



# Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, and Systemic Immune-Inflammation Index Association with Nutritional Markers in Maintenance Hemodialysis Patients

Toktam Alirezaei<sup>1</sup>, Farhad Esmailsorkh<sup>2</sup>, Sara Assadiasl<sup>3</sup>, Mohsen Aghabagheri<sup>4</sup>, Nooshin Dalili<sup>5</sup>, Hossein Amini<sup>6</sup> and Mahboobeh Freidoon<sup>4\*</sup>

1. Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2. Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3. Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

4. Department of Nephrology, Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

5. Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

6. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## \* Corresponding author

**Mahboobeh Freidoon, MD**

Men's Health and Reproductive Health Research Center, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

**Email:**

[m.freidoon@sbmu.ac.ir](mailto:m.freidoon@sbmu.ac.ir)

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## Abstract

**Background:** Cardiovascular Disease (CVD) is the leading cause of death in patients with End-Stage Renal Disease (ESRD) undergoing Hemodialysis (HD). Recent studies have demonstrated that the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-Inflammation Index (SII) may help identify individuals at high risk of CVD. Malnutrition and inflammation have also been identified as significant risk factors for CVD in HD patients.

**Methods:** Eighty-nine patients undergoing maintenance hemodialysis were included in the study. Nutritional parameters—including albumin, uric acid, Blood Urea Nitrogen (BUN), creatinine, triglycerides, cholesterol, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), Fasting Blood Sugar (FBS), and Hemoglobin A1c (HbA1c)—were measured. The relationship between these parameters and NLR, PLR, and SII, was analyzed.

**Results:** BUN, creatinine, uric acid, ferritin, FBS, HbA1c, LDL, and triglycerides were positively correlated with PLR, NLR, and SII ( $p < 0.05$ ). Conversely, albumin was negatively correlated with NLR and SII; as albumin levels increased, NLR and SII decreased ( $p < 0.05$ ). The correlation between albumin and PLR was not statistically significant ( $p > 0.05$ ). HDL was significantly negatively associated with NLR, PLR, and SII. Additionally, age had a significant effect on the variation of SII, NLR, and PLR ( $p < 0.05$ ).

**Conclusion:** The three novel inflammatory composite indices—SII, NLR, and PLR—were closely associated with common nutritional biomarkers and may serve as cost-effective and convenient markers for predicting clinical prognosis in ESRD patients with CVD risk.

**Keywords:** Hemodialysis, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Systemic immune-inflammation index

## Introduction

Cardiovascular Disease (CVD) is the leading cause of mortality in patients with End-Stage Renal Disease (ESRD) undergoing Hemodialysis (HD) (1,2). The underlying pathophysiology of this condition remains poorly understood. Traditional risk factors—including age, male sex, hypertension, diabetes, dyslipidemia, and physical inactivity—are common in HD patients; however, they do not fully account for the high burden of cardiovascular complications. As a result, non-traditional risk factors such as malnutrition and chronic inflammation have been identified as additional contributors to CVD in this population (3,4). Malnutrition and inflammation are strong prognostic indicators of CVD in patients with ESRD (5).

Inflammatory markers such as Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and ferritin are frequently elevated in patients undergoing HD and are associated with increased mortality in ESRD patients (6). A prospective study reported that elevated CRP levels in chronic HD patients are strongly correlated with atherogenic vascular risk factors and cardiovascular death (7).

Several nutritional markers have also been linked to CVD risk in HD patients. Elevated levels of Triglycerides (TG), Low-Density Lipoprotein (LDL) cholesterol, and total cholesterol are associated with an increased risk of cardiovascular complications, whereas low levels of HDL are similarly considered a risk factor for CVD (8-10). A lower serum albumin concentration is associated with increased mortality in HD patients and is regarded as a critical prognostic factor (11). Elevated blood levels of uric acid and creatinine have also been linked to all-cause mortality and increased cardiovascular risk (12-14). Additionally, higher levels of HbA1c and Fasting Blood Sugar (FBS) are associated with an elevated risk of CVD (15,16).

