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ORIGINAL RESEARCH

The Effect of C-Reactive Protein/Lymphocyte Ratio (CLR) on PFS in Metastatic Breast Cancer Patients Treated with CDK4/6 Inhibitors: A Novel Biomarker

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Objective: Hormone positive breast cancer is a tumor with high mortality. Combining antihormonal therapy with cyclin dependent kinase 4/6 inhibitors (CDK4/6i) has resulted in longer survival. The effect of inflammatory parameters such as c-reactive protein and c-reactive protein/lymphocyte ratio (CLR) on efficacy and survival in CDK4/6i treatment is unknown. In our study, we aimed to investigate the role of CLR and some parameters in predicting progression-free survival (PFS) with CDK4/6i.

Methods: This retrospective cohort study included 78 patients with denovo and recurrent metastatic breast cancer treated with CDK4/6i. Cut off values for the prediction of mortality by various numerical parameter scores were performed by ROC Curve analysis. The effect of clinical variables, inflammatory and histopathological parameters on survival was analyzed by Kaplan–Meier method.

Results: Neutrophil/lymphocyte ratio (NLR) and CLR were statistically significant in predicting mortality ($p < 0.05$). Ki67 and CLR were correlated with PFS. Age and CLR were correlated with OS ($p < 0.05$). CLR was statistically significant for both PFS ($p = 0.022$) and OS ($p = 0.006$).

Conclusion: In patients with metastatic hormone-positive breast cancer using CDK4/6i, low CLR and low Ki67 were correlated with longer PFS duration.

Keywords: C-reactivated protein/lymphocyte ratio, hormone-positive breast cancer, progression-free survival

Introduction

Breast cancer is the most common cancer in women worldwide and is one of the leading causes of cancer mortality.[1] While the median age of breast cancer in Western countries is 60–70 years, the median peak age in Asian countries is 45–50 years. Hormone positive breast cancer is the most common type with a rate of 66–75%.[2–5] In the hormone positive HER2 negative group, anti-hormonal therapy is used as adjuvant in the early period. Approximately 25% of patients show recurrence due to endocrine resistance and progress to metastatic stage.[6–9] Recent studies have shown that cyclin-dependent kinase inhibitor treatment (CDK4/6i) is effective in breast cancer that develops endocrine resistance.[10]

CDK4/6i block the cell cycle by reducing retinoblastoma phosphorylation. They prevent the transition from G1 phase to S phase. When administered concomitantly with endocrine therapy, prolongation of disease-free survival, prolongation of overall survival (OS) and better clinical benefit have been found superior to endocrine therapy alone. Endocrine therapy with CDK4/6i in metastatic hormone positive breast cancer has become a standard treatment.[11,12]

In the treatment of metastatic breast cancer, drug selection may vary depending on factors, such as the patients age, comorbidities and visceral crisis status. The clinical benefit of using CDK4/6i in earlier series has been shown.[13]

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However, some side effects and financial burden may affect the clinicians choice. Personalized treatment of metastatic hormone-positive breast cancer does not achieve the same response from the same treatment. Although CDK4/6i treatment is effective, there is generally no chance of cure and resistance to these drugs develops after a while and patients progress.[14] Some factors such as retinoblastoma deficiency and cyclin E expression have been accused in intrinsic resistance to CDK4/6i.[15] Therefore, factors predicting the efficacy of CDK4/6i therapy are important.

In breast cancer, young age is considered to be risky, and the disease may have a more aggressive course. Age may be a reason for differences in tumor biology and molecular structure of the tumor.[16]

Neutrophils are involved in tumor-related inflammation and suppress lymphocyte functions and cause tumor progression.[17,18] Lymphocytes play an important role in antitumor immune response. Lymphocyte count has been found to be related with some treatment responses and overall survival.[19,20]

C-reactive protein (CRP) is an inflammatory marker secreted from the liver in response to cytokines released by the inflammatory response in the tumor microenvironment. Inflammation plays an important role in tumorigenesis, tumor invasion, metastasis and angiogenesis. CRP has been shown to be prognostic in some cancers.[21]

Ki67 is a proliferation marker used in the evaluation of luminal A and luminal B breast cancer. Its relation with prognosis has been shown in many tumors. It is also an important marker in hormone positive HER2 negative breast cancer and provides information about tumor aggressiveness and clinical course of the disease.[22]

In this study, we aimed to investigate the efficacy of CDK4/6i in the treatment of patients with hormone positive breast cancer and the effect of clinical and biochemical markers in predicting PFS and OS.

