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Novel biomarkers for the assessment of disease activity in patients with sarcoidosis: a case-control study

Hossam Hosny Masoud[1], *Amani Moustafa Ali*[1], *Fatma AbdelWahab*[2], *Hoda M. Abdel-Hamid*[1]
[1]Department of Chest Diseases, Cairo University, Cairo, Egypt; [2]Department of Clinical and Chemical Pathology, Cairo University, Cairo, Egypt

Abstract. *Background and aim:* The prognosis of sarcoidosis is challenging and largely depends on the persistence of disease activity and the degree of organ dysfunction. Various biomarkers have been evaluated for diagnosis, disease activity assessment, and prognosis. This study aimed to determine if the ratios of monocytes to high-density lipoprotein cholesterol (MHR), platelets to lymphocytes (PLR), neutrophils to lymphocytes (NLR), and lymphocytes to monocytes ratio (LMR) could be used as novel sarcoidosis activity markers. *Methods:* In a case-control study, 54 patients with biopsy-confirmed sarcoidosis were divided into two groups; group 1: consisted of 27 patients with active sarcoidosis who were newly diagnosed and treatment-naive, and group 2: consisted of 27 patients with inactive sarcoidosis who had been on treatment for at least 6 months. All patients were subjected to a comprehensive history, physical examination, laboratory tests, chest imaging, spirometry, and screening for extrapulmonary organ involvement by means of electrocardiogram and eye examination. *Results:* The mean age of the patients was 44 ± 11 years (79.6% were females & 20.4% were males). MHR, NLR, and LMR were significantly higher in patients with active sarcoidosis than in an inactive disease with a cut-off value of 8.6, a sensitivity of 81.5%, and a specificity of 70.4% *(P-value < 0.001),* a cut-off value of 1.95, sensitivity of 74% and specificity of 66.7% *(P-value 0.007)* and a cut-off value of < 4, a sensitivity of 81.5%, and a specificity of 85.2% *(P-value < 0.001),* respectively. In contrast, PLR was not statistically significant between active and inactive sarcoidosis patients. *Conclusions*: The lymphocytes monocytes ratio is a highly sensitive and specific biomarker that could be used to assess the disease activity in sarcoidosis patients.

Keywords: Sarcoidosis, Activity, Monocyte/HDL-C ratio, Neutrophil lymphocyte ratio, platelet lymphocyte ratio, lymphocytes monocytes ratio, biomarkers.

Introduction

Sarcoidosis is a systemic inflammatory disease of uncertain cause that can affect nearly every organ in the body. Typical organs affected include the lungs, lymph nodes, skin, and eyes. Once established, granulomas may spontaneously resolve, persist as chronic inflammation, or progress, resulting in fibrosis and organ dysfunction (1). Generally, sarcoidosis follows one of the two unique clinical courses. Approximately two-thirds of individuals recover, typically within the first two to three years after diagnosis. Other patients suffer from persistent chronic disease (2).

Traditionally, the activity of sarcoidosis is measured in two ways: using tests indicative of active

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Hoda Mohamed Abdel-Hamid, MD
Department of Chest Diseases, Kasr Alainy,
Faculty of Medicine, Cairo University
Cairo, Egypt
Phone: 01115229342
E-mail: Hodam.mabdelhamid@cu.edu.eg

granulomatous inflammation and monitoring the clinical deterioration of organ function (3).

Patients with symptoms and no prior treatment; patients with an established diagnosis, persistent symptoms, and current treatment; patients with symptoms and radiographic evidence of disease progression; or patients with symptoms and biological/immunological markers of active alveolitis/active granuloma or active progression to fibrosis constituted the active disease state. In patients with inactive illness, clinical symptoms, and signs regress or remain stable, biological/immunological markers are within normal limits, and chest radiographs demonstrate disease improvement (4, 5).

Numerous biomarkers have been studied for sarcoidosis diagnosis, assessment of disease activity, prognosis, and treatment response. The majority of biomarkers studied for sarcoidosis are insufficiently specific or sensitive to be utilized alone to guide clinical decisions. However, when combined with clinical data, various sarcoidosis biomarkers play a significant role in the clinical management of sarcoidosis (6).