Systemic Immune-Inflammation index (SII) is a hematological marker that reflects systemic inflammatory status (17,18). Two additional composite indices derived from blood cell counts—Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR)—have also shown promise in predicting Coronary Artery Disease (CAD) and its complications (19,20).

Although the role of inflammation and malnutrition in CVD, the leading cause of death in HD patients, has been established in numerous studies (21-24), the precise relationship between these conditions and their combined impact on cardiovascular outcomes remains incompletely understood. Therefore, this study aims to evaluate the association between malnutrition-related markers and PLR, NLR, and SII to assess their utility as predictive indicators of adverse clinical outcomes in ESRD.

## Materials and Methods

### *Study population and design*

This observational study was conducted as a cross-sectional comparative-descriptive analysis and the review board of ethics committee approved the study protocol (code: IR.SBMU.MSP.REC.1401.380) and the study was performed in accordance with the declarations of Helsinki. The inclusion criteria included age above 18 years and under HD treatment above 6 months. The exclusion criteria were acute or chronic infections, anticoagulant consumption in the past 6 months, decompensated heart failure, history of active malignancy or chemotherapy, systemic inflammation or autoimmune disease, pregnancy, hypothyroidism, hyperthyroidism, hematologic disorder, liver failure or cirrhosis, history of bariatric surgery, gastroparesis, active weight management program, hematologic disorder. This study was designed as a pilot and 89 patients were considered based on other studies and expert opinion and total number of eligible patients.

The informed consent form was obtained from each patient. After considering inclusion and exclusion criteria, 89 successive patients with ESRD who were on maintenance HD were enrolled. Dialysis adequacy was evaluated using Kt/V ( $>1.2$ ) criteria. Ischemic Heart Disease (IHD) was defined as a history of myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention. Congestive Heart Failure (CHF) was described as an ejection fraction under 40% which was calculated with doppler echocardiography. Laboratory measurements venous blood samples were collected *via* standard venipuncture procedures on patient admission to the hospital before initiation of the hemodialysis procedure. The mentioned blood samples were

composed in tubes accommodating potassium Ethylenediaminetetraacetic Acid (EDTA) as an anticoagulant and were analyzed by the laboratory of the hospital with an automated and daily-calibrated Coulter CBCH1 counter. The hemoglobin levels and total white blood cell, neutrophil, lymphocyte, and platelet counts were captured from laboratory reports. Blood samples were obtained after 8 to 10 hours of fasting and before HD. Nutrition factors such as creatinine, BUN, albumin, uric acid, total cholesterol, LDL, HDL, TG, FBS, HbA1C, and inflammatory markers including ESR, CRP, ferritin, and cell blood count were assessed in a single lab with a single standard method. The PLR was calculated as the platelet count per  $mm^3$  of blood divided by the lymphocyte count per  $mm^3$  of blood. NLR was calculated as the neutrophil count per  $mm^3$  of blood divided by the lymphocyte count per  $mm^3$  of blood. The SII was calculated by the formula  $SII = \text{platelets} \times \text{neutrophils/lymphocytes}$ .

### Statistical analysis

A descriptive analysis of the study population was performed using appropriate software SPSS version 21 (*i.e.*, mean $\pm$ standard deviation for continuous variables with normal distribution and percentages for discrete variables). A p-value  $<0.05$  was considered significant.

The correlation of the SII, NLR, and PLR with nutritional markers and inflammatory factors was assessed, and due to the non-normality of the data distribution, the Spearman coefficient was used. The normal distribution of data was checked by using the Kolmogorov–Smirnov test. A linear regression analysis was performed to evaluate the effect of age, sex, smoking, body mass index (BMI), diabetes,

