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Neutrophil–Lymphocyte Ratio and Platelet–Lymphocyte Ratio Combination Can Predict Prognosis in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Abstract

We assessed the effect of combination of neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) in predicting in-hospital and long-term mortality in patients (n = 2518) undergoing primary percutaneous coronary intervention (pPCI). Cutoff values for NLR and PLR were calculated with receiver–operating characteristic (ROC) curves. If both PLR and NLR were above the threshold, patients were classified as "high risk." If either PLR or NLR was above the threshold individually, patients were classified as "intermediate risk." High-risk (n = 693) and intermediate-risk (n = 545) groups had higher in-hospital and long-term mortality (7.2 4% vs 0.7%, $P < .001$; 14.1, 9.5% vs 4.5%, $P < .001$, respectively). Classifying patients into intermediate-risk group (hazards ratio [HR]: 1.492, 95% confidence interval [CI]: 1.022-2.178, $P = .038$) and high-risk group (HR: 1.845, 95% CI: 1.313-2.594, $P < .001$) was an independent predictor of in-hospital and long-term mortality. The combination of PLR and NLR can be useful for the prediction of in-hospital and long-term mortality in patients undergoing pPCI.

Keywords

acute ST-segment elevation myocardial infarction, primary angioplasty, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio

Introduction

The role of inflammation in coronary artery disease (CAD) has been demonstrated.[1,2] Previous studies have shown that the white blood cell count and its subtypes, possibly due to their association with inflammation, provide information about cardiovascular (CV) outcomes.[3,4] The neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) were investigated in an attempt to find inexpensive and readily available markers for inflammation and CV prognosis. The NLR was shown to be a potential prognostic marker in patients undergoing primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI).[5,6] The PLR is also associated with adverse CV outcomes.[7,8] However, the combined use of both these markers for CV prognosis has not been evaluated.

We assessed whether admission NLR and PLR provide significant prognostic information in patients undergoing pPCI for STEMI. We also determined whether the combination of these ratios can provide additional information in contrast to using NLR or PLR alone.

Methods

After obtaining approval from the local ethics committee, 2518 consecutive patients with STEMI who presented within

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12 hours from the onset of symptoms and underwent pPCI were enrolled in the study. All patients gave their written informed consent. Patients with active infection, autoimmune diseases, hematologic proliferative disease, and neoplasia were excluded.

All pPCI procedures were performed by experienced interventional cardiologists who were unaware of the patient's clinical information. The patients were given 300 mg acetylsalicylic acid and a loading dose of 300 mg clopidogrel before pPCI. Emergency coronary angiography was performed using the percutaneous femoral route. Heparin (100 U/kg) was administered when the coronary anatomy was first assessed. The use of glycoprotein IIb/IIIa inhibitors was left to the preference of the operator. Follow-up data were obtained from patient files or by telephone interview with patients, family members, or primary care physicians.

Venous blood samples were obtained from all patients on admission. An automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc, Mervue, Galway, Ireland) was used to measure platelets, lymphocytes, neutrophils, and other basic hematologic parameters. The PLR was calculated as the ratio of the platelets and lymphocytes, and the NLR was calculated as the ratio of the neutrophils and lymphocytes both obtained from the same blood sample at admission of the study. The 12-hour fasting serum levels of triglyceride, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels were measured by standard enzymatic methods.

ST-segment elevation myocardial infarction was defined as symptoms of myocardial ischemia and ST-segment elevation $\geq$1 mm in 2 contiguous electrocardiographic leads or new onset of complete left bundle-branch block. Diabetes mellitus (DM) was defined as a previous diagnosis, use of antidiabetic medicines, or a fasting venous blood glucose level $\geq$126 mg/dL on 2 occasions in previously untreated patients. Hypertension (HT) was defined as previous use of antihypertensive medication, a systolic pressure >140 mm Hg, or a diastolic pressure >90 mm Hg on at least 2 separate measurements. Hypercholesterolemia was defined as total cholesterol of >200 mg/dL. Anemia was defined as a baseline hemoglobin <13 mg/dL in men and <12 mg/dL in women. The estimated glomerular filtration rate was calculated at admission using the Modification of Diet in Renal Disease equation. Left ventricular systolic function was assessed by modified biplane Simpson method in 2-dimensional echocardiography.[9]

Definition of reinfarction was made according to Third Universal Definition of Myocardial Infarction.[10] Target vessel revascularization (TVR) was defined as need for PCI or coronary surgery because of restenosis or reocclusion of the infarct-related artery. Major adverse cardiac events (MACEs) were defined as CV death, reinfarction, or TVR.