Materials and Methods

Patients and Follow-Up

Between January 2003 and September 2022, 78 hormone positive and HER2 negative patients who were diagnosed at metastatic stage or subsequently metastatic were included in our study from two centres, namely Ankara Etlik City Hospital and Atatürk University Hospital. The follow-up the starting time is the diagnosis date and the deadline is July 16, 2023. PFS is defined as the time from CDK4/6i initiation to the progression or death of metastatic breast cancer. OS is defined as the time from date of diagnosis to deadline follow-up or death. It was decided by 18F-fluorodeoxyglucose-positron emission tomography (PET)/computed tomography (CT) that the patients were denovo metastatic or progression.

Exclusion and Inclusion Criteria

Patients with missing data, HER2 positive, triple negative, other malignancies, chronic inflammatory disease and hematological malignancies were excluded from the study. Patients with denovo metastatic, recurrent metastatic after adjuvant therapy, and patients with progression after hormonal therapy in the metastatic period were included in the study. Patients with an estrogen receptor (ER) positivity rate of 11% and above were included in the study. Patients without active infection were included in the study by starting CDK4/6i treatment.

Data Collection

Demographic data, age, gender, Eastern Cooperative Oncology Group (ECOG) performance scores 0, 1, 2, 3 and 4, smoking status such as smoker and non-smoker, Ki67, degree, bone, liver, lung metastasis areas and multiple metastasis information taken from patient files. Those with diabetes, hypertension, ischemic heart disease were considered to have comorbidity. Leukocyte, neutrophil, lymphocyte, monocyte, hemoglobin, red blood cell distribution width (RDW), red blood cell (RBC), platelet, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), albumin and CRP values were obtained from the hospitals information system. Blood samples of our patients were taken before starting CDK4/6i treatment.

Standardization was achieved by taking blood samples simultaneously for biochemical parameters such as CRP and albumin and hematological parameters such as neutrophils and lymphocytes. Beckman Coulter AU5821 and Roche Cobas 8000 devices were used for biochemical parameters. Sysmex XN-9000 (Kobe, Japan) automatic machine was used for complete blood count. SII formula was calculated as platelet (P) × neutrophil (N)/lymphocyte (L), NLR formula was calculated as the ratio of neutrophil count to lymphocyte count and PNI was calculated as (10× albumin (g/L) + (0.005 ×

total lymphocyte count). Neutrophil, lymphocyte, SII, NLR, CRP/Lymphocyte ratio (CLR) and PNI cutoff values were calculated by ROC curve. Approval was obtained from the ethics committee of Atatürk University Faculty of Medicine (2023/792). The Declaration of Helsinki was complied with during all procedures.

Statistical Analyses

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables and Mean ± SD for continuous variables. The results of ROC Curve analysis of the prediction of mortality by various numerical parameter scores are given. Kaplan Meier method was used to compare OS and PFS durations between various clinical parameter groups. $p < 0.05$ was considered statistically significant.

Results

Table 1 shows the distribution of sociodemographic and clinical characteristics of the patients. Seventy-seven (98.7%) patients were female and 1 (1.3%) patient was male. Forty-seven (60.3%) patients had bone metastases, 1 (1.3%) patient had liver metastases, and 25 (32.1%) patients had multiple metastases. Eighteen (23.1%) patients in the first line, 40 (51.3%) patients had previously received hormonal therapy, and 20 (25.6%) patients had previously received chemotherapy. In Table 2, the estimates of NLR ($p = 0.022$) and CLR ($p = 0.016$) parameters were statistically significant to discriminate the presence of mortality. As shown in Table 3, the overall median OS (months) was 109.86 (95% CI:

Table 1 Sociodemographic and Clinical Data (n = 78)

Variables	N	%
Age		
Mean±SD	50.53±12.64	
≤55 55>	54 24	69.2 30.8
Sex		
Female	77	98.7
Male	1	1.3
Comorbidity		
None Yes	52 26	66.7 33.3
Smoking		
Yes No	63 14	81.8 18.2
Grade		
≤2 2>	45 14	57.7 17.9
Ki67		
≤20	29	52.7
>20	35	47.3

(*Continued*)

Table 1 (Continued).