**Table 1.** Descriptive statistics of the patient's characteristics and background parameter

| Parameters                       | Descriptive statistics |
|----------------------------------|------------------------|
| <b>Sex</b>                       | No. (%)                |
| Male                             | 56(62.9%)              |
| Female                           | 33(37.1%)              |
| <b>Age (year)</b>                |                        |
| Mean $\pm$ SD                    | 56.57 $\pm$ 7.05       |
| <b>Smoking</b>                   | No. (%)                |
| Smoker                           | 11(12.4%)              |
| <b>BMI (<math>kg/m^2</math>)</b> |                        |
| Mean $\pm$ SD                    | 24.52 $\pm$ 4.05       |
| Ischemic heart disease (%)       | 12(13.5%)              |
| Hypertension (%)                 | 72(80.9%)              |
| Diabetes (%)                     | 27(30.3%)              |

Body Mass Index (BMI)

hypertension, and heart disorder on SII, PLR, and NLR measurements in these patients.

### Results

In this study, 89 patients with a mean age of 56.57 $\pm$ 7.05 years were surveyed, including 56 (62.9%) males, 11 (12.4%) smokers, 12 (13.5%) with IHD, 72 (80.9%) with hypertension, and 27 (30.3%) with diabetes mellitus. The descriptive statistics of the patients' characteristics and backgrounds are presented in table 1, while the descriptive results of clinical measurements are summarized in table 2.

Due to the non-normal distribution of the data, the Spearman correlation coefficient was used to examine the relationships between the SII, NLR, and PLR and each nutritional and inflammatory marker. As shown in table 3, BUN, Cr, uric acid, ferritin, FBS, HbA1C, ESR, CRP, LDL, and TG were positively correlated

**Table 2.** Descriptive statistics of patient's characteristics and clinical measurements

| Variable                                | Descriptive statistics | Variable                   | Descriptive statistics |
|-----------------------------------------|------------------------|----------------------------|------------------------|
| <b>Systolic blood pressure (mmHg)</b>   |                        | <b>Fasting blood sugar</b> |                        |
| Mean $\pm$ SD                           | 130.70 $\pm$ 20.99     | Mean $\pm$ SD              | 116.48 $\pm$ 46.99     |
| <b>Diastolic blood pressure (mm Hg)</b> |                        | <b>HbA1c</b>               |                        |
| Mean $\pm$ SD                           | 80.00 $\pm$ 8.1        | Mean $\pm$ SD              | 6.53 $\pm$ 5.48        |
| <b>Blood urea nitrogen</b>              |                        | <b>TG</b>                  |                        |
| Mean $\pm$ SD                           | 123.645 $\pm$ 33.12    | Mean $\pm$ SD              | 137.13 $\pm$ 75.95     |

Contd. table 2.

|                              |               |                               |                 |
|------------------------------|---------------|-------------------------------|-----------------|
| <b>Creatinine</b><br>Mean±SD | 9.16±3.32     | <b>HDL</b><br>Mean±SD         | 35.29±9.11      |
| <b>Calcium</b><br>Mean±SD    | 8.76±1.28     | <b>LDL</b><br>Mean±SD         | 72.70±8.86      |
| <b>Phosphorus</b><br>Mean±SD | 5.61±1.80     | <b>Cholesterol</b><br>Mean±SD | 135.952±38.39   |
| <b>Ferritin</b><br>Mean±SD   | 339.75 ±31.57 | <b>ESR</b><br>Mean±SD         | 44.08±24.45     |
| <b>Fe</b><br>Mean±SD         | 74.09±25.29   | <b>CRP</b><br>Mean±SD         | 15.06±11.88     |
| <b>TIBC</b><br>Mean±SD       | 234.77±71.00  | <b>Uric acid</b><br>Mean±SD   | 6.99±1.71       |
| <b>Hemoglobin</b><br>Mean±SD | 10.72±1.98    | <b>Albumin</b><br>Mean±SD     | 4.07±0.59       |
| <b>NLR</b><br>Mean± SD       | 2.98±1.84     | <b>WBC</b><br>mean±SD         | 5993.26±1824.19 |
| <b>PLR</b><br>Mean±SD        | 3007±653.70   | <b>Hemoglobin</b><br>Mean±SD  | 10.72±1.98      |
| <b>SII</b><br>Mean±SD        | 577140±4400   | -                             | -               |

Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-Inflammation Index (SII), Total Iron Binding Capacity (TIBC).