A PLR of 162.31 and an NLR of 6.65 were found as threshold values by receiver–operating characteristic (ROC) curves. If both PLR and NLR were above the selected threshold values, patients were classified as "high risk." If either PLR or NLR was above the threshold individually, patients were classified as "intermediate risk." If both levels were under threshold values, patients were classified as "low risk."

Analyses were performed using SPSS Statistics, version17.0 (SPSS Inc, Chicago, Illinois). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test and expressed as mean $\pm$ standard deviation or median and minimum–maximum values as appropriate. The Student t test was used to compare data with normal distribution and the Mann-Whitney U test was applied to compare data that were not normally distributed. Categorical variables were expressed as numbers and percentiles. Categorical variables were compared by chi-square and Fisher exact tests. The cutoff point of PLR and NLR was determined through ROC curve analysis to distinguish between life and mortality. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to determine the combination of PLR–NLR predictors that exhibited the best diagnostic performance. Effects of possible prognostic factors on all-cause mortality were evaluated by a stepwise multivariate Cox-Regression model. Kaplan-Meier survival curves and the log-rank test were used to compare all-cause mortality between the low-, intermediate-, and high-risk groups. A 2-sided P <.05 was considered significant.

Results

Overall 2518 patients, 2092 (83.1%) males and 426 (16.9%) females, participated in our study. Mean age of the participants was 56.5 $\pm$ 11.3 years. There were no differences in medications such as acetylsalicylic acid, clopidogrel, statin, and tirofiban use among the groups. Median follow-up time was 22 (1-54) months. In ROC curve analysis, the area under the ROC curve was 0.619 (95% confidence interval [CI] 0.600-0.638, P < .001) for an NLR cutoff of >6.65 and 0.604 (95% CI 0.585-0.624, P < .001) and for a PLR cutoff of >162.31. The sensitivity% (95% CI), specificity% (95% CI), PPV% (95% CI), and NPV % (95%CI) were calculated for an NLR 59.6 (52.6-66.3), 66.8 (64.8-68.7), 13.9 (11.7-16.4), 94.8 (93.6-95.9) and for a PLR 62.8 (53.2-66.4), 60.39 (58.4-62.4), 11.9 (10.0-14.1), and 94.3 (93-95.4), respectively.

Baseline characteristics of the patients are summarized in Table 1. Mean platelet volume (MPV) levels were significantly different among the study groups. Although distribution of culprit vessels, number of diseased vessels, stent length, stent diameter, and tirofiban use were similar among risk groups, patients with postprocedural Thrombolysis in Myocardial Infarction 3 flow, which is defined as patients with normal perfusion in whom the contrast is minimally persistent at the end of the washout phase in the coronary angiography,[11] were less frequently seen in the high-risk group (Table 2). Overall 81 (3.2%) deaths and 181 (7.1%) MACEs occurred during the in-hospital period. Patients with a high risk had the highest in-hospital mortality and MACE rates (Table 3). All-cause mortality was also higher in the high-risk group compared with others during the long-term follow-up (Table 4 and Figure 1). A log-rank P < .001 was obtained when comparing survival among 3 risk groups (Figure 2).

Table 1. Baseline Characteristics of Study Patients.