Variables	N	%
Metastasis site		
Bone	47	60.3
Liver	1	1.3
Lung	5	6.4
Multiple	25	32.1
Which line		
1st line	18	23.1
Prior Hormone Therapy	40	51.3
Adjuvant	23	29.5
Metastatic	17	21.8
Prior Chemotherapy	20	25.6
ER%		
11–50	9	11.5
50>	69	88.5
Progression		
No	21	26.9
Yes	57	73.1
Mortality		
Alive	49	62.8
Ex	29	37.2
Average follow-up time	62.37±43.35	

Table 2 Analysis of the Predictive Values of Various Parameter Values in Differentiating Mortality

Variables	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	p
NLR	0.729	0.564–0.894	≥2.54	61.5	60.0	**0.022**
SII	0.652	0.473–0.832	≥754.25	53.8	56.0	0.128
PNI	0.654	0.481–0.827	≤41.00	57.1	57.7	0.112
CRP/Lymphocyte (CLR)	0.742	0.557–0.926	≥6.04	76.9	72.0	**0.016**

Note: P<0.05 is bolded to indicate statistical significance.
Abbreviations: AUC, Area under the curve; %95CI, Confidence interval; NLR; neutrophil/lymphocyte ratio; SII, systemic inflammatory index; PNI, prognostic nutritional index; CRP, c-reactive protein; CLR, CRP/lymphocyte ratio.

68.34–151.38). Median OS (months) according to age groups was statistically significant (p = 0.008). The median OS (months) in the ≤55 group was 121.63 (95% CI: 95.89–147.37), while the median OS (months) in the >55 group was 53.16 (95% CI: 24.34–81.98). Median OS (months) according to ER % (p = 0.245), Grade (p = 0.769), Ki67 (p = 0.339), NLR (p = 0.448) groups was not statistically significant.

Median OS (months) according to CLR groups was statistically significant (p = 0.006). While median overall survival (months) was inaccessible in the group with CLR value <6.04, median OS (months) was 54.33 (95% CI: 15.07–93.59) in the CLR ≥ 6.04 group.

Person-year survival and death rates are shown in Table 4. At 24. months, 66 (92%) patients and 32 (70%) patients at 60. months were still alive.

Table 3 OS Comparisons of Patients

OS (Months)	2 Years %	5 Years %	Median (%95 CI)	p
OS	94.7	72.6	109.86 (68.34–151.38)	
Age				
≤55 55>	98.1 86.8	82.0 44.8	121.63 (95.89–147.37) 53.16 (24.34–81.98)	**0.008**
Comorbidity				
No Yes	98.1 88.3	79.2 60.2	109.86 (84.45–135.28) 78.13 (36.59–119.67)	0.171
ER%				
11–50 50>	88.9 95.7	77.8 69.2	71.93 (59.98–83.87) 109.86 (77.71–142.01)	0.245
Grade				
≤2 2>	95.6 92.9	69.0 77.1	102.13 (39.60–164.66) 78.13 (52.95–103.31)	0.769
Ki67				
≤20 20>	94.9 94.1	80.1 65.5	102.13 (42.02–162.24) 92.73 (63.09–122.37)	0.339
NLR				
<2.54 ≥2.54	94.6 94.4	75.4 67.1	121.63 (53.46–189.80) 92.73 (61.04–124.42)	0.448
CRP/ lymphocyte (CLR)				
<6.04 ≥6.04	100.0 88.5	77.8 48.0	– (–) 54.33 (15.07–93.59)	**0.006**

Note: P<0.05 is bolded to indicate statistical significance.
Abbreviations: OS, overall survival; ER, estrogen receptor; NLR, neutrophil/lymphocyte ratio; CRP, c-reactive protein; CLR, CRP/lymphocyte ratio.