**Table 3.** Spearman correlation between SII, NLR, and PLR with nutrition markers and inflammatory factors

|            |             | <b>BUN</b> | <b>Creatinine</b> | <b>Acid uric</b>   | <b>Albumin</b> | <b>Ferritin</b> | <b>FBS</b> | <b>HbA1C</b> |
|------------|-------------|------------|-------------------|--------------------|----------------|-----------------|------------|--------------|
| <b>PLR</b> | p-value     | <0.001     | 0.001             | 0.032              | 0.056          | <0.001          | <0.001     | <0.001       |
|            | Correlation | 0.453      | 0.351             | 0.299              | -0.204         | 0.542           | 0.555      | 0.511        |
| <b>NLR</b> | p-value     | <0.001     | <0.001            | 0.003              | 0.007          | <0.001          | <0.001     | <0.001       |
|            | Correlation | 0.562      | 0.373             | 0.316              | -0.288         | 0.444           | 0.594      | 0.491        |
| <b>SII</b> | p-value     | <0.001     | <0.001            | <0.001             | 0.001          | <0.001          | <0.001     | <0.001       |
|            | Correlation | 0.602      | 0.414             | 0.374              | -0.334         | 0.495           | 0.624      | 0.581        |
|            |             | <b>ESR</b> | <b>CRP</b>        | <b>Cholesterol</b> | <b>LDL</b>     | <b>HDL</b>      | <b>TG</b>  |              |
| <b>PLR</b> | p-value     | <0.001     | <0.001            | <0.001             | <0.001         | 0.032           | <0.001     | -            |
|            | Correlation | 0.548      | 0.447             | 0.516              | 0.548          | -0.234          | 0.436      | -            |
| <b>NLR</b> | p-value     | <0.001     | <0.001            | <0.001             | <0.001         | 0.014           | <0.001     | -            |
|            | Correlation | 0.555      | 0.470             | 0.585              | 0.592          | -0.268          | 0.461      | -            |
| <b>SII</b> | p-value     | <0.001     | <0.001            | <0.001             | <0.001         | 0.002           | <0.001     | -            |
|            | Correlation | 0.629      | 0.526             | 0.619              | 0.664          | -0.328          | 0.458      | -            |

Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-Inflammation Index (SII), Blood Urea Nitrogen (BUN), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Triglyceride (TG), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Fasting Blood Sugar (FBS).

with PLR, NLR, and SII.

Conversely, albumin was negatively correlated with both NLR and SII, while its correlation with PLR was not statistically significant. Although the correlation coefficients between PLR and albumin and HDL, as well as between NLR and albumin and HDL, were statistically significant, these associations can be considered negligible given that their absolute values were less than 0.3. In contrast, SII showed stronger correlations with BUN, FBS, ESR, cholesterol, and LDL.

The correlations between age, sex, smoking status, BMI, diabetes, hypertension, and IHD and the values of SII, PLR, and NLR are presented in tables 4, 5, and 6, respectively. According to these results, age

had a statistically significant effect on the variation in SII, NLR, and PLR, while the effects of the other variables were not statistically significant.

Specifically, the results indicate that with each one-year increase in age, the mean values of SII and PLR increased by approximately 12,532 and 161.089 units, respectively, on average. According to the regression coefficients in table 5, although the effect of age on NLR was statistically significant, it was of negligible magnitude.