	Low Risk, n = 1280	Intermediate Risk, n = 545	High Risk, n = 693	*P*
Age, years	55.4 ± 11.7	56.7 ± 11.1	58.3 ± 12.2	.001
Male gender	1081 (84.5)	429 (78.7)	582 (84.0)	.482
Diabetes	291 (22.7)	132 (24.2)	196 (28.3)	.023
Hypertension	498 (38.9)	225 (41.3)	265 (38.2)	.518
Smoking	774 (60.5)	307 (56.3)	399 (57.6)	.089
CABG	47 (3.7)	13 (2.4)	11 (1.6)	.022
PCI	102 (8.0)	42 (7.7)	59 (8.5)	.860
Killip class > 1	54 (4.2)	36 (6.6)	62 (8.9)	.001
LVEF	49.5 ± 10.2	47.8 ± 12.0	45.9 ± 12.0	.001
Creatinine	0.9 (0.6-4.2)	0.9 (0.6-4.9)	0.9 (0.6-10)	.658
Peak CK-MB	143 (12-1827)	175 (13-1459)	224 (17-1389)	.001
Cholesterol	192 ± 37	186 ± 38	185 ± 44	.001
LDL-C	119 ± 29	117 ± 28	116 ± 29	.034
HDL-C	41 ± 8	41 ± 8	41 ± 8	.628
MPV	8.4 ± 1.0	8.6 ± 0.9	8.7 ± 0.6	.001
Triglycerides	132 (26-1649)	128 (20-637)	121 (22-1108)	.001
Glucose	128 (52-486)	133 (74-530)	141 (48-614)	.001
WBC	12.05 ± 3.38	12.45 ± 4.59	13.83 ± 4.25	.001
Hemoglobin	14.8 ± 1.6	13.8 ± 1.8	13.5 ± 1.8	.001
GFR	89 ± 23	87 ± 24	85 ± 26	.001
HbA_{1C}	6.6 ± 0.8	6.8 ± 0.8	7.0 ± 0.7	.001
PLR	111.7 (26.8-162.2)	173.1 (33.0-620)	228.6 (162.5-806.6)	.001
NLR	3.78 (1-6.63)	5.93 (1-16)	9.6 (6.67-26.8)	.001

Abbreviations: CAD, coronary artery disease; CABG, coronary artery by-pass graft operation; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase myocardial band; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MPV, mean platelet volume; WBC, white blood cell; GFR, glomerular filtration rate; PLR, platelet–lymphocyte ratio; NLR, neutrophil–lymphocyte ratio; HbA_{1C}, hemoglobin A_{1C}.

Table 2. Angiographic and Procedural Characteristics of Patients.

	Low Risk, n = 1280	Intermediate Risk, n = 545	High Risk, n = 693	*P*
Culprit lesion, n (%)				
LMCA	3 (0.2)	–	–	.566
LAD	607 (47.3)	276 (50.5)	356 (50.9)	
CX	170 (13.3)	72 (13.2)	90 (13.0)	
RCA	489 (38.2)	193 (35.4)	246 (35.5)	
Graft	11 (0.9)	4 (0.7)	2 (0.3)	
No. of diseased vessels, n (%)				
1	552 (43.1)	226 (41.5)	292 (42.1)	.898
2	415 (32.4)	174 (31.9)	223 (32.2)	
3	313 (24.5)	145 (26.6)	178 (25.7)	
Preprocedural TIMI grade				
1	1102 (86.1)	483 (88.6)	624 (90.0)	.107
2	118 (9.2)	39 (7.2)	48 (6.9)	
3	60 (4.7)	23 (4.2)	21 (3.0)	
Postprocedural TIMI grade				
1	96 (7.5)	53 (9.7)	73 (10.5)	.007
2	51 (4.0)	32 (5.9)	46 (6.6)	
3	1133 (88.5)	460 (84.4)	574 (82.8)	
Stent length, mm (SD)	18 (8-52)	18 (8-50)	18 (8-56)	.588
Stent diameter, mm (SD)	3.11 ± 0.35	3.09 ± 0.34	3.13 ± 0.35	.655
Tirofiban use	619 (48.4)	264 (48.4)	336 (48.5)	.998

Abbreviations: LMCA, left main coronary artery; LAD, left anterior descending coronary artery; CX, circumflex coronary artery; RCA, right coronary artery; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction.