Table 4 Person-Year Mortality Rates

Months	n Patients	Survival %
0	78	100
12	76	96
24	66	92
36	55	84
48	39	77
60	32	70
72	25	61
84	20	58
96	13	54

(*Continued*)

Table 4 (Continued).

Months	n Patients	Survival %
108	11	46
120	9	41
132	5	29
144	2	29
156	2	29
168	2	29
180	2	29
192	1	29
204	1	29
216	1	29
228	1	29
240	1	29

As seen in Table 5, the overall median PFS (months) was 14.86 (95% CI: 11.66–18.06) (Figure 1A). Median PFS (months) according to Ki67 groups was statistically significant (p = 0.021) (Figure 1B). The median PFS (months) in the Ki67≤20 group was 23.63 (95% CI: 10.85–36.41), while the median PFS (months) in the Ki67 > 20 group was 12.20 (95% CI: 7.79–16.60).

Median PFS (months) according to CLR groups was statistically significant (p = 0.022) (Figure 1C). The median PFS (months) in the <6.04 group was 29.70 (95% CI: 16.88–24.51), while the median PFS (months) in the ≥6.04 group was 8.40 (95% CI: 0.02–16.78).

Table 5 PFS Comparisons of Patients

PFS (Months)	2 Years %	5 Years %	Median (% 95 CI)	p
PFS	30.4	–	14.86 (11.66–18.06)	
Age				
≤55 55>	26.1 40.4	– –	14.50 (11.75–17.24) 15.60 (9.38–21.81)	0.286
Comorbidity				
No Yes	98.1 88.3	79.2 60.2	54.00 (39.69–68.30) 76.63 (34.40–118.86)	0.299
ER%				
11–50 50>	33.3 29.6	– –	13.70 (0.00–38.82) 15.23 (11.42–19.04)	0.770
Grade				
≤2 2>	42.0 12.5	– –	16.00 (8.61–23.90) 14.50 (3.33–25.67)	0.370

(*Continued*)

Table 5 (Continued).

PFS (Months)	2 Years %	5 Years %	Median (% 95 CI)	p
Ki67				
≤20 20>	48.7 13.9	– –	23.63 (10.85–36.41) 12.20 (7.79–16.60)	**0.021**
NLR				
<2.54 ≥2.54	35.8 25.6	– –	17.26 (7.89–26.63) 14.86 (12.80–16.93)	0.701
CRP/ lymphocyte (CLR)				
<6.04 ≥6.04	31.6 20.0	– –	29.70 (16.88–24.51) 8.40 (0.02–16.78)	**0.022**

Note: P<0.05 is bolded to indicate statistical significance.
Abbreviations: PFS, progression free survival; ER, estrogen receptor; NLR, neutrophil/ lymphocyte ratio; CRP, c-reactive protein; CLR, CRP/lymphocyte ratio.

Median PFS (months) according to age (p = 0.286), ER % (p = 0.770), Grade (p = 370), NLR (p = 0.701) groups were not statistically significant.

Discussion

In hormone-positive metastatic breast cancer, the addition of CDK4/6i to endocrine therapy has shown survival benefit.[23] Age, menopausal status, ethnicity and many other factors have been investigated in predicting the activity of CDK4/6i.

Age is an important parameter in breast cancer and studies have shown that younger patients may have a more aggressive tumor biology.[24] There are many factors besides age that affect tumor biology. Age was not found to be significant in PFS in our study. In the study conducted by Shikanai et al, age was not found to be significant in PFS in the use of CDK4/6i similarly our study.[11] OS was found to be longer in the group aged 55 years and younger in our study. The difference in OS caused by age may be due to factors in tumor biology, stage, grade, Ki67, lymph node involvement, patient performance and treatment differences.