## Discussion

Inflammation accelerates atherosclerosis, while malnutrition is directly associated with mortality in ESRD patients (25). A large cohort study involving

**Table 4.** Regression results for SII measurements

| Variable               | Regression coefficient | p-value | 95% confidence interval for regression coefficient |             |
|------------------------|------------------------|---------|----------------------------------------------------|-------------|
|                        |                        |         | Lower bound                                        | Upper bound |
| Age                    | 12532.193              | <0.001  | 19153.886                                          | 5910.501    |
| Sex                    | -120760.953            | 0.253   | 88352.776                                          | -329874.682 |
| Smoking                | 240941.703             | 0.122   | 548190.479                                         | -66307.074  |
| Ischemic heart disease | 85605.784              | 0.598   | 408568.030                                         | -237356.463 |
| Hypertension           | 6140.324               | 0.963   | 269497.099                                         | -257216.450 |
| Diabetes               | -163133.160            | 0.162   | 67476.956                                          | -393743.276 |
| BMI                    | -10984.077             | 0.384   | 14077.077                                          | -36045.231  |

Body Mass Index (BMI).

**Table 5.** Regression results for NLR measurements

| Variable               | Regression coefficient | p-value | 95% confidence interval for regression coefficient |             |
|------------------------|------------------------|---------|----------------------------------------------------|-------------|
|                        |                        |         | Lower bound                                        | Upper bound |
| Age                    | 0.050                  | <0.001  | 4.482                                              | -1.177      |
| Sex                    | -0.535                 | 0.217   | 0.077                                              | 0.023       |
| Smoking                | 0.825                  | 0.195   | 0.322                                              | -1.392      |
| Ischemic heart disease | -0.429                 | 0.519   | 2.084                                              | -0.434      |
| Hypertension           | -0.279                 | 0.607   | 0.894                                              | -1.753      |
| Diabetes               | -0.565                 | 0.237   | 0.800                                              | -1.359      |
| BMI                    | -0.047                 | 0.366   | 4.482                                              | -1.177      |

Body Mass Index (BMI).

**Table 6.** Regression results for PLR measurements

| Variable               | Regression coefficient | p-value | 95% confidence interval for regression coefficient |             |
|------------------------|------------------------|---------|----------------------------------------------------|-------------|
|                        |                        |         | Lower bound                                        | Upper bound |
| Age                    | 161.089                | 0.001   | 8731.387                                           | -11474.797  |
| Sex                    | -977.943               | 0.525   | 257.980                                            | 64.197      |
| Smoking                | 2999.218               | 0.187   | 2081.902                                           | -4037.787   |
| Ischemic heart disease | 2085.442               | 0.381   | 7495.017                                           | -1496.582   |
| Hypertension           | 576.125                | 0.766   | 6811.168                                           | -2640.283   |
| Diabetes               | -2624.072              | 0.125   | 4429.677                                           | -3277.427   |
| BMI                    | -183.569               | 0.321   | 750.317                                            | -5998.461   |

Body Mass Index (BMI).

44,144 ESRD patients undergoing hemodialysis reported that elevated neutrophil counts and reduced lymphocyte counts were significant predictors of mortality (26). NLR and PLR have emerged as novel markers of systemic inflammation and have been shown to be independently associated with other inflammatory parameters (27). These indices have demonstrated prognostic value in various diseases, including chronic obstructive pulmonary disease<sup>28</sup>, metastatic renal cell carcinoma (29), non-small cell lung cancer (30), and cervical cancer (31). Moreover, PLR and NLR have been shown to predict proteinuria (32).

In the current study, NLR was negatively associated with serum albumin levels, whereas Zhang *et al* reported negative correlations between both NLR and PLR and serum albumin in a larger ESRD cohort with longer follow-up (33). It was also observed that TG, LDL, and total cholesterol were positively associated with PLR and NLR, while HDL was negatively correlated. In contrast, another study on maintenance HD patients found NLR to be negatively correlated with total cholesterol but not significantly associated with HDL, f, or TG (34). Similarly, PLR was significantly correlated with LDL in a separate HD cohort (35), and Yuan *et al* reported a significant association between NLR and TG, total cholesterol, and hyperlipidemia in stage 4 chronic kidney disease (CKD) patients (36).

Further studies have investigated glucose metabolism

markers. In a cohort of 177 HD patients, NLR was significantly correlated with FBS, but not with HbA1c (37). Similarly, among diabetic patients with impaired renal function who were not on HD, NLR and HbA1c were not significantly correlated (38). In this study, both NLR and PLR were positively associated with FBS and HbA1c.