In a stepwise multivariate Cox-regression analysis, intermediate-risk group, high-risk group, age >70 years, DM, Killip class > 1, creatinine, LDL cholesterol, hemoglobin, and inotrope use were independently associated with long-term, all-cause mortality. The association of the high-risk group with mortality (hazards ratio [HR] 1.670, 95% CI 1.181-2.361, $P = .004$) was more pronounced than the association of the intermediate-risk group (HR 1.395, 95% CI 1.052-2.044, $P = .033$; Table 5).

Table 3. In-Hospital Cardiac Events.

Event	Low Risk, n = 1280	Intermediate Risk, n = 545	High Risk, n = 693	*P*
Death	9 (0.7)	22 (4.0)	50 (7.2)	.001
Reinfarction	22 (1.7)	15 (2.8)	16 (2.3)	.318
TVR	53 (4.1)	25 (4.6)	33 (4.8)	.784
MACE	61 (4.8)	44 (8.1)	76 (11.0)	.001
Stroke	4 (0.3)	4 (0.7)	9 (1.3)	.031
CPR	16 (1.3)	27 (5.0)	5 (8.1)	.001
Hemodialysis	2 (0.2)	4 (0.7)	11 (1.6)	.001
VT/VF	26 (2.0)	29 (5.3)	52 (7.5)	.001
Heart failure	122 (9.5)	90 (16.5)	122 (17.6)	.001
Inotrope use	55 (4.3)	58 (10.6)	87 (12.6)	.001
Cardiogenic shock	18 (1.4)	32 (5.9)	51 (7.4)	.001
Atrial fibrillation	16 (1.3)	7 (1.3)	13 (1.9)	.516
Temporary pacemaker	26 (2.0)	20 (3.7)	45 (6.5)	.001
GI bleeding	6 (0.5)	6 (1.1)	15 (2.2)	.003
Access site complication	50 (3.9)	21 (3.9)	30 (4.3)	.881
Acute stent thrombosis	12 (0.9)	7 (1.3)	4 (0.6)	.432
Blood transfusion	28 (2.2)	29 (5.3)	42 (6.1)	.001

Abbreviations: TVR, target vessel revascularization; MACE, major adverse cardiovascular event; CPR, cardiopulmonary resuscitation, VT/VF, ventricular tachycardia/fibrillation; GI, gastrointestinal.

Table 4. Long-Term Cardiac Events.

Event	Low Risk, n = 1280	Intermediate Risk, n = 545	High Risk, n = 693	*P*
All-cause mortality	58 (4.5)	52 (9.5)	98 (14.1)	.001
Heart failure	75 (5.9)	41 (7.5)	66 (9.5)	.011
Stroke	10 (0.8)	3 (0.6)	7 (1.0)	.666
Reinfarct	91 (7.1)	46 (8.4)	54 (7.8)	.588
TVR	173 (13.5)	101 (18.5)	108 (15.6)	.021
MACE	235 (18.4)	135 (24.8)	152 (21.9)	.006
Subacute stent thrombosis	33 (2.6)	19 (3.5)	20 (2.9)	.547
Late stent thrombosis	20 (1.6)	15 (2.8)	17 (2.5)	.164

Abbreviations: TVR, target vessel revascularization; MACE, major adverse cardiovascular event.

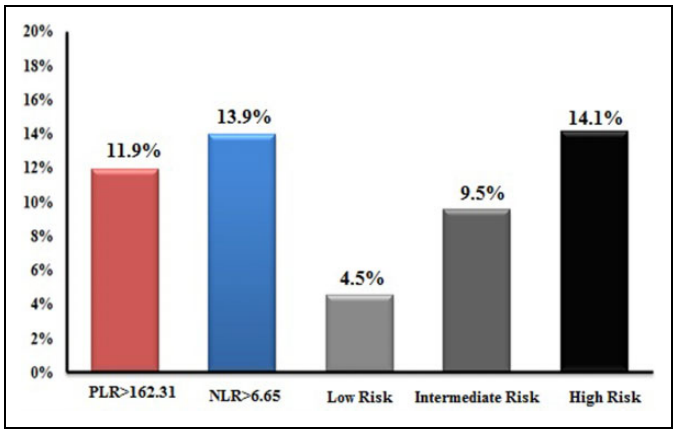

Figure 1. All-cause mortality according to the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR).