It is known that comorbidity reduces the tolerability of cancer treatment, increases the incidence of side effects and causes a decrease in survival.[25] In Wadasadawala et al study, the presence of multiple comorbidity was found to be

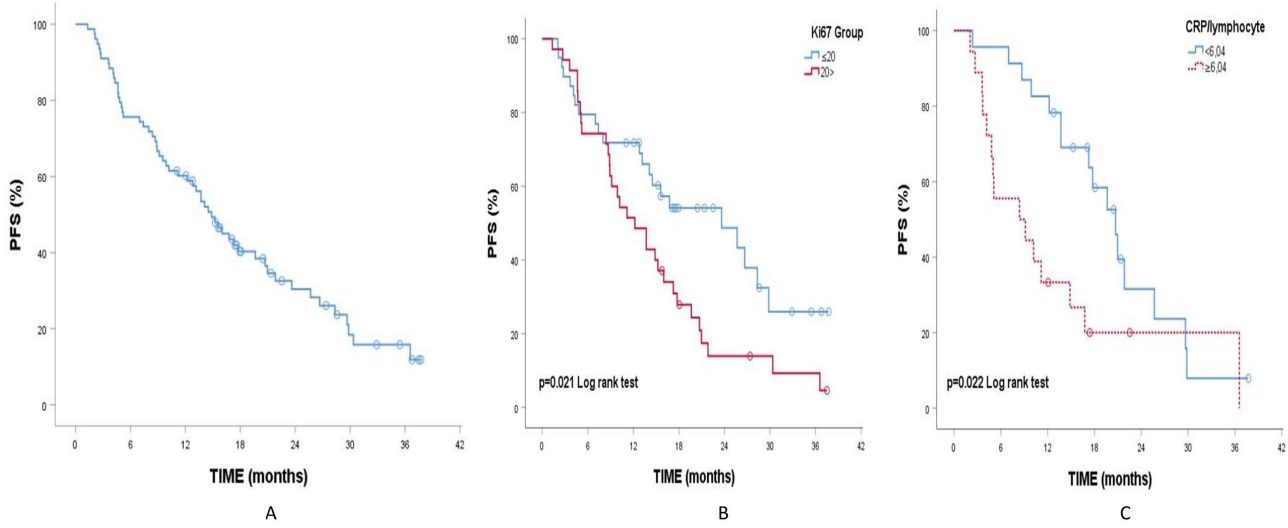

Figure 1 PFS time treatment with CDK4/6i (**A**), Ki67 ve PFS time (**B**), CLR ve PFS time (**C**).

associated with shorter PFS and OS in patients treated for breast cancer.[26] In our study, the effect of comorbidity on PFS and OS was not statistically significant. This may be due to our small number of patients.

In hormone-positive breast cancer, better PFS times are achieved as the ER positivity rate increases.[27] In our study, ER positivity was not found to be significant in PFS. ER positivity was found to be statistically significant for PFS in the study by Müller et al. As ER positivity increased (71–100%), longer PFS was obtained with CDK4/6i+endocrine therapy unlike our study.[28] This may be due to the use of different threshold values for ER positivity. In our study, ER positivity was classified as 11–50% and 51–100%, while Müller et al classified it as 11–70% and 71–100%.

Tumor grade provides information about the biology and clinical course of the tumor and has been found to be correlated with PFS and OS in many studies. In our study, grade was not found to be significant for PFS and OS. In Mason et al study with 4415 patients tumor grade was found to be predictive for both PFS and OS.[29] This may be due to the small sample size of our patients.

Ki67 is helpful and guiding for clinicians in many prognostic classifications including luminal A and luminal B in hormone positive breast cancer and tumor biology. Ki67 was found to be prognostic for PFS in our study. Palleschi et al found Ki67 proliferation index prognostic for PFS in their study. As Ki67 increases, PFS is negatively affected similarly our study.[22] Ki67 values ≤20% and >20% were taken as basis in our study. Different threshold values have also been used in the literature. In the study conducted by Shikanai et al based on 33% value, Ki67 was found to be prognostic.[11] In the PALOMA-2 and MONALEESA-2 studies, PFS was 27.6 and 25.3 months, respectively. In our study, PFS was 23.6 months in the group with Ki67 ≤20% and was similar to the literature. PFS was lower with 12.2 months in the group with Ki67 >20%.[30] In our study, there was no distinction between denovo metastatic and recurrent metastatic, but there was a distinction between chemotherapy, hormonotherapy and firstline treatment before CDK4/6i treatment and there was no difference in PFS and OS between these groups. There was no patient treated with abemaciclib. No distinction was made between our patients treated with ribociclib and palbociclib. While previous studies mostly investigated denovo metastatic CDK4/6i firstline treatment, our study includes real life data with a more heterogeneous group.

