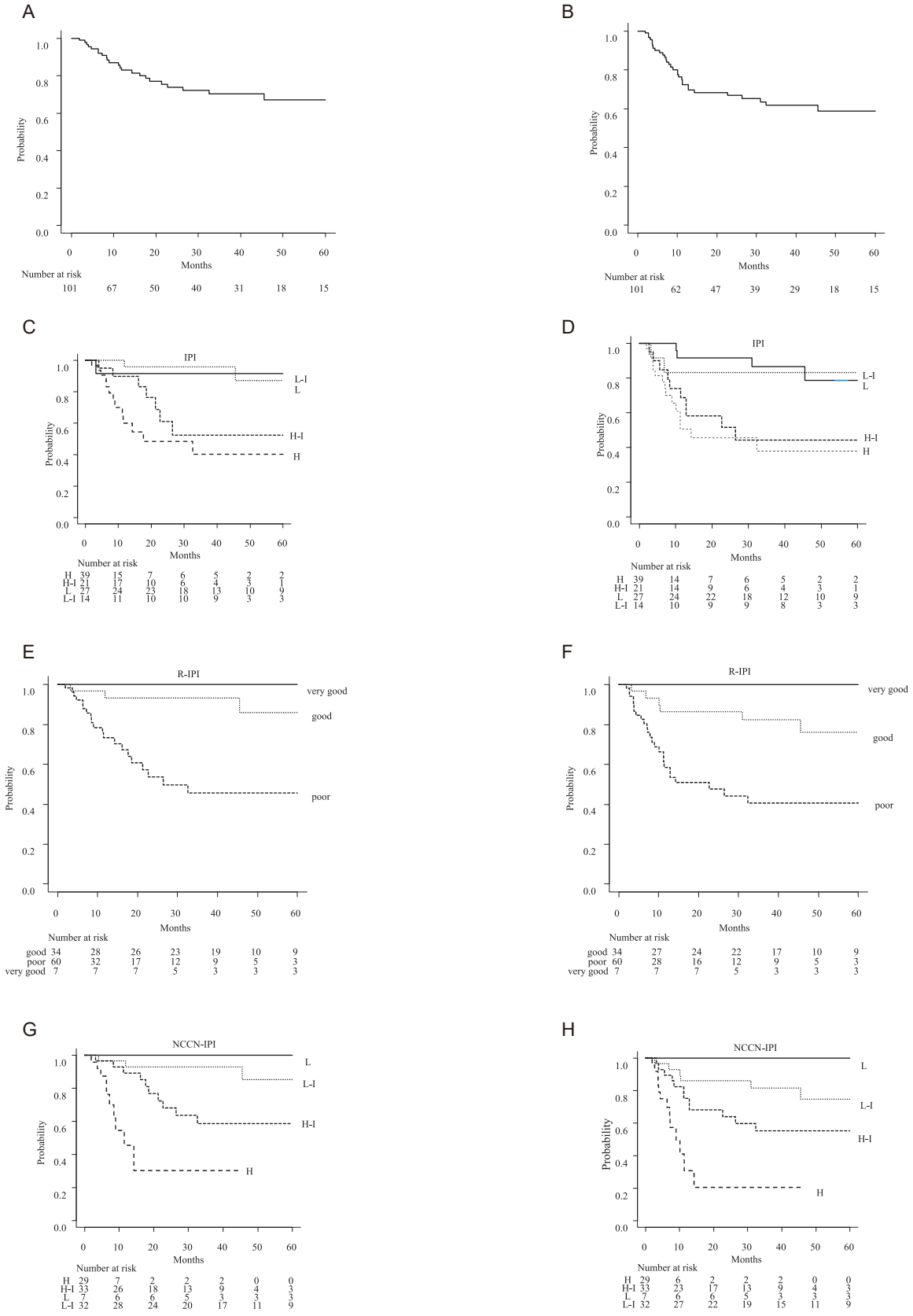

Fig. 1. (***A***) The overall survival (OS) curve. (***B***) The progression-free survival (PFS) curve. OS (***C***) and PFS (***D***) of patients assigned to IPI. OS (***E***) and PFS (***F***) of patients assigned to R-IPI. OS (***G***) and PFS (***H***) of patients assigned to NCCN-IPI.
L: Low, L-I: Low-intermediate, H: High, H-I: High-intermediate
OS was calculated from the day of the diagnosis until death or last follow up. PFS was calculated from the day of the diagnosis until disease progression or death. The survival durations were estimated by the Kaplan-Meier method.