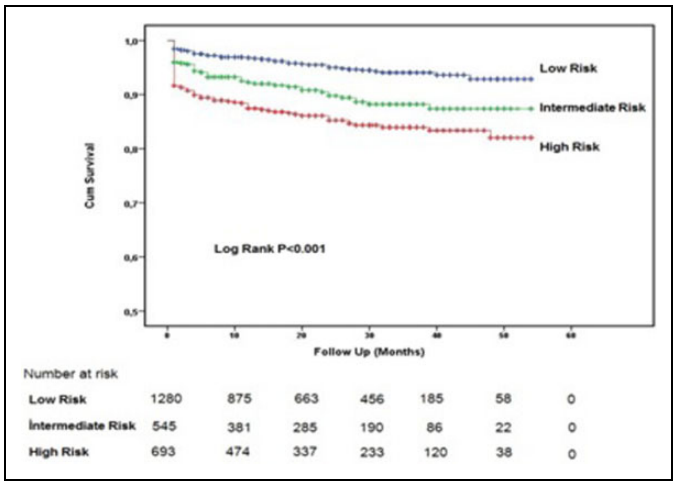

Figure 2. Kaplan-Meier cumulative survival curves for patients with all-cause mortality according to combined neutrophil–lymphocyte ratio and platelet–lymphocyte ratio risk stratification.

Discussion

We demonstrated for the first time that the combined use of NLR and PLR can predict prognosis in patients undergoing pPCI for STEMI. Both high- and intermediate-risk groups, according to NLR and PLR, were independent predictors of in-hospital and long-term mortality in our study. In-hospital MACEs were also related to our risk stratification.

Table 5. Independent Predictors of All-Cause Mortality.

	Univariable		Multivariable	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age ≥ 70, years	4.577 (3.482-6.016)	<.001	2.609 (1.917-3.551)	<.001
Male gender	0.451 (0.335-0.606)	.001	–	–
Diabetes mellitus	3.374 (2.571-4.429)	<.001	1.467 (1.055-2.039)	.0023
Hypertension	1.711 (1.303-2.245)	.001	–	–
Killip class > I	9.761 (7.289-13.072)	<.001	2.083 (1.433-3.029)	<.001
Anemia	2.734 (2.080-3.595)	.001	–	–
LVEF	0.901 (0.875-0.988)	.001		
Creatinine	1.644 (1.505-1.796)	<.001	1.256 (1.098-1.457)	.001
LDL-C	0.937 (0.928-0.947)	<.001	0.985 (0.970-0.995)	.046
Triglyceride	0.997 (0.995-0.998)	.012	–	–
MPV	1.148 (1.006-1.310)	.040		
Glucose	1.006 (1.005-1.007)	<.001	–	–
Hemoglobin	0.742 (0.695-0.792)	<.001	0.866 (0.807-0.930)	.001
PLR	1.004 (1.002-1.005)	<.001	–	–
NLR	1.082 (1.052-1.114)	.001	–	–
Inotrope use	12.753 (9.688-16.787)	<.001	5.193 (3.599-7.494)	<.001
Blood transfusion	3.222 (2.089-4.970)	.001	–	–
Intermediate risk PLR–NLR	2.107 (1.449-3.064)	.001	1.395 (1.052-2.044)	.033
High risk PLR–NLR	3.172 (2.292-4.389)	<.001	1.670 (1.181-2.361)	.004

Abbreviations: HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; PLR, platelet–lymphocyte ratio; NLR, neutrophil–lymphocyte ratio; MPV, mean platelet volume.