A proposed new set of biomarkers for detecting systemic inflammation is Monocyte/high-density lipoprotein cholesterol ratio (MHR) (7), platelets/lymphocyte ratio (PLR) (8), neutrophil/lymphocyte ratio (NLR) (9), and lymphocytes monocytes ratio (LMR) (10). Circulating monocytes as a source of various cytokines and molecules, they interact with platelets and endothelial cells, causing the stimulation of inflammatory and prothrombotic pathways. High-density lipoprotein cholesterol (HDL-C) reduces the pro-inflammatory and pro-oxidant effects of monocytes by inhibiting macrophage migration (7), protecting endothelium from the negative effects of low-density lipoprotein cholesterol (LDL-C), and inhibiting the oxidation of LDL molecules. Therefore, HDL has anti-inflammatory and antioxidant properties (11).

Platelets, neutrophils, and lymphocytes are involved in the inflammatory process. Lymphocytes are the regulatory and protective components of a systemic inflammatory response, whereas neutrophils are the initial barrier to activating the defensive mechanism. Platelets play a crucial role in inflammation due to their ability to release chemokines and cytokines (12).

Therefore, the purpose of this study was to determine the role of MHR, PLR, NLR, and LMR in the evaluation of sarcoidosis activity.

Material and methods

Study design and participants

This case-control study was carried out on 54 patients suffering from sarcoidosis. Patients were recruited between October 2021 and March 2022 from the Chest outpatient clinic at Kasr AlAiny Hospital, Cairo University.

The diagnosis of sarcoidosis is based on three key criteria: a compatible clinical presentation, the identification of non-necrotizing granulomatous inflammation in tissue samples, and the exclusion of other causes of granulomatous disease (13). According to organ involvement and accessibility, confirmed tissue biopsies were taken (14).

According to the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) statement on sarcoidosis, patients were categorized into active and inactive sarcoidosis according to the disease state; Patients with symptoms and no prior therapy; patients with symptoms and radiographic evidence of disease progression; or patients with symptoms and biological/immunological indicators of active alveolitis / active granuloma or active progression to fibrosis constituted the active disease state. In patients with inactive illness, clinical symptoms, and signs regress or remain stable, biological/immunological markers are within the normal range, and chest radiographs demonstrate disease improvement (4, 5).

In our study, patients were categorized as active or inactive based on their disease state; group 1: consisted of 27 patients with active sarcoidosis who were newly diagnosed and with no prior treatment, and group 2: consisted of 27 patients with inactive sarcoidosis who were on treatment for at least six months and followed up at the chest outpatient clinic, where their medical records are reviewed to identify their presenting symptoms, laboratory tests, and chest radiographs.

The inactive disease state of group 2 is confirmed by the decrease of symptoms and inflammatory biomarkers, improvement of chest imaging in patients

with stages 1 and 2, improvement/stability of lesions in stages 3 and 4, and improvement of extrapulmonary organ involvement if initially present.

This study was eligible for any adult patient (18 years old) with sarcoidosis confirmed by biopsy. Those who are on lipid-lowering medications and patients with hepatic, renal, hematological, or rheumatological illnesses, cancer, coronary artery disease, or other pulmonary diseases were excluded from the study.

Data collection

We gathered patient demographic and smoking status data. In addition to baseline clinical data, presenting clinical symptoms using a yes/no checklist that queried each patient about constitutional symptoms (fever, fatigue, weight loss, and bony pain) and respiratory symptoms (dyspnea, cough, chest pain, and hemoptysis). The modified Medical Research Council (mMRC) scale was used to grade the severity of dyspnea (15). The pulmonary function was evaluated using spirometry and the six-minute walk test (6MWT) for patients with active sarcoidosis at the time of their first diagnosis and for patients with inactive sarcoidosis at their follow-up visit at least six months following treatment.

According to the American Thoracic Society Clinical Practice Guideline (ATSCG), screening for extrapulmonary organ affections consisted of an electrocardiogram and eye examination (8).

CBC (complete blood count), serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Kidney function tests, liver function tests, serum calcium, and 24-hour urinary calcium, HDL-C, and lactate dehydrogenase (LDH) were collected from patients with active sarcoidosis at the time of their first diagnosis and from patients with inactive sarcoidosis at their follow-up visit at least six months following treatment.