A separate study examining diabetic patients with normal HbA1c levels (4–5.6%) found a significant association between NLR/PLR and BUN and Creatinine (Cr), although this association was not observed in patients with elevated HbA1c (39). In a study involving 966 ESRD patients with biopsy-proven IgA nephropathy, NLR was significantly associated with creatinine (40). The current study findings were consistent, showing positive correlations between both NLR and PLR with BUN and Cr in HD patients, although a prior study with a similar sample size reported negative correlations (41).

Both NLR and PLR were positively correlated with ferritin and CRP in the ESRD cohort. This aligns with previous studies in non-dialysis ESRD patients, where both indices were associated with CRP, and NLR alone was correlated with ferritin (42). However, other HD-based studies found no significant association between NLR/PLR and ferritin (35,41). It is important to consider that routine intravenous iron supplementation in HD patients and oral iron intake in non-HD ESRD patients may elevate serum ferritin

and potentially confound these associations.

Inflammation and malnutrition significantly contribute to adverse cardiovascular outcomes (26). Qin *et al* found that higher SII levels were associated with greater urinary albumin excretion (43), while a meta-analysis by Wang *et al* concluded that elevated SII predicted poorer survival in renal, prostate, bladder, and testicular carcinomas (44). Motivated by these findings, SII's associations were evaluated with biochemical and clinical parameters in ESRD.

Both BUN and Cr are recognized risk factors for acute coronary syndrome, and several studies have confirmed their associations with cardiovascular events. One study found BUN to be a stronger predictor than Cr, while another emphasized Cr's role in predicting cardiovascular outcomes (45). In the present analysis, SII was significantly associated with both BUN and Cr, with BUN showing a stronger correlation. However, in peritoneal dialysis patients, elevated SII was associated with lower Cr levels (46). In diabetic patients, SII was positively associated with Cr, suggesting a role in predicting kidney injury (47). Uric acid has also been examined in relation to SII. One study suggested that reducing uric acid levels may improve survival in HD patients (48). A significant positive association was found between serum uric acid and SII in ESRD patients. This is supported by NHANES data demonstrating that uric acid was significantly associated with elevated SII in adolescents (49).

To further assess the utility of SII, its correlation with classical inflammatory markers, including ESR, CRP, and ferritin, was evaluated. The findings of the present study demonstrated positive correlations with all three markers, suggesting that SII may enhance prediction accuracy and deepen understanding of systemic inflammation in ESRD.

Also, the impact of comorbid conditions such as IHD, hypertension, and diabetes mellitus on inflammatory indices was assessed. While previous studies found direct associations between these conditions and

inflammatory markers (26,50,51), the study results indicated no statistically significant relationship between IHD or hypertension and SII, NLR, or PLR (52). This discrepancy may be attributable to the smaller sample size. Similarly, while Catabay *et al* reported significant associations between diabetes and inflammatory indices (53), such associations were not found in the present study's cohort.

Demographic factors including age, BMI, smoking status, and gender were also evaluated. No significant association was found between these variables and SII, NLR, or PLR, except for age, which was significantly associated with SII and PLR. Although the effect of age on NLR was statistically significant, it was negligible in magnitude. This contrasts with previous findings where BMI, smoking, and gender were associated with inflammatory markers (54,55).

## Conclusion

In conclusion, the study findings indicate that SII, NLR, and PLR are significantly associated with several of these markers, suggesting their potential as surrogate indicators of malnutrition and inflammation in HD patients. The primary advantages of these indices are their accessibility and cost-effectiveness, especially for healthcare settings where routine assessment of inflammatory and nutritional markers is not feasible. The principal limitation of current study was relatively small sample size. Additionally, the use of iron supplements—administered intravenously in HD patients and orally in non-HD patients—may have influenced serum ferritin levels, thereby affecting some associations.

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## Conflict of Interest

Authors declare no conflict of interest.

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