The role of inflammation in tumorigenesis is well known. Chronic inflammation may affect the development of many malignancies such as pancreatic cancer, as well as disease stage, treatment response and survival.[31,32] Estrogen has an anti-inflammatory effect at low levels, while it has a pro-inflammatory effect at high levels. In hormone-positive breast cancer, the inflammation-tumor relationship is more complex due to these effects of estrogen. High estrogen levels have been shown in high CRP levels.[33,34] Patients with chronic inflammatory diseases were excluded from the study as hematological, biochemical parameters and survival may be affected. Patients with active infection were included in the study after treatment of the infection, as hematological and biochemical parameters may be affected.

High NLR rate has been found to be correlated with low PFS in many studies.[35,36] High NLR is an indicator of increased inflammation and suppression of lymphocytes in the tumor microenvironment, which may lead to tumor progression. In our study, NLR was not statistically significant for PFS. In the study of Shikanai et al unlike our study, lower NLR was correlated with longer PFS was statistically significant. This may be due to the difference in cut-off values and the heterogeneity of our patient group.

CLR, the ratio of two contrasting parameters, a marker of inflammation (CRP) and an antitumor marker (lymphocytes), was found to be prognostic in colorectal cancer, cholangiocellular cancer and hepatocellular cancer. CLR could reflect systemic inflammation and immunological response, while high CLR represents enhancement of systemic inflammatory response and an impaired immunological response in cancer patients. Lu et al found lymphocyte/CRP ratio to be related with OS in their study conducted in patients with operative cholangiocellular carcinoma.[37] Iseda et al found lymphocyte/CRP ratio to be predictive for recurrence free survival and OS in a study conducted in patients with operated hepatocellular carcinoma.[38] Okugawa et al found that the lymphocyte/CRP ratio was correlated with undifferentiated histology and advanced TNM stage and was prognostic for PFS and OS in colorectal cancer patients undergoing surgery.[39]

In our study, CLR was found to be correlated with PFS. Real-world data with different results regarding the PFS duration of CDK4/6i therapy have been published. In our study, PFS was 29.7 months in the patient group with CLR < 6.04 and 8.4 months in the patient group with CLR ≥ 6.04 ($p = 0.022$). In our study, CLR was also found to be correlated with OS ($p = 0.006$). This is the first study showing that CLR may have prognostic significance in predicting PFS and OS

in CDK4/6i patient group. CLR may help the clinician in predicting survival in clinical studies and real-life data where CDK4/6i treatment has different survival results.

Our study had some limitations. Some of the limitations of our study may be that it was a retrospective study, the number of patients was small, due to the health policies in our country, there are only patients with ER positivity of 11% and above, the patient group was heterogeneous, not only denovo metastatic but also recurrent metastatic patients were included, CDK4/6i discrimination was not made (ribociclib/palbociclib/abemaciclib). Separate statistics could not be made due to the small number of patients in the specified subgroups. Our results should be confirmed by further studies in a larger patient group.

Conclusion

This is the first study to show the correlation of CDK4/6i pre-treatment CLR value with PFS and OS. PFS durations of CDK4/6i treatment are different in phase studies and real-life data. In addition, the importance of CLR predicting PFS is increasing today when many parameters in CDK4/6i activity are investigated. CLR is an easily calculable and accessible parameter from peripheral blood samples. In our study, the fact that the PFS times were longer in the patient group with low Ki67 proliferation index was another indicator of CDK4/6i activity. These parameters will become more important in future studies to predict the efficacy of CDK4/6i therapy and PFS in patients with metastatic breast cancer.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Approval was obtained from the ethics committee of Atatürk University Faculty of Medicine (2023/792). The Declaration of Helsinki was complied with during all procedures. Due to the retrospective nature of the study the informed consent requirement was waived by the Ethics Committee of Atatürk University Faculty of Medicine. In this retrospective study, data were anonymized and no patient identifiers were used.

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Disclosure

The authors have declared that no competing interest exists in this work.

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