The MHR at baseline was computed by dividing the absolute monocyte count by the HDL-C concentration. The PLR was computed by dividing the platelet count by the absolute lymphocyte count, the NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count, and the LMR was obtained by dividing the absolute lymphocyte count by the absolute monocyte count. CBC with differential was performed using an automated cell counter (Sysmex XN-1000TM) and the differential count was confirmed using a light microscopy examination of peripheral blood smears. HDL was measured using an automated chemistry analyzer (Cobas 6000). (Roche, Germany).

Scadding of the chest radiograph and chest CT (computed tomography) was reviewed for both groups at the time of their first diagnosis (16).

Statistical analysis

The data were coded using version 28 of the statistical package for the social sciences (SPSS) (IBM Corp., Armonk, NY, USA). The data were summarised using the mean and standard deviation for quantitative variables, and the frequencies and percentages for categorical variables. Active and inactive sarcoidosis groups were compared using an unpaired t-test or analysis of variance (ANOVA) with multiple comparisons post hoc tests for normally distributed quantitative variables. In contrast, the non-parametric Kruskal-Wallis and Mann-Whitney tests were applied to non-normally distributed quantitative data. The Chi-square test was utilized for categorical data. Correlations between quantitative variables were established using the Spearman correlation coefficient. Analyzing the area under the curve to establish the appropriate MHR, NLR, and LMR cut-off value for diagnosing active sarcoidosis was used to develop the receiver operating curve (ROC). P-values less than 0.05 were considered statistically significant.

Ethical considerations

The research ethics committee of the Chest Department at Cairo University has reviewed and approved the study proposal (no. 468-2021). Before each patient was enrolled, the purpose and nature of the study were discussed. The policy on data confidentiality was strictly adhered to. Before enrolment, all participants provided informed written consent. The design of the study complied with the biomedical ethics criteria of the Revised Helsinki Declaration.

Results

Demographics and clinical characteristics of the studied patients

The studied patients included 54 patients who had biopsy-proven sarcoidosis with a mean age of 44 ± 11. The study included 43 females (79.6%) and 11 males (20.4%). All patients in the current study were presented with pulmonary sarcoidosis and investigated for extrapulmonary organ affection. Spleen and liver are the most commonly involved organs (23 cases; 43%) (20 cases; 37%) respectively, followed by cutaneous sarcoidosis (14 cases; 26%), uveitis (9 cases; 17%) and sarcoid arthropathy (7 cases; 13%). Less commonly involved organs included the nervous system, lacrimal glands, peripheral lymphadenopathy, and pleura. Concerning symptoms of the studied patients, the most commonly reported symptoms were dyspnea (96%), cough (38%), and fatigue (60%). Other clinical characteristics of the studied patients are summarized in Table 1.

Characteristics of the studied patients about laboratory data

Patients with active sarcoidosis had significantly higher monocyte count, serum CRP, ESR, and calcium levels and significantly lower lymphocyte count than patients with inactive sarcoidosis. Other labs showed no significance between patients with active and inactive sarcoidosis as outlined in Table 2.

Characteristics of the studied patients concerning pulmonary function assessment

There was no statistical significance between active and inactive sarcoidosis patients in the mMRC scale, 6MWT, and spirometry parameters, including FEV1 (Forced Expiratory volume in 1st second), FVC (Forced Vital Capacity), and FEV1/FVC (Table 2).

MHR, PLR, NLR, and LMR concerning the activity of sarcoidosis

Each MHR, NLR, and LMR significantly differed between active and inactive sarcoidosis patients (Table 2). Post hoc pairwise comparisons of the Kruskal Wallis Test showed that MHR, NLR, and LMR were significantly higher in patients with active sarcoidosis than in those with inactive disease (*P* 0.001, 0.013, <0.001), respectively. In contrast, PLR was not significantly different between active and inactive sarcoidosis patients (*P* 0.264).