Table 2. Response rate

	No (N = 101)	(%)
Complete response (CR)	64	63.5
Complete response/unconfirmed (CRu)	8	7.9
Partial response (PR)	13	12.9
Stable disease (SD)	5	4.9
Progressive disease (PD)	11	10.8

Complete response: CR, Complete response/unconfirmed: CRu, Partial response: PR, Stable disease: SD, Progressive disease

Table 3. Adverse event

	R-THP-COP (N = 101)				
	No (%)				
	All grade	gradeI	gradeII	gradeIII	gradeIV
Hematological					
Neutropenia	93 (92.1)	0 (0)	9 (8.8)	21 (20.6)	63 (62.7)
Anemia	98 (97.0)	33 (32.7)	33 (32.7)	32 (31.6)	0 (0)
Thrombocytopenia	86 (85.2)	57 (56.7)	11 (10.8)	11 (10.8)	7 (6.9)
Non-hematological					
Cre	20 (19.6)	15 (14.7)	3 (2.9)	0 (0)	2 (1.9)
ALT	63 (62.3)	33 (32.7)	17 (16.9)	12 (11.8)	1 (0.9)
AST	38 (37.6)	27 (26.9)	8 (7.9)	2 (1.9)	1 (0.9)
Bil	15 (14.7)	6 (5.9)	8 (7.9)	1 (0.9)	0 (0)
Alb	98 (97)	57 (56.4)	34 (33.7)	7 (6.9)	0 (0)
Fbg	73 (72.3)	25 (24.7)	36 (35.7)	12 (11.9)	0 (0)
AMY	17 (16.6)	11 (10.8)	1 (0.9)	5 (4.9)	0 (0)
infusion reaction	10 (9.8)	0 (0)	9 (8.9)	1 (0.9)	0 (0)
Febrile neutropenia	32 (31.6)			32 (31.6)	0 (0)
Sepsis	4 (3.9)			3 (3.0)	1 (0.9)
Catheter infection	4 (3.9)		0 (0)	4 (3.9)	0 (0)
Pneumonia	5 (4.8)		0 (0)	4 (3.9)	1 (0.9)
Hyperkalemia	3 (2.9)	3 (2.9)	0 (0)	0 (0)	0 (0)
Intracranial hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fever	34 (33.6)	22 (21.8)	7 (6.9)	5 (4.9)	0 (0)
Oral mucositis	6 (5.8)	1 (0.9)	5 (4.9)	0 (0)	0 (0)
Diarrhea	19 (18.7)	13 (12.9)	3 (2.9)	3 (2.9)	0 (0)

Cre: Creatinine, ALT: Alanine transaminase, AST: Aspartate transaminase, Bil: Bilirubin
Alb: Albumin, Fbg: Fibrinogen, AMY: Amylase

DISCUSSION

This retrospective study showed a CRR of 63.5%, 5y-OS of 67%, and PFS of 58.9%. Our results indicate that the IPI, R-IPI, and NCCN-IPI predict the outcomes of patients treated with R-THP-COP.

Hara *et al.* compared the therapeutic outcomes of R-THP-COP and R-CHOP in patients younger than 70 with DLBCL (median age, 60 years range 27–71). The CRR of the R-THP-COP regimen was 85%, and the 5-year OS and 5-year PFS were 82% and 79%, respectively.[8] Araie *et al.* also compared the therapeutic outcomes of R-THP-COP and R-CHOP in elderly patients with DLBCL (median age, 77 years range 68–88). The CRR for the R-THP-COP regimen was 79.3%, and the 2-year OS and 2-year PFS were 77.6% and 68.5%, respectively.[5] The efficacy of our study was inferior to that of previous studies. This may be due to the inclusion of more high-risk patients with poor health conditions in this study.

The IPI, R-IPI, and NCCN-IPI predicted the prognosis of patients treated with R-CHOP. Zhou *et al.* reported that the NCCN-IPI is a prognostic factor, with age and serum LDH subdivided and external nodal sites (bone marrow, CNS, liver/gastrointestinal tract, and lungs) added as predictors.[17] Therefore, the NCCN-IPI discriminated between the low- and high-risk subgroups better than the IPI. To our knowledge, no studies have assessed the prognosis of patients treated with R-THP-COP by NCCN-IPI. Our results showed that the patient's prognosis with the R-THP-COP regimen was stratified according to several outcome predictors applied in

R-CHOP, especially in NCCN-IPI.

Based on the results of this study, we believe that the R-THP-COP regimen may be indicated for patients with low or low-intermediate NCCN-IPI, especially the elderly. In contrast, the R-THP-COP regimen may not be indicated for patients with high-risk NCCN-IPI scores. Japanese guidelines recommend that such patients should be treated with regimens including a novel agent, Pola-R-CHP. As part of our analysis, we also evaluated cardiac function. The six patients who underwent echocardiography before and after treatment did not show a decline in cardiac function. However, due to the small sample size, this result was not included in this paper. The limitations of this study are its retrospective design and small sample size. In conclusion, the prognosis of patients with newly diagnosed DLBCL treated with R-THP-COP can be predicted using the IPI, R-IPI, and NCCN-IPI, like that with R-CHOP. The NCCN-IPI was the best predictor of outcomes. Therefore, prospective studies are required to confirm this conclusion.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

YO conducted the study, analyzed the data, and wrote the manuscript. TO, SK, KA, TS, TM, KK, SM, AO, MN, RS, SK, YI, and SI conducted the study and edited the manuscript.

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