Elements of the complete blood count, a basic laboratory assessment, have been assessed in order to define their predictive role in CV diseases. The blood components of interest were neutrophil count,[12] platelet count,[13] red cell distribution width,[14] NLR,[15] PLR,[7] and MPV.[16] Neutrophils are the most abundant type of the white blood cells and they play a role in inflammatory processes. After an acute myocardial infarction (MI), the lymphocyte count declines and the neutrophil count rises as a consequence of the stress response to myocardial damage[17] Neutrophils release various enzymes and cytokines and activate other cells of the immune system to trigger and enhance inflammatory reactions. These processes play an important role in inflammatory tissue damage.[18,19] Furthermore, neutrophil–platelet aggregates can be seen in the microcirculation and cause no-reflow phenomenon, greater MI size, and worse prognosis.[20-22] A decreased lymphocyte count has also been related to poor prognosis in patients with MI.[23-26] The NLR is a cheap and readily available marker, which can provide additional information to conventional markers in patients with STEMI. In patients with STEMI undergoing pPCI, a high NLR is associated with increased in-hospital mortality, long-term mortality,[6] no reflow, and in-hospital MACEs.[5,27]

Platelet activation is one of the factors that have been associated with CAD.[28,29] Release of various mediators such as interleukin (IL) 1, IL-3, and IL-6 during proinflammatory state causes megakaryocyte proliferation and increase in circulated platelet count.[30,31] Thus, increased platelet counts may indicate enhanced thrombocyte activation and a prothrombotic state.[32] High platelet count and high platelet activation may play a role in the initiation and progression of atherosclerosis.[33,34] Mean platelet volume is a useful marker of platelet activity. Several studies indicated the close relationship between MPV levels and poor clinical outcomes in patients with acute coronary syndromes.[35-37] In addition, recent studies have shown that patients with CAD have increased platelet and monocyte aggregates in their bloodstream, which were associated with plaque instability, worse in-hospital outcomes, and increased risk of future cardiac events.[38,39] High PLR level may be an indicator of increased circulating platelet–monocyte aggregates, but specific studies are needed to investigate this. Even so, combination of higher platelet and lower lymphocyte count was found to be associated with increased major adverse CV outcomes.[40-42] The advantage of the PLR is that it reflects activity of both the hemostatic and the inflammation pathways, and it may be superior to either the individual platelet or lymphocyte count in predicting impaired reperfusion.[40-42] Some CV studies with PLR have been performed. Azab et al found that higher PLR values were associated with increased long-term mortality in patients with non-STEMI.[8] Sunbul et al showed that the PLR was a significant predictor of nondipper status in patients with HT.[43] Acar et al showed the independent relationship between the PLR and coronary collateral development in patients with chronic total occlusions.[44] Recently, Yildiz at al demonstrated that high preprocedural PLR and NLR levels are significant and independent predictors of no reflow in patients undergoing pPCI.[7] The prognostic significance of the PLR has also been reported in patients with various cancers.[45,46] The NLR seems to reflect inflammation in vessel wall, and PLR reflects high blood viscosity in addition to inflammation.[32] Moreover, PLR was found to be a more sensitive inflammation marker than NLR.[47,48] The NLR or PLR alone was not found to

be an independent predictor of all-cause mortality in our study. In contrast, combined use of NLR and PLR gave significant results. Thus, the combined use of these 2 may have greater value.

This study has several limitations. It is a single-center, retrospective study without randomization and thus subject to selection bias. However, consecutive patients were selected in order to lessen possible effects of selection bias. Inflammatory markers, such as high-sensitivity C-reactive protein, B-type natriuretic peptide, other proinflammatory cytokines, and markers of oxidative stress were not analyzed. Despite adjusting for multiple risk factors, it is possible that there might have been residual confounding conditions and medications.

The results of the present study suggest that significant prognostic information can be obtained from routine blood test results in patients undergoing pPCI for STEMI. Combined use of PLR and NLR may be an easy, inexpensive, and useful marker for in-hospital and long-term prognosis of these patients. Multicenter, prospective and randomized studies are needed to confirm our findings.

Declaration of Conflicting Interests

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