Table 1: Demographics and clinical characteristics of the studied patients

		All patients n= 54	Active n= 27	Inactive n= 27
Age [Mean (SD)]*		44±11	43±9	45±11
Gender [n (%)]**	**Males**	11 (20.4%)	7 (26%)	4 (15%)
	Females	43 (79.6%)	20 (74%)	23 (85%)
Smokers [n (%)]		1 (2%)	1 (4%)	0 (0%)
Presenting Symptoms [n (%)]				
Dyspnea		52 (96%)	26 (96%)	26 (96%)
Cough		21 (38%)	13 (48%)	8 (30%)
Chest pain		1 (2%)	1 (4%)	0 (0%)
Hemoptysis		1 (2%)	1 (4%)	0 (0%)
Fever		2 (4%)	2 (8%)	0 (0%)
Fatigue		34 (62%)	17 (63%)	17 (63%)
Loss of weight		1 (2%)	1 (4%)	0 (0%)
Bony aches		0 (0%)	0 (0%)	0 (0%)
Presenting Scadding [n (%)]				
Stage 0		0 (0%)	0 (0%)	0 (0%)
Stage 1		20 (37%)	10 (37%)	10 (37%)
Stage 2		32 (59.2%)	15 (56%)	17 (63%)
Stage 3		2 (3.7%)	2 (7%)	0 (0%)
Stage 4		0 (0%)	0 (0%)	0 (0%)
Presenting organ affection [n (%)]				
Lungs		34 (65.4%)	17 (63%)	17 (63%)
Mediastinal lymph nodes		52 (96%)	25 (92.5%)	27 (100%)
Spleen		23 (43%)	13 (48%)	10 (37%)
Liver		20 (37%)	11 (41%)	9 (33%)
Skin		14 (26%)	8 (30%)	6 (22%)
Eyes		9 (17%)	5 (19%)	4 (15%)
Joints		7 (13%)	3 (11%)	4 (15%)
Neurosarcoidosis		2 (4%)	2 (7%)	0 (0%)
Peripheral lymph nodes		2 (4%)	0 (0%)	2 (7%)
Lacrimal glands		1 (2%)	1 (4%)	0 (0%)
Pleura		1 (2%)	1 (2%)	0 (0%)

SD: standard deviation, * P value = 0.468, **P value = 0.31, P value significant if < 0.05

Table 2: Laboratory findings and functional assessment of the studied patients

		Active n= 27	**Inactive n= 27**	**P-value**
laboratory data (Median, IQR)				
Hb (gm/dl)		12 (11.5-13)	12 (11-13)	0.36
Platelets (/μL)		277 (230-322)	322 (245-345)	0.063
TLC (/cmm)		6 (4.5-7)	6 (5-7)	0.82
Neutrophils count (/μL)		3596 (2385-4620)	3200 (2880-3850)	0.382
Monocytes count (/ μL)		540 (392-720)	300 (200-396)	0.001
lymphocytes count (/ μL)		1600 (1221-1800)	2170 (1650-2400)	0.002
MPV		9.5(9-10)	9(8-11)	0.993
Urea		22 (19-28)	25 (20-33)	0.445
Creatinine		0.8 (0.65-1)	0.8 (0.7-0.9)	0.834
ALT (U/L)		22 (13-26)	20 (15-25)	0.808
AST (U/L)		23 (18-31)	22 (19-32)	0.808
LDH		220 (200-300)	222 (186-245)	0.401
ESR 1st hr.(mm/hr.)		55 (30-60)	30 (30-60)	0.010
CRP (mg/L)		10 (5-24)	3 (1-6)	<0.001
Serum Calcium (mg/dL)		10 (9.5-10)	9.5 (9-10)	0.010
24 hrs. Urine Calcium (mmol/24 hr.)		150 (130-220)	130 (101-238)	0.350
HDL (mg/dL)		41 (37-46)	44 (37-50)	0.903
MHR		13.8 (8.7-16.8)	7 (4.9-9.6)	0.001
NLR		2.45 (1.75-3.1)	1.78 (1.30-2.13)	0.013
PLR		175.9 (143-230.6)	143.7 (124.6-209)	0.264
LMR		2.75 (2-3.5)	7.5 (4.7-8.5)	<0.001
Functional assessment (Median, IQR)				
mMRC no., (%)	0	1 (4%)	0 (0%)	0.7
	1	7 (26%)	10 (37%)	
	2	15 (56%)	14 (52%)	
	3	4 (15%)	3 (11%)	
	4	0 (0%)	0 (0%)	
6 min walk distance (m)		345 (300-345)	345 (330-360)	0.583
FEV1%		75 (67-83)	80 (73-90)	0.254
FVC %		76 (72-91)	78 (74-83)	0.936
FEV1/FVC %		80 (75-90)	85 (80-92)	0.084
MMEF 25-75%		55 (37-57)	56 (35-65)	0.327

IQR: Interquartile Range, Hb: Hemoglobin, TLC: Total leucocytes count, MPV: mean platelet volume, ALT: **alanine aminotransferase**, AST: **Aspartate aminotransferase**, LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive Protein, *HDL:* High-Density Lipoprotein, MHR: monocytes high-density lipoprotein cholesterol ratio, NLR: neutrophil-lymphocyte ratio, PLR: platelets lymphocyte ratio, LMR: lymphocyte monocyte ratio, mMRC: modified Medical Research Council, FEV1: Forced expiratory volume in 1 sec, **FVC: Forced vital capacity,** MMEF: maximal mid-expiratory flow, P-value significant if < 0.05.

Sensitivity and Specificity of MHR, NLR, and LMR in the detection of sarcoidosis activity

MHR and NLR were significantly higher in patients with active sarcoidosis with a cut-off value of 8.6, sensitivity of 81.5% and specificity of 70.4% (P-value < 0.001) and a cut-off value of 1.95, sensitivity of 74% and specificity of 66.7% *(P-value 0.007)* respectively (Table 3, Figure 1).

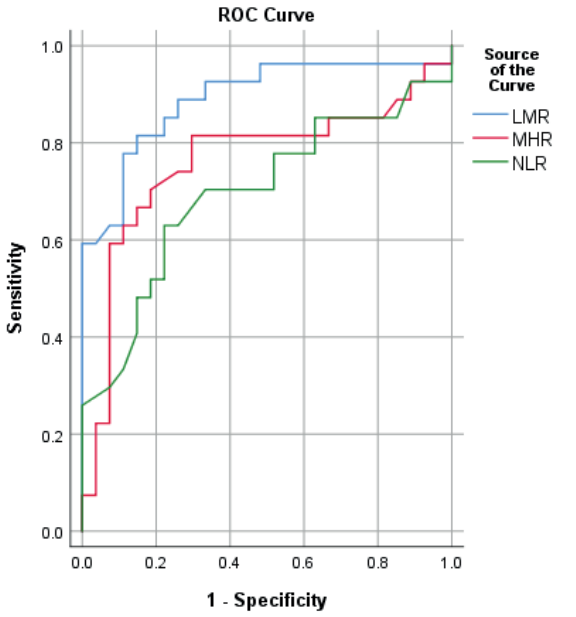

Fig (1): Receiver operating curve for the sensitivity and specificity of MHR and NLR in the detection of sarcoidosis activity

Discussion

Numerous biomarkers for the diagnosis, assessment of disease activity, and prognosis of sarcoidosis have been evaluated (6). This is the first study to evaluate MHR, PLR, NLR, and LMR for the identification of sarcoidosis activity. When paired with clinical and radiological characteristics of the disease activity, this will assist in identifying patients with disease activity who require early and targeted management.

The ideal biomarker for measuring disease activity would be simple, inexpensive, reproducible, readily available, and repeatable, and would show with high sensitivity and specificity whether the pathogenic or immunological process is currently active or inactive. So we decided to examine novel markers like MHR, PLR, NLR, and LMR for the identification of sarcoidosis activity.

Regarding the laboratory findings of the studied patients, the absolute monocyte count was higher in active sarcoidosis patients (P 0.001). This is attributed to the central involvement of monocytes in the pathogenesis of sarcoidosis since they stimulate T-cells and create pro-inflammatory cytokines that cause sarcoidosis inflammation. Moreover, monocytes are powerful TNF producers that contribute to local and systemic inflammation (17).

The current study showed that absolute lymphocyte count was 1500 ±500 (/μL) in patients with active sarcoidosis and 1700 ±550 (/μL) in patients with inactive disease (P 0.001). This could be explained by peripheral blood lymphocyte depletion caused by enhanced infiltration of target organs. Alternately, lymphopenia may indicate lymphogenesis suppression due to cytokines or enhanced peripheral destruction due to activation-driven cell death (18). Crouser et al. highlighted the role of lymphopenia as a measure of active and severe disease, as patients with active disease experienced a significant rise in absolute peripheral blood lymphocyte and CD4+ T-cell counts in response to infliximab (19).

ESR and CRP have been utilized as non-specific inflammatory biomarkers in a variety of conditions. They are simple tests for measuring the extent of systemic inflammation (20). In the present study,

Table (3): Sensitivity and Specificity of MHR and NLR in the detection of sarcoidosis activity

	Area Under the Curve	95% Confidence Interval		Cut off	Sensitivity %	Specificity %	P-value
		Lower Bound	Upper Bound				
MHR	0.761	0.622	0.900	8.6	81.5	70.4	< 0.001
NLR	0.698	0.553	0.842	1.95	74	66.7	0.007
LMR	0.891	0.799	0.983	<4.02	81.5	85.2	<0.001

MHR: monocytes high-density lipoprotein cholesterol ratio, PLR: platelets lymphocyte ratio, NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte monocyte ratio, P-value significant if < 0.05.

active sarcoidosis patients had significantly higher serum ESR 1st hr. and CRP values (P 0.010, 0.001), respectively. This accorded with the findings of Gupta et al. and Ilias S et al (21, 22).

Although Salazar A et al. found that patients with active sarcoidosis had significantly lower HDL-C concentrations than inactive sarcoidosis patients and healthy control subjects (P = 0.00001) (23), and Salazar A et al. confirmed that steroid therapy, used in the treatment of active sarcoidosis to reduce disease activity, returned HDL-C levels to the normal range (24), we found no difference in HDL-C level between active and inactive.

The present study showed that MHR, NLR, and LMR were significantly higher in patients with active sarcoidosis compared to inactive patients with a cut-off value of 8.6, sensitivity of 81.5 %, and specificity of 70.4 % (P-value < 0.001), a cut-off value of 1.95, sensitivity of 74% and specificity of 66.7% (P-value 0.007) and a cut-off value of < 4, a sensitivity of 81.5%, and a specificity of 85.2% *(P-value < 0.001),* respectively. The authors chose MHR and NLR cut-off values based on the high sensitivity of these indicators, so as not to miss patients with disease activity and to provide them the best chance for early detection and treatment, resulting in a better prognosis and outcome. Whereas LMR cut-off values showed more sensitivity and specificity in the assessment of disease activity in addition to skipping the need for a lipid panel when compared to MHR.

The decision to treat pulmonary sarcoidosis has been based on evidence of granulomatous inflammation along with physiologic dysfunction and significant pulmonary symptoms (3).

Granulomatous inflammation has been linked to elevated oxidative stress, which causes cell injury and may lead to organ failure (25), therefore prompt identification and treatment of patients with active sarcoidosis are recommended. Therefore, the utilization of Monocyte count, HDL-C serum level, neutrophil count, and lymphocyte count as ratios to avoid missing individuals with an active disease state. The strength of our study is that it was the first to detect the role of MHR, PLR, NLR, and LMR in assessing sarcoidosis activity. The most significant drawback of our study is the small number of patients with stage 3, no patients with stage 4 sarcoidosis were included and the proposed biomarkers are not tested to predict disease progression. Future research should employ sarcoidosis patients in stages 3 and 4 to evaluate the effect of MHR, NLR, and LMR in detecting disease activity and predicting disease progression in different disease stages.

Conclusion

Lymphocyte monocyte ratio is a novel highly sensitive and specific biomarker in the assessment of disease activity in sarcoidosis patients. Also, it is a simple, cheap, reliable, and promising biomarker to reveal inflammatory status in sarcoidosis. More studies on a larger population cohort are recommended for standardization and additional research be conducted to determine the role of LMR in monitoring therapy response and illness remission, disease prognosis, and disease outcome